Recommendations from the ICM-VTE: general

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Recommendations from the ICM-VTE: General

The ICM-VTE General Delegates*

1 - Are certain patients identified to be at greater risk for venous thromboembolism than others?

Response/Recommendation: Certain patient populations have been identified to be at greater risk for venous thromboembolism (VTE).

Strength of Recommendation: Limited.

Delegates vote: Agree 94.63% Disagree 2.93% Abstain 2.44% (Strong Consensus).

Rationale: Multiple studies have been published to better identify patient populations with an elevated VTE risk. Current literature states those with hypoalbuminemia, inflammatory disease, non-optimal body mass index (BMI), active adenocarcinoma and hematologic malignancies, blood dyscrasias, chronic kidney disease (CKD) and/or human immunodeficiency virus (HIV) are at an increased risk for VTE. In addition, ethnicity has been investigated for association with VTE.

Several studies have investigated the association of hypoalbuminemia and VTE. A 2019 study of 188 patients with advanced gastric cancer reported a significantly lower mean serum albumin concentration in individuals that experienced VTE compared to controls as an independent variable in multivariate analysis (3.38 mg/dL vs 3.65 mg/dL, respectively)[1]. A multivariate analysis indicated hypoalbuminemia was significantly correlated with VTE providing further evidence of the association. A separate study focused on identifying risk factors for VTE in total shoulder arthroplasty (TSA) patients found those with VTE were more likely to have a preoperative albumin level lower than 3.5 g/dL[2]. Lastly, a study based in China with the aim of identifying the incidence and appropriate risk factors for VTE in lung cancer patients found patients with hypoalbuminemia (albumin < 3.5 g/dL) to have significantly more VTE events, as an independent risk factor[3].

Current literature suggests inflammation is a risk factor for VTE. The activation of platelets and leukocytes can trigger the coagulation system through tissue factor induction[4]. A 2018 European Heart Journal article shows that patients with rheumatoid arthritis (RA) and mild psoriasis have significantly elevated risks of VTE following traditional risk factor adjustment[5]. Meanwhile, severe psoriasis and psoriatic arthritis patients with an anti-rheumatic drug prescription were found to have an elevated but non-statistically significant risk for VTE. A separate research project performed in Sweden indicated an increased VTE risk with increasing RA disease activity[6]. Those with inflammatory bowel disease (IBD), including ulcerative colitis and Crohn's disease, have an increased risk of VTE as well[7,8]. Research published by the Canadian association of gastroenterology approximates this risk in IBD to be 3-fold higher[9]. Lastly, patients with cystic fibrosis can have an increased VTE risk through thrombophilia secondary to inflammation, the use of central venous catheters, and the decrease of anticoagulant proteins[10].

Having an optimal BMI is one way to mitigate the risk of experiencing VTE. A 2020 study by Pahlkotter et al., showed that morbidly obese (BMI > 40 Kg/m^2) patients undergoing emergency surgical procedures were 1.7 times more likely to be diagnosed with pulmonary embolism (PE) compared with normal BMI patients. Increased BMI was also associated with the co-diagnosis of PE and deep venous thrombosis (DVT). In addition to this, patients with BMI < 18.5 Kg/m^2 or > 40 Kg/m^2 were 1.4 times more likely to experience a VTE compared with normal BMI patients[11].

All forms of cancer, most commonly active adenocarcinoma, have been shown to increase VTE rate by increasing levels of leukocytes, platelets, and tissue factor-positive (TF+) microvesicles. Current literature suggests cancer types can be broadly divided into 3 groups according to VTE risk. High-risk cancer types include pancreatic, ovarian, brain, stomach, gynecologic, and hematologic. Intermediate VTE risk cancers include colon and lung. While the low-risk VTE category consists of breast and prostate cancer[12]. Hematologic malignancies are also associated with a higher risk of VTE[13-15]. This subgroup represents a unique entity that undergoes therapy

*A list of the ICM-VTE General Delegates is included in a note at the end of the article.

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that can be thrombogenic[13]. The overall risk of VTE in patients with leukemia depends on the use of L-asparaginase treatment, older age, comorbidities, and central venous catheters[13]. Patients with acute promyelocytic leukemia are at particularly high-risk of VTE but also have an increased risk of bleeding[13]. Patients with aggressive lymphomas have a high incidence of VTE, roughly 10%[13]. Patients with multiple myeloma at highest risk of VTE are those receiving immunomodulatory agents such as thalidomide or lenalidomide[13]. Allogeneic stem cell transplantation carries a risk of thrombosis, particularly in patients developing graft vs. host disease[13].

Certain populations with blood dyscrasias have been identified to be at greater risk for VTE. Sickle cell anemia is seen to be associated with VTE and is more common in African and African American populations[16]. Kujovich, showed that Factor V Leiden thrombophilia is characterized by a poor anticoagulant response to activated protein C (APC) and an increased risk for VTE. Evidence suggests that heterozygosity for the Leiden variant has at most a modest effect on risk for recurrent thrombosis after initial treatment of a first VTE. A short course of prophylactic anticoagulation when circumstantial risk factors are present may prevent initial thrombosis in Leiden variant heterozygotes[17]. In a prospective cohort study, Tormene et al., described how antithrombin, protein C, and protein S defects are well-recognized inherited risk factors for VTE in adults. Screening for thrombophilia in children who belong to families with these defects seems justified to identify those who may benefit from thromboprophylaxis during risk periods for thrombosis[18].

CKD is associated with an approximately two-fold increase in VTE risk and a higher VTE mortality rate than the population[19]. The increased risk of VTE is graded by a declining estimated glomerular filtration rate (eGFR) and albuminuria. eGFR is also inversely correlated with Factor VIII, an essential cofactor in the coagulation cascade. The lower eGFR seen in CKD patients effectively raises Factor VIII levels and increases the coagulability of blood to raise the risk of VTE.

HIV-positive patients are inherently hypercoagulable. HIV viral proteins effectively attack the function of the endothelium via pathways that reduce the synthesis of nitric oxide and upregulate monocyte chemoattractant protein-1 and adhesion. This results in increased leukocyte and platelet activation/adhesion to the endothelium[20]. Clinically, in a recent multicenter study of 110 HIV-positive and 240 HIV-negative patients showcased increased rates of symptomatic VTE in the HIV-positive cohort after total hip or total knee arthroplasty. A multivariable logistic regression adjusting for sex, smoking, history of VTE, and joint replaced identified HIV as an independent predictor of VTE[21]. With respect to viral load, one group of authors concluded that a higher viral load, and lower $CD4^+$ cell count, was associated with a higher risk of thrombosis[22], conversely others have found no correlations[23].

Ethnicity has been studied but has yielded largely variable results. Several studies propose African Americans as having higher VTE incidence than Hispanics and Asian-Pacific Islanders[2,24]. In contrast, a study conducted within an integrated healthcare system found no significant difference in postoperative VTE amongst white, African American, and Hispanic populations. However, the model of universal insurance in the study does not mirror the current United States system[25,26]. In communities where health access is not as robust, it is unclear if these results are applicable.

In conclusion, certain patients can be identified to be at a greater risk for VTE. Current literature reveals an association between VTE with the following comorbidities: hypoalbuminemia, inflammatory disease, non-optimal BMI, active adenocarcinoma and hematologic malignancies, blood dyscrasias, CKD and/or the presence of HIV. In addition to this, ethnicity has been investigated with no clear association with VTE risk. In the case of all the proposed risk elevators, additional research is needed to develop appropriate risk mitigation therapies likely for the specific disease process.

Jeremiah Taylor, William Jiranek, Jerzy Bialecki, Ronald Navarro

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2 - Are there genetic predisposing factors for VTE?

Response/Recommendation: There are 5 classic thrombophilias that have a genetic predisposition for venous thromboembolism (VTE). A large proportion of the inherited risk factors for VTE remain undiscovered and many new loci associated with VTE risk continue to be identified.

Strength of Recommendation: Strong.

Delegates vote: Agree 98.60% Disagree 0.47% Abstain 0.93% (Strong Consensus).

Rationale: VTE, comprising deep venous thrombosis (DVT) and pulmonary embolism (PE), is a multifactorial disease with many known acquired and inherited risk factors. Family history of VTE has been estimated to have an odds ratio (OR) of 2.2 - 2.7[27,28]. Over the last 60 years, many gene variations that affect VTE risk have been identified through family-based studies. Initial reports of familial aggregation of VTE was first described in the 1990s. Five thrombophilias have been described including: hereditary antithrombin deficiency; protein C deficiency; protein S deficiency; Factor V Leiden and prothrombin mutation. These classic thrombophilias have been associated with increased VTE risk and familial aggregation of VTE[29,30]. Other loci such as non-O blood (ABO), fibrinogen gamma (FGC) and hyperhomocystenemia (MTHFR) have since been associated with increased VTE risk. Many more loci associated with increased VTE risk continue to be discovered through genome-wide association[31-35].

Protein C, protein S and antithrombin are natural coagulation inhibitors and deficiencies result in a hypercoagulable state. Mutations are typically due to loss of function mutations in the PROC, PROS1 and SERPINC1 genes encoding proteins C, protein S and antithrombin, respectively. Protein C and protein S are vitamin K-dependent glycoproteins that inhibit Factor VIIIa and Factor Va, cofactors in the activation for Factor X and prothrombin, respectively[36]. Protein C and protein S deficiency are both autosomal dominant traits and present in less than 1% of the general population and 2 - 3% in patients with VTE[30]. Patients with DNA analysis confirmed protein C deficiency have been reported to have relative risk of 6.5 for VTE, compared to control subjects[37]. In a family study, first-degree relatives with protein S deficiency had a 5 times greater risk of thrombosis compared to subjects with normal PROS1 gene[38]. In a case-control study comparing patients with first time VTE to controls, patients with S levels in the 2.5th percentile and < 0.10th percentile had a OR of 2.31(95% confidence interval [CI], 1.06 - 5.05) and 5.44 (95% CI, 0.61 - 48.78), respectively[39].

Antithrombin is a serine protease inhibitor and functions to inhibit thrombin and activated Factor X (FXa), resulting in decreased generation and half-life of thrombin. The SERPIN1 gene is located at chromosome 1q 23 - 25, and the most common mutations are missense and nonsense mutations. Of the 5 classic thrombophilias, antithrombin deficiency is the least common, present in less than 0.2% of the general population and 1% in patients with VTE[30]. A meta-analysis evaluating VTE in antithrombin deficient individuals compared to controls found an OR of 14.0 (95% CI, 5.5 to 29.0) for the first VTE and the annual VTE risk in antithrombin deficient subject to be 2.3% (95% CI, 0.2 - 6.5%)[40]. While antithrombin deficiency is the least common of the classic thrombophilias, deficiencies result in high relative risk of a first VTE and recurrence.

Factor V and prothrombin are coagulation factors and gain of function mutations result in hypercoagulable state. Factor V Leiden is due to resistance to activated protein C (APC-resistance) on Factor V. When inactivated protein C attaches to thrombin, APC is formed and inactivates Factor Va and VIIIa by cleaving specific sites. The most common mutation, rs6025, is due to a single-point mutation that replaces arginine with glutamine at the APC cleavage site[31,41]. Factor V Leiden mutation is the most common thrombophilia and has been estimated to be associated with up to 20% of patients with first VTE events[37]. Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study evaluated patients with a first VTE events, heterozygous mutations were found in 14.8% of patients and 5.2% of controls, and homozygous mutations in 0.7% and 0.2%, respectively. Subjects with Factor V Leiden mutation had an OR of 3.3 compared to control subjects (95% CI, 2.6 - 4.1)[42].

Prothrombin is a precursor to thrombin, that is proteolytically cleaved by Xa to form thrombin. The most common mutation of gene F2 is G20210A, a point mutation that substitutes adenosine for guanosine and results in a gain-of function mutation[43]. Patients who are heterozygote for prothrombin G20210A have higher levels of plasma prothrombin, however, the exact mechanism of increased VTE risk is not well understood. In a case-control study the prothrombin A20210 allele was found in 8.01% of VTE patients compared to 2.29% control subjects ($p < 0.001$), and was associated with an increased risk of VTE (OR 3.88; 95% CI, 2.23 - 6.74)[44]. Other case-control series have reported similar OR from 2.8 - 3.8[43,45].

A large proportion of VTE's heritability remains undiscovered. There is a continued effort to identify loci associated with VTE through genome-wide association studies (GWAS), which compare the DNA of large cohorts of patients with VTE to

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TABLE I Genome-wide significant VTE loci from three GWAS[34,35,46]

Gene/Locus	rs ID †	Chromosome	Position †	A1	A2	Consequence
F5	rs6025	1	169519049	T	C	Arg534Gln
C4BPA	rs2842700	1	207282149	A	C	intron
F5	rs4524	1	169511755	C	T	Lys858Arg
KIF26B	rs1756912	1	245588095	A	G	intronic
RGSL1	rs55897462	1	182512200	G	T	intronic
CSRNP1	rs13084580	2	127962493	T	C	5'UTR
PROS1	rs6795524	2	68619981	G	A	intron
POLE4	rs74965230	2	75182831	C	T	intergenic
RP11-122C5.1	rs16867574	3	39188182	C	T	downstream
STXBP5	rs7739314	3	93650604	C	A	downstream
FGG	rs2066865	4	155525276	A	G	downstream
F11	rs4253417	4	187199005	C	T	intron
FGG	rs2066864	4	155525695	A	G	intron
F11	rs2289252	4	187207381	T	C	intron
F11	rs2036914	4	187192481	T	C	intron
F11	rs4253421	4	187204937	A	G	intron
HLA-C	rs2074492	5	38708554	T	C	upstream
OSMR-AS1	rs4869589	5	38707871	T	G	intron
SCARA5	rs10087301	6	147709180	A	G	intron
GRK5	rs10886430	6	31239869	G	A	intron
STXBP5	rs9373523	6	147701133	T	G	intron
ZFPM2	rs4734879	8	106583124	A	G	intron
MYRF	rs174536	8	27820792	A	C	intron
ZFPM2	rs4541868	8	106590705	A	C	intron
ASH2L	rs149680046	8	37968307	T	C	missense
ABO	rs9411377	9	136145404	A	C	intron
ABO	rs8176749	9	136131188	T	C	synonymous
ABO	rs687289	9	136137106	A	G	intron
ABO	rs2519093	9	136141870	T	C	intron
ABO	rs579459	9	136154168	C	T	intron
TSPAN15	rs78707713	10	71245276	T	C	intron
SBNO1	rs12824685	10	121010256	G	T	intron
TSPAN15	rs78707713	10	71245276	C	T	intron
NRG3	rs1649936	10	83969121	T	C	intronic
F2	rs1799963	11	46761055	A	G	3'UTR
VWF	rs216296	11	61551927	G	A	intron
F2 (LRP4)§	rs191945075	11	46933311	A	G	Downstream (intron)
F2	rs3136516	11	46760756	G	A	intron
F10	rs3211752	12	123817569	G	A	intron
CATSPERB	rs57328376	12	6154670	G	A	intron
MPHOSPH9	rs2851436	12	123667354	G	T	intron
VWF	rs1558519	12	6153738	G	A	intron
VWF	rs216311	12	6128443	T	C	Thr1381Ala
PLCG2	rs12445050	13	113787459	T	C	intron

continued

TABLE I (*continued*)

Gene/Locus	rs ID †	Chromosome	Position ‡	A1	A2	Consequence
SMG6	rs1048483	14	92235039	T	C	intron
AGBL1	rs72755680	15	87509243	C	A	ncRNA intronic
PEPD	rs731839	16	81870969	A	G	intron
GP6	rs1654425	17	1966457	C	T	synonymous
SLC44A2	rs2288904	19	10742170	G	A	Gln154Arg
CYP27C1	rs7585314	19	33899065	T	C	intron
PLEK	rs1867312	19	55538980	C	A	intron
SLC44A2	rs4548995	19	10740871	G	C	intron
GP6(NLRP2) §	rs1671135	19	55511873	G	C	Downstream (intron)
PSG8	rs59559305	19	43283623	A	G	intronic
SNRNP70	19:49596145	19	49596145	C	T	intronic
(CD93)	rs6083037	20	23182559	A	T	intergenic
EDEM2	rs10747514	20	33775369	A	G	intron
PROCR	rs6088735	20	33745676	T	C	intron
PROCR	rs867186	20	33764554	G	A	Ser219Gly
NCAM2	rs62207434	21	22780048	T	C	intronic
A4GALT	rs9607928	22	43111772	A	C	intron
BRCC3	rs7051718	X	154332656	T	C	intron
F9	rs6048	X	138633280	A	G	Thr194Ala
(BCOR) §	rs3002417	X	39708724	T	C	intergenic
F8	rs143478537	X	154424170	G	C	upstream

VTE=Venous thromboembolism; GWAS=Genome-wide association studies; A1=Reference Allele; A2: Alternate Allele. †Reference SNP Cluster ID. ‡ Variant position on chromosome. §Genes of variants that are outside of protein-coding transcript bounds are shown with nearest gene in parentheses.

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control subjects. In three recent GWAS, 14, 22, and 20 susceptibility genes for VTE have been discovered, respectively[33-35]. Previously identified and novel single nucleotide polymorphisms (SNPs) identified in these three studies can be found in Table I. Many previously known VTE loci are associated with the coagulation cascade. Herrera-Riveor et al., identified 20 susceptibility genes for VTE that do not participate directly in the coagulation cascade and proposed increased VTE risk was due to possible effect on platelet formation or function, cardiovascular development, and repair, and/or inflammation[33]. Ideally, in the future, genetic profiles could be established for surgical patients to assess the risk for developing a VTE. Further studies will need to evaluate mechanism of actions of newly found VTE loci and their potential mechanism of VTE.

The 5 classics inherited thrombophilias include protein C deficiency, protein S deficiency, antithrombin deficiency, Factor V Leiden, and prothrombin G20210A. Protein C, protein S, and antithrombin deficiencies are most commonly due to a loss of function mutation, resulting in a hypercoagulable state. Factor V Leiden and prothrombin G20210A are due to gain of function mutations and are more commonly found in unselected patients with VTE. However, the classic thrombophilias make up a small proportion of inherited risk for VTE, and research on new loci and their risk for VTE need to be determined.

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3 - Is there a correlation between age and the risk of VTE in patients undergoing orthopaedic procedures?

Response/Recommendation: Increasing age is associated with an increased risk of postoperative venous thromboembolism (VTE) in patients undergoing orthopaedic procedures.

Strength of Recommendation: Strong.

Delegates vote: Agree 99.53% Disagree 0.47% Abstain 0.00% (Strong Consensus).

Rationale: Increasing age is an important risk factor for the development of VTE[47-55] as well as for a poor outcome following an acute VTE[54,56-61]. The incidence of this complication has been shown to increase exponentially with age[55,62] and this increase in risk is similar in both male and female individuals[55]. Studies have revealed that the prevalence of established VTE risk factors also varies with age[63]. In addition to major surgery, malignancy accounts for approximately 20% of the overall incidence of VTE[64,65]. Familial and genetic factors are also important for the development of VTE, although the relative contribution of familial factors declines with age[55]. Several epidemiologic studies have shown that the rate of VTE events following knee or hip joint replacements increases significantly with a patient's age[66-84].

The results of some key studies are presented as follows: White et al., demonstrated that patients' age was independently associated with a thromboembolic complication (odds ratio [OR] 1.15 for each 10-year increase in age over 50 years and a 95% confidence interval [CI], 1.1 - 1.3) among 19,586 patients who underwent primary hip arthroplasties and 24,059 who underwent primary knee arthroplasties[70]. In a large nationwide study on hip replacements including 1,885,839 patients from 2005 - 2016 in Germany, Keller at al., reported that the number of VTE events increased with age (β 0.33 per age decade [95% CI 0.30 - 0.35])[67]. A second study including 1,804,496 hospitalized patients who had elective primary knee joint replacement demonstrated that VTE risk was age-dependent (β 0.14 [95% CI 0.12 - 0.15], per age decade)[68]. In accordance with these findings, in the Danish Knee Arthroplasty Registry, Pedersen et al., identified 37,223 primary knee arthroplasties performed from 1997 - 2007 in patients who received pharmacological thromboprophylaxis[77]. The risk of a hospitalization with VTE increased with increasing age, and this risk was highest in patients > 80 years old (adjusted relative risk [RR] 1.58 [95% CI 1.01 - 2.47]) compared to patients < 50 years[77]. Yhim et al., analyzed 306,912 patients with total joint replacement (261,260 total knee arthroplasties [TKA] and 45,652 total hip arthroplasties [THA]) in the Health Insurance Review and Assessment Service (HIRA) database[81]. Patients ≥ 60 years (OR 2.20 [95% CI 1.98 – 2.45]) showed a higher risk of postoperative VTE compared to patients < 60 years[81]. In the New York State database from 1985 - 2003, Lyman et al., analyzed 152,461 patients who had THA and 162,085 who had TKA[84]. Increased age was associated with higher number of VTE events (TKA: OR 1.03 per 10-year increase in age [95% CI 1.00 - 1.06]; THA: OR 1.10 per 10-year increase in age [95% CI 1.07 - 1.13])[84]. In a separate study, Wu et al., analyzed 114,026 patients undergoing THA (n = 61,460) or TKA (n = 52,566) between 2002 - 2006 using the National Health Insurance database of Taiwan and found that VTE rates in patients aged 60 – 69 (OR 2.33 [95% CI 1.34 - 4.06]) and 70 – 79 (OR 1.90 [95% CI 1.15 - 3.16]) years were higher compared to those who were younger than 50 years[76].

In contrast, only a very few studies have reported no relationship between age and the incidence of VTE[85-87]. Furthermore, others have reported divergent results for THA and TKA[78,80]. Data from the Spanish National Discharge Database in 2005 – 2006 revealed that age > 70 years was associated with VTE in THA (OR 1.5 [95% CI 1.1 – 1.9]), but not associated with VTE in TKA[79]. When analyzing 93,071 THA and 223,600 TKA in the Nationwide Inpatient Sample (NIS) database from 2003 - 2006, Kapoor et al., observed that age ≥ 80 years was accompanied by a higher postoperative VTE rate following

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THA compared to patients aged 65 - 69 years (OR 1.30 [95% CI 1.05 - 1.60]), but advanced age was not associated with a higher VTE rate in patients who underwent TKA[78].

Although the rate of VTE after orthopaedic surgeries of the upper limb is substantially lower than after orthopaedic surgeries of the lower extremities[88], an age-dependent increase was also found in most of these studies[84,89-91]. In the study by Lyman et al., including 13,759 patients who underwent shoulder arthroplasty, an increase in VTE occurrence (OR 1.19 [95% CI 1.02 - 1.37]) was seen with every 10-year increase in age[84]. Consistent with this, Kunutsor et al., conducted a large study of 672,495 primary shoulder and elbow replacements, observing that age ≥ 70 years was associated with an elevated risk for VTE (RR 1.15 [95% CI 1.08 - 1.22])[89]. Jameson et al., similarly found an increased VTE risk after arthroscopy of the shoulder in 65,302 patients aged ≥ 70 years vs. < 60 years, but this association was not demonstrated in 10,229 patients undergoing elective shoulder replacement and 4,696 patients undergoing proximal humeral fracture surgery[90].

The influence of age on VTE risk in patients with fractures of the lower extremity and oncologic orthopaedic surgeries were not consistent[92-101]. In patients undergoing surgical treatment of fractures below the hip, age ≥ 60 years was identified as a risk factor for VTE (RR 1.85 [95% CI 1.34 - 2.55]) in 191,294 patients[92]. Similarly, Park et al., showed that advanced age of ≥ 60 years was associated with higher risk of VTE (OR 3.1 [1.3 - 7.4]) in 901 patients who underwent surgical treatment of fractures below the hip[95]. In addition, Zhang et al., reported that patients ≥ 65 years of age had a higher risk of preoperative deep vein thrombosis following closed distal femur fractures (OR 4.39 [95% CI 1.73 - 11.16)[102].(p65) In contrast, the study by McNamara et al., that analyzed 5,300 hip fracture patients revealed no age-dependent impact on VTE occurrence[94].

A study by Congiusta et al., utilized the NIS database to determine the VTE rate after benign as well as malignant musculoskeletal tumor surgery[101]. After analyzing more than 18,000 patients with benign tumors and more than 69,000 patients with malignant musculoskeletal tumors, all age groups except for patients ≥ 80 years had a higher frequency of VTE following malignant tumor surgery compared to the < 30 years age group[101]. In patients who had surgery for benign musculoskeletal tumors, only patients ≥ 80 years had a higher VTE risk[101]. Fu et al., showed that in patients who had surgery for musculoskeletal tumors, an age of > 60 years was associated with a higher VTE rate in comparison to patients aged < 60 years (26.4% vs. 21.2%)[93]. The study by Yamaguchi et al., identified age > 70 years as a risk factor for VTE events in 94 patients undergoing musculoskeletal tumor resection[98]. In contrast, other studies were not able to detect an association between age and VTE occurrence[96,97,99,100].

In view of the wealth of national registry-based studies with large cohorts undergoing primary major joint replacements, fracture surgeries and orthopaedic tumor surgeries, there is ample evidence demonstrating an association between increasing age and a higher risk of VTE after orthopaedic surgery[66-82,84,89-92,95,101]. This association was stronger for patients who underwent THA[66-82] compared to TKA[78-80]. Although a patient's age seems to be a weaker risk factor compared to other VTE risk factors (e.g., immobilization), it should be recognized that the prevalence of important concomitant VTE risk factors (e.g., malignancy) also increases with advanced age[64,65,69,71,75,103].

Karsten Keller, Lukas M.A. Hobohm

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4 - Is the risk of VTE following orthopaedic procedures related to ethnicity or race? If yes, should VTE prophylaxis be altered or changed based on race and/or ethnicity?

Response/Recommendation: At this time, evidence is insufficient to suggest that venous thromboembolism (VTE) prophylaxis should be altered based on race/ethnicity.

Strength of Recommendation: Limited.

Delegates vote: Agree 95.12% Disagree 2.44% Abstain 2.44% (Strong Consensus).

Rationale: As VTE is a post-operative complication of utmost importance to orthopaedic surgeons, studies in recent years have examined the relationship between race and post-operative VTE to determine whether a patient's racial background is correlated to their risk of developing VTE. Multiple studies have found black patient populations to disproportionately suffer from higher rates of VTE following orthopaedic procedures[104-114]. Multiple studies examining post-operative complications in total knee arthroplasty (TKA) and total hip arthroplasty (THA) found a significant correlation between black race and incidence of VTE[104-109]. Other studies

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examining post-operative complications in total shoulder arthroplasty, hip fracture surgery, and spine surgery similarly found an association between black race and VTE[110-114]. However, this is not a universal finding. A few studies have found no significant correlation between post-operative VTE and race[115-119]. Blum et al., found no association between VTE and African American race in analysis of a regional database[115]. However, the patients in the African American group within that study were significantly younger and healthier compared to other racial groups, which may infer an inherent selection bias (as stated by the authors) in patients opting for TKA in that regional study. Another one of these studies demonstrated no significant correlation between race and post-operative VTE and only included elective pediatric orthopaedic procedures, thus the generalizability of these results to older populations is questionable[116]. One study examining short-term complications following patellofemoral arthroplasty had similar findings, however the time course chosen excludes any potential VTE events that could have occurred beyond thirty days[117]. Furthermore, a retrospective study conducted at a Level 1 trauma center found no difference in outcomes with respect to race for operatively treated tibia fractures[118]. However, the authors note that the study was underpowered to definitively state that there is no difference between the two groups and the analysis of one specific center limits the generalizability of the results. Moreover, a cross-sectional study analyzing data from the Nationwide Inpatient Sample (NIS) database in the U.S. did find black race to significantly increase patients' risks of VTE following TKA[104]. The large statistical power within this study (n = 1'460,901) and the use of national data increases the generalizability of this study's findings compared to the aforementioned studies.

It is currently unclear whether these disparities are associated with environmental differences, such as access to care, implicit bias, and socioeconomic status, or biologic/genetic differences across races. Two recent studies examining post-operative complications in TKA and TKA procedures conducted within an integrated healthcare system found no significant difference in post-operative VTE amongst white, black, and Hispanic populations and a significantly lower rate amongst Asian-Americans[120,121]. A notable characteristic of these studies is universally insured status of the populations, which may have played a role in mitigation of these disparities. As the model of integrated care and universal insurance within this specific system may not mirror most current systems within the U.S., it is unclear if these results are applicable to other health care delivery systems where access to care is not as robust. Another study seeking to examine whether racial disparities are associated with complications in tibial plateau fracture care, found that while treatment choices were impacted by patient's racial backgrounds (African Americans and Hispanics were more likely to undergo nonoperative treatment), there was no significant difference in rates of deep venous thrombosis (DVT) or pulmonary embolism (PE) when patients did receive operative treatment[119]. Additional studies are needed to address the underlying factors contributing to possible differences in VTE due to treatment course amongst races.

There are numerous studies conducted in Asia that have suggested that Asian patients experience lower rates of VTE[122-133]. An issue with most of these studies is that populations are exclusively Asian and results within these studies are compared to results in Western studies, rather than directly comparing multiple races within a single study. Additionally, several of these studies are retrospective, which is inherently susceptible to bias[122-126]. One therapeutic study following 184 patients found a low incidence of asymptomatic VTE (5%) and no episodes of fatal or symptomatic VTE in Asian patients undergoing elective hip surgery at a single center[127]. Additionally, a systematic review examined studies from 1979 - 2009 that included post-operative VTE in Asian patients undergoing hip fracture surgery, THA, and TKA and similarly found lower rates of proximal and symptomatic DVT compared to Western reports with no fatal cases of VTE[128]. A meta-analysis reviewed studies from 1996 - 2011 pertaining to Asian patients undergoing TKA and found an overall incidence of symptomatic PE to be 0.01%, overall incidence of DVT to be 40.4%, proximal DVT to be 5.8% and symptomatic DVT to be 1.9%[129]. Similar results were demonstrated in a meta-analysis conducted by Liew et al., however there is a discrepancy in the conclusion drawn between these two papers. The former questions the potential benefit of chemical prophylaxis based on lower rates of VTE within these populations. The latter states that though incidence is lower, rates are still significant enough to warrant consideration of prophylaxis for Asian patients[130]. Complicating the picture further is a prospective study following 724 Taiwanese patients undergoing TKA found a similar incidence of DVT compared to Western studies[134]. Thus, there remains disagreement as to whether chemoprophylaxis should be routinely utilized within Asian patients who lack significant prothrombotic risk factors. In two studies examining prevalence of VTE in Asian patients undergoing TKA and THA, respectively, who were treated solely with mechanical prophylaxis, Kim et al., found a low overall incidence of VTE[131,132]. Yeo et al., found similar results in Asian patients undergoing knee arthroscopy or arthroplasty who were given a regimen of rehabilitation and mechanical prophylaxis[133]. Loh et al., found that there was no significant difference in VTE between Asian patients given mechanical thromboprophylaxis and those given chemoprophylaxis in addition to mechanical prophylaxis post TKA[122]. Sugano et al., retrospectively reviewed 3,016 Asian patients undergoing hip surgery at 5 different centers and concluded that mechanical thromboprophylaxis without anticoagulant drugs is safe and effective for this patient population[123].

Furthermore, little is known about whether race can sufficiently be utilized as a factor considered when risk stratifying a patient and whether chemoprophylaxis will lead to mitigation of these disparities or create additional disparities (i.e., hemorrhage). Many of the previously mentioned studies within Asian populations demonstrated that mechanical prophylaxis alone may be sufficient for thrombosis prevention, however additional

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TABLE II Rates of VTE and Odds ratios for various races reported in studies

Study	Procedure	White rate of post-operative VTE (%)	Latino/ Hispanic rate of post-operative VTE (%)	Black rate of post-operative VTE (%)	Asian rate of post-operative VTE	Odds ratio of VTE Black race relative to White race	Odds ratio of VTE Asian race relative to White race	Odds ratio of VTE Hispanic ethnicity relative to White race
Dai et al.[104]	TKA	0.83	0.81	1.06	-	1.34	-	0.98
Owens et al.[105]	TKA	1.4	-	2.2	1.1	1.14	0.94	-
Cram et al.[106*]	TKA	0.6	-	1.14	-	-	-	-
Cram et al.[106*]	THA	0.2	-	0.4	-	-	-	-
Dua et al.[107**]	TKA	-	-	-	-	1.3	-	-
Dua et al.[107**]	THA	-	-	-	-	2.2	-	-
Zhang et al.[108]	THA/TKA	-	-	-	-	1.29	-	-
SooHoo et al.[109*]	TKA	-	-	-	-	1.74	-	0.84
Lung et al.[110]	TSA	0.6	0	1	0	3.26	-	-
Nayar et al.[111*]	Hip Fracture Surgery	0.73	-	1.28	0.45	1.8	-	-
Best et al.[112*]	TSA/RTSA	-	-	-	-	1.97	-	-
Best et al.[112**]	TSA/RTSA	-	-	-	-	0.97	-	-
Sanford et al.[113*]	Cervical Spine Surgery	0.1	-	0.5	-	4.343	-	-
Sanford et al.[113*]	Lumbar Fusion	0.8	-	1.3	-	1.55	-	-
Sanford et al.[113*]	Decompression Laminectomy	0.2	-	1.1	-	5.764	-	-
Sanford et al.[113**]	Cervical Spine Surgery	0.1	-	-	-	-	-	-
Sanford et al.[113**]	Lumbar Fusion	1.1	-	3.3	-	3.72	-	-
Sanford et al.[113**]	Decompression Laminectomy	0.8	-	0.6	-	0.773	-	-
Fineberg et al.[114]	Lumbar Decompression/ Lumbar Fusion	-	-	-	-	1.8	-	-
Blum et al.[115]	TKA	2.6	-	2.2	-	-	-	-
Georgopoulos et al.[116]	Elective pediatric surgeries	0.06	0.07	0.04	0.15	-	-	-
Driesman et al.[119]	Closed treatment and operative fixation of tibial plateau	0.7	0.6	0.7	-	-	-	-

continued

TABLE II (*continued*)

Study	Procedure	White rate of post-operative VTE (%)	Latino/ Hispanic rate of post-operative VTE (%)	Black rate of post-operative VTE (%)	Asian rate of post-operative VTE	Odds ratio of VTE Black race relative to White race	Odds ratio of VTE Asian race relative to White race	Odds ratio of VTE Hispanic ethnicity relative to White race
Hinman et al.[120]	TKA	1.1	0.9	1.1	0.7	1.03	0.59	0.9
Okike et al.[121]	THA	1	0.8	1.1	0.3	1.1	0.29	0.85
Piper et al.[135]	Spine surgery	-	-	-	-	2.11	-	-
Kim et al.[136]	Elective adult spinal deformity procedures	1.9	0.9	1.8	-	-	-	-
Kim et al.[137]	Posterior Lumbar Spine Fusion	1	1	1.1	-	-	-	-

VTE=Venous thromboembolism; TKA=Total knee arthroplasty; THA=Total hip arthroplasty; TSA=Total shoulder arthroplasty; RTSA=Reverse total shoulder arthroplasty. *Pulmonary embolism was specifically measured rather than overall VTE. **Deep venous thrombosis was specifically measured rather than overall VTE.

studies conducted with diverse racial/ethnic populations are needed to generalize such results. Piper et al., sought to identify risk factors associated with VTE in patients undergoing spine surgery and found African American race to significantly increase patients' risk of experiencing VTE[135]. Researchers in this study also created a risk score based on identified factors, which included African American race, and found that the score was able to predict postoperative VTE rate. Two additional studies incorporated race/ethnicity into a computer learning model that demonstrated proficiency in predicting post-operative VTE in patients undergoing spinal surgeries. These studies suggest the feasibility of indeed utilizing race as a concrete risk factor while risk stratifying patients. However, additional studies are needed to suggest that chemoprophylaxis in conjunction with risk stratification may reduce incidence of VTE in at-risk groups[136,137]. A study conducted by Heijiboer et al., retrospectively examined data on patients undergoing orthopaedic below-knee surgery and found that nonwhite race was significantly correlated with increased risk of VTE in patients who did not receive chemoprophylaxis. While assessing risk factors for patients who did receive chemoprophylaxis, Heijiboer et al., found no significant correlation between race and VTE[138]. While it is known that Virchow's triad (intravascular vessel wall damage, hypercoagulable state, and stasis of flow) contribute to thrombosis, this study may suggest that environmental factors, such as access to care and underuse, impact these factors to a greater extent than inherent biological differences between racial groups. See Table II for the rates and odds ratios of VTE for various races reported in the studies. At this time, evidence is insufficient to suggest that VTE prophylaxis should be altered based on race/ethnicity.

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5 - Is there a definite association between BMI and VTE?

Response/Recommendation: Extensive evidence confirms a definite association between unprovoked venous thromboembolism (VTE) and increasing body mass index (BMI). However, the evidence linking BMI to postoperative VTE is more equivocal.

Strength of Recommendation: Moderate.

Delegates vote: Agree 95.15% Disagree 3.88% Abstain 0.97% (Strong Consensus).

Rationale: VTE is a multifactorial disease, resulting from the interaction of genetic and acquired risk factors. Multiple observational population based studies demonstrate that obesity, as assessed by increased BMI, is an independent risk factor for increased risk of VTE in the nonsurgical patient[139-142]. This association between BMI and VTE has been demonstrated to likely be causal in Mendelian randomization studies[143,144]. The World Health Organization (WHO) classifies BMI into underweight (BMI < 18.5 Kg/m^2), normal weight (BMI between 18.5 - 24.9 Kg/m^2), overweight (BMI between 25 - 29.9 Kg/m^2), Class 1 obese (BMI between 30 - 34.9 Kg/m^2), Class 2 obese (BMI between 35 - 39.9 Kg/m^2), and Class 3 obese (BMI ≥ 40 Kg/m^2)[145]. In clinical practice obesity is typically defined as BMI > 30 Kg/m^2[146]. With regards to orthopaedic surgery, conflicting evidence has been reported. The majority of studies have found that BMI > 30 Kg/m^2 correlates to a greater risk of VTE in both total hip arthroplasty (THA) and total knee arthroplasty (TKA)[147-161]. However, other studies have refuted these findings and have not detected and a correlation between high BMI and postoperative VTE[162-167]. In a systematic review and metanalysis, Zhang et al., found BMI > 30 Kg/m^2 to increase the risk of VTE in patients undergoing primary TKA and THA[157]. A larger metanalysis of 89 studies including 14'763,963 joint replacements found an increasing risk of VTE with increasing BMI, relative risks > 25 Kg/m^2 vs. < 25 Kg/m^2 1.40 (1.24 - 1.57), > 30 Kg/m^2 vs. < 30 Kg/m^2 1.65 (1.23 - 2.22), and > 50 Kg/m^2 vs. < 50 Kg/m^2 1.72 (1.10 - 2.67)[153]. In analysis of the American College of Surgeons - National Surgical Quality Improvement Program (ACS-NSQIP) database, Sloan et al., found elevated BMI did not increase the risk of deep venous thrombosis (DVT) in revision TKA or THA, however in patients undergoing primary THA and TKA elevated BMI was associated with elevated risk of pulmonary embolism (PE)[147]. In a single institution study of 26,391 primary and revision TJA Parvizi et al., found that elevated BMI ($p < 0.035$) was an independent risk factor for symptomatic PE[150].

Obesity, as reflected in increased BMI, has not only been proven as a risk factor for VTE in THA and TKA but also in patients undergoing several other areas of orthopaedic surgery. In total shoulder arthroplasty obesity has been found to be a risk factor for VTE[168,169]. Obesity is also an independent risk factor for increased incidence of VTE after hip arthroscopy[170,171], as well as shoulder and knee arthroscopy[172]. Obese patients have also found to be at an increased risk of VTE following foot and ankle surgery[173-175]. Although in patients with chronic Achilles tendon ruptures, elevated BMI trended towards association with VTE but did not reach statistical significance[176]. The literature in spine surgery generally continues to support BMI as a risk factor for VTE[177-182], although there is not a universal consensus[183,184]. In patients who underwent lumbar spine surgery the risk for DVT was higher in overweight patients and increased for subsequent obesity classes[177]. This is supported by metanalysis performed by Jiang et al., who noted odds ratio

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[OR] of 3.15 (95% confidence interval [CI] 1.92 - 5.17) for increased risk of VTE in obese patients, being defined as BMI > 30 Kg/m^2[178].

The exact etiology of a possible correlation between obesity and increased risk of VTE remains unknown. Obese patients may be at increased risk for VTE secondary to longer operative times, lower postoperative mobility, and ineffectiveness of mechanical prophylaxis[147]. Obesity has been associated with inflammatory states that may contribute to increased thrombus formation and subsequent embolization[141,185]. Furthermore obesity is associated with reduced fibrinolysis attributable to increased concentrations of type-1 plasminogen activator inhibitor (PAI-1), an inhibitor of endogenous fibrinolysis, shifting the balance between thrombosis and thrombolysis towards thrombosis[186].

The association between BMI and VTE remains unproven. Obese patients are also at higher risk of bleeding and wound related complications. Thus, the use of any thromboprophylaxis should be balanced against the increased risk for complications and bleeding in obese patients[147,187].

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6 - Does a history of prior VTE influence the rate of subsequent VTE in patients undergoing orthopaedic procedures?

Response/Recommendation: Patients with a previous history of venous thromboembolism (VTE), including both deep venous thrombosis (DVT) and pulmonary embolism (PE), are at a higher risk of developing VTE following orthopaedic procedures.

Strength of Recommendation: Strong.

Delegates vote: Agree 99.51% Disagree 0.00% Abstain 0.49% (Strong Consensus).

Rationale: Patients with a previous history of VTE, including both DVT and PE, present a challenge to orthopaedic surgeons when considering postoperative VTE prevention. The recent VTE prophylaxis guidelines presented by the American College of Chest Physicians (ACCP) as well as the American Academy of Orthopaedic Surgeons (AAOS) have identified patients with a previous history of VTE as high-risk for thromboembolism[188,189]. While questions concerning history of VTE are an important part of a patient's preoperative protocol when undergoing orthopaedic surgery, it is important to determine if a prior history of VTE, is a significant risk factor for VTE following orthopaedic surgery.

A substantial body of literature exists that reports an increased risk of VTE following surgery in patients with a prior history of a VTE event[190-192]. Nemeth et al., longitudinal follow-up cohort study determined that patients with a history of VTE who undergo surgery have a significantly higher risk of recurrent VTE compared to those with no history of VTE[190]. Major orthopaedic surgery was associated with one of the highest risks of recurrence. These findings corroborate with those presented by Bahl et al., which utilized data from the National Surgical Quality Improvement Program (NSQIP) to validate an external VTE risk calculator[191]. History of VTE was identified as a significant risk factor for developing VTE after general and major orthopaedic surgery.

The association between a previous history of VTE and an increased VTE risk has also been thoroughly studied in the orthopaedic surgery literature. Many of these studies focus on total joint arthroplasty (TJA)[193-196], spine surgery[194,197,198], and below the knee procedures[199], as they carry the highest risk of postoperative VTE[200]. Zhang et al., systematic review on VTE risk factors following TJA identified nine significant risk factors for VTE and found history of VTE to be the most significant[196]. Additionally, a VTE risk calculator developed by Parvizi et al., for patients undergoing TJA using National Inpatient Sample (NIS) data identified history of VTE to be a major risk factor[193]. Studies focusing on VTE in other orthopaedic specialties, such as spine and foot and ankle, have similarly found history of VTE to incur a greater postoperative VTE risk. The NSQIP data utilized in McLynn et al., study, looked into characterize risk factors for VTE after elective spine surgery[201]. Through the use of multivariate logistic regression analysis, the authors found a significant association between history of prior VTE with postoperative VTE. Similarly, in Heijboer et al., study on VTE following below the knee orthopaedic surgeries, they determined history of VTE to be a significant risk factor[199]. While the incidence is low, history of VTE has also been associated with an increased rate of VTE following both lower and upper limb arthroscopic procedures[202-204].

While it is widely accepted that a previous history of VTE is associated with a greater VTE risk, it is difficult to validate through a randomized controlled trial as patients with a history of VTE are generally excluded from these studies. However, the vast amount of retrospective data from both institutional and national patient databases demonstrates the important association between the two events. Additionally, as many externally validated risk stratification tools include history of VTE in their calculation, it is essential to consider history of VTE when deciding on postoperative VTE prevention in patients undergoing orthopaedic surgery[193,205].

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7 - Does the type (DVT vs. PE) or timing (remote vs. recent) of prior VTE influence the risk of subsequent VTE following orthopaedic procedures?

Response/Recommendation: While it seems a reasonable assumption that patients with a history of venous thromboembolism (VTE) are at higher risk of post-operative VTE, there is little high-quality literature available regarding the effect of type or timing of prior VTE on subsequent VTE risk.

Strength of Recommendation: Limited.

Delegates vote: Agree 93.60% Disagree 3.45% Abstain 2.96% (Strong Consensus).

Rationale: It is well understood that surgical patients are at increased risk of VTE[206-215]. A collection of systematic reviews, consensus opinions, meta-analysis, and personal opinion statements all suggest that patients with a history of VTE are at a higher risk of subsequent VTE after orthopaedic procedures[206-210,213,216]. Based on one systematic review, these patients are up to 6 times more likely to develop symptomatic VTE after total joint arthroplasty (TJA) and have higher rehospitalization rates than average[217]. Unfortunately, little high-quality data is available specifically addressing patients with a history of VTE as most prospective trials evaluating VTE prophylaxis exclude patients with a history of VTE[218,219].

As such, there is no concrete evidence to suggest whether the time interval or type of VTE affects the risk of subsequent VTE following orthopaedic surgical procedures. One of the largest studies of orthopaedic patients with a history of VTE found multimodal thromboprophylaxis to be effective in this population but they did not analyze the relative risk of subsequent VTE conferred by remote vs recent clot or deep venous thrombosis (DVT) vs. pulmonary embolism (PE)[220]. A large retrospective study by Ahmed et al., demonstrated that personal history of VTE was significantly associated with postoperative VTE but did not report the type or timing of prior VTE[214]. One study on non-surgical patients with prior VTE, demonstrated an increased risk of recurrent VTE as time passed. In this study, the risk of recurrent VTE was 17.5% after 2 years, 24.6% after 5 years, and 30.3% after 8 years[221]. Finally, a recent study evaluating risk stratified VTE prophylaxis included patients with history of VTE in their high-risk cohort but did not report whether patients had history of DVT or PE[222].

Given the lack of data on the subject, it is not possible to answer the question as to whether prior history of DVT and/or PE and the timing of these VTE events (remote vs. recent) definitely influence the risk of subsequent VTE following orthopaedic procedures. Studies directly addressing the question of how the type and timing of prior VTE affects the risk of subsequent VTE after orthopaedic surgery are recommended.

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8 - Do patients with an underlying diagnosis of infection (local or systemic) undergoing orthopaedic procedures have an elevated risk for subsequent VTE?

Response/Recommendation: Patients with a systemic infection undergoing orthopaedic procedures have a higher risk of postoperative venous thromboembolism (VTE). This relationship for local infection is not proven.

Strength of Recommendation: Moderate.

Delegates vote: Agree 95.07% Disagree 2.46% Abstain 2.46% (Strong Consensus).

Rationale: The incidence of the VTE after musculoskeletal procedures on patients with the diagnosis of infection has not been well studied in the literature[223]. Grimnes et al., found that hospitalization with acute infection was a strong VTE trigger with a 20-fold higher risk[224]. Other studies also supported this finding, showing that hospitalization with infection cases were an independent risk factor for VTE[225-228].

Amaro et al.[228], in a study on the relationship between C-reactive protein (CRP) and VTE prevalence in pediatric population with musculoskeletal infection (MSKI), demonstrated that the rate of VTE in children with MSKI was markedly elevated compared with hospitalized children in general. The results of their study showed that every 20 mg/L increase in peak CRP was associated with a 29% increased risk of thrombosis ($p < 0.001$). Peak and total CRP were strong predictors of thrombosis[228]. Baker et al., reported that surgery for infection was the procedure with the highest VTE rate (1.2%) in a cohort of 14,776 pediatric orthopaedic procedures[229]. Bokshan et al., in a study on risk factors for deep venous thrombosis (DVT) or pulmonary embolism (PE) following anterior cruciate ligament reconstruction reviewed 9,146 cases and found that presence of wound infection was associated with increased risk of developing VTE[230]. Parvizi et al., in a study on individualized risk model for VTE, utilized the National Inpatient Sample (NIS) data. They identified 1'721,806 patients undergoing total joint arthroplasty (TJA), among whom 15,775 (0.9%) developed VTE after index arthroplasty. They identified all independent predictors of VTE after TJA and determined the weight for each factor. Systemic sepsis was among the highest scores in predicting VTE after arthroplasty[231]. Accordingly, in a recent meta-analysis including 672,495 primary total shoulder and elbow replacements, Kunutsor et al., reported that there is evidence of statistically significant associations of VTE with urinary tract infection[232].

The pathogenesis of VTE in infection cases has been linked to neutrophil activation and release of neutrophil extracellular traps (NET) via a process called NETosis[233]. While effective for bacterial clearance, the innate immune response could also trigger vascular thrombosis[233]. The case of infection also has been found to contribute to the pathogenesis of VTE by accelerating the effects of immobilization[234]. Furthermore, the presence of bacteremia (either community-acquired or hospital-acquired) has been reported to be associated with a higher risk of VTE[235-237]. Kaplan et al., reported that the systemic inflammatory milieu in sepsis is believed to uniquely predispose patients to VTE[238]. A nationwide population-based cohort study in China reported that the risk of developing DVT was 2.49-fold in patients with chronic osteomyelitis compared with the comparative group after adjusting for age, sex, and comorbidities[239]. Perioperative infections were associated with a higher risk for VTE in patients who received total hip arthroplasty (THA) and total knee arthroplasty (TKA)[240,241].

A number of studies reported patients with an underlying diagnosis of infection undergoing orthopaedic procedures have a higher risk of VTE[223,242-244]. Boddapati et al., studied differences in 30-day outcomes including postoperative complications in revision TKA between revisions for infection and revisions for non-infection causes. They included and compared 162,981 primary TKA with 12,780 revision TKA, of which 2,196 were performed for periprosthetic joint infection (PJI). They found greater risk of short-term morbidity and mortality including higher rate of VTE in patients who underwent implant revision for infection. Incidence of VTE was 0.85% in non-infection revisions and 1.37% in revisions for infection[242]. Courtney et al., in a study on incidence of VTE in revision THA within 30 days from surgery, reviewed 74,405 patients including 7,566 revision cases. They found that, although revision THA alone was not an independent risk factor for DVT and PE when compared to primary THA, patients undergoing an arthroplasty procedure for infection, operating time > 3 hours, and age > 70 years were at higher risk for VTE[243].

Despite few publications in favors of relationship between infection and rate of VTE, there are some publications that do not draw the same conclusion. Boylan et al., in a study on comparing rate of VTE in revision and primary TKA compared 208,954 primaries and 16,630 revisions for the incidence of VTE in 30 and 90 postoperative days. They found the risk of VTE was lower for revision TKA compared with primary TKA[245]. They did not exclude revisions for infection cases. Georgopoulos et al., in another study on 143,808 admissions of children for elective surgery found that overall rate of VTE was 0.05%. They found that VTE happened more frequently in cases of increasing age, admission type, diagnosis of metabolic conditions, obesity, and/or syndromes, and complications of implanted devices and/or surgical procedures. They did not find infection as a factor for increasing incidence of VTE[246].

In the absence of concrete evidence, it is the opinion of this workgroup that patients with systemic sepsis undergoing orthopaedic procedures are at increased risk of VTE. The

relationship between local infections (such as urinary tract infection, PJI, etc.) and the risk for subsequent VTE remains unknown.

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9 - Does the presence of varicosities and/or superficial lower extremity thrombosis increase the risk of VTE in patients undergoing orthopaedic procedures?

Response/Recommendation: The presence of varicose veins increases the risk of postoperative venous thromboembolism (VTE) by approximately 3 times in patients undergoing major orthopaedic procedures (Strong). A history of superficial venous thrombosis (SVT) increases the risk of postoperative VTE by 5 - 10 times in patients undergoing lower limb orthopaedic surgery (Limited). Acute SVT further increases the risk of VTE, and elective orthopaedic procedures should be postponed for at least 3 months if possible (Limited).

Strength of Recommendation: Limited.

Delegates vote: Agree 95.10% Disagree 0.98% Abstain 3.92% (Strong Consensus).

Rationale: There is a strong association between varicose veins (VV) and VTE in the general population. VV are associated with an increased deep venous thrombosis (DVT) incidence by 5 - 7 times and pulmonary embolism (PE) incidence by 1.7 times[247,248]. VV are one of the most common risk factors for VTE in non-orthopaedic surgical and medical inpatients[249-254]. VV are included in the Caprini risk assessment model for postoperative VTE[255] as well as the VTEstimator[256].

The presence of VV can increase the risk of venous thromboembolism after major orthopaedic procedures by a varying extent of 1.5 - 15 times. Three large database studies included a risk assessment of VV, which were recorded in 0.2% - 0.3% of the cohort. This incidence is low compared to the population prevalence of 19%[257]. The study by Parvizi et al., that analyzed 1.7 million arthroplasty patients in the U.S. reported a VTE odds ratio [OR] of 1.53 for patients with VV, prompting the authors to include VV in their risk assessment tool[256]. Fuji et al., reported VTE risk factors in 37,000 Japanese patients undergoing lower extremity orthopaedic surgery; the presence of VV increased the risk of PE (OR 10.9, 95% confidence interval [CI] 2.5 - 47.5) and DVT (OR 3.3, 95% CI 0.8 - 13.3)[258]. The Scottish Arthroplasty Project included 109,223 patients and reported an increased risk of DVT after total hip arthroplasty (THA) in patients with untreated VV[259]. The DVT rate was 0.8% in patients who had previously undergone VV surgery and those with no previous VV diagnosis, compared to 3.1% with those with untreated VV. There was no significant difference in PE rates following THA and no difference in DVT or PE following total knee arthroplasty (TKA) in patients with VV, treated VV or no history of VV.

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Prospective observational studies reported increased VTE risk with VV, although most studies included relatively few patients with VV and obtained wide CI. Markovic-Denic L et al., studied 499 THA and TKA patients and found an increased VTE risk of VTE (OR 3.1, 95% CI 1.03 - 9.5) in patients with VV[260]. In Asian patients undergoing major orthopaedic surgery without thromboprophylaxis, VV were recorded in 4.3% of 2,420 patients, and this increased the risk of VTE by 3.6 times (95% CI, 1.2 - 1.06)[261]. A meta-analysis by Zhang et al., found that the presence of VV was associated with a 2.7 (95% CI, 1.1 - 7.1) fold increase of VTE after THA and TKA[262]. Another meta-analysis by Tan et al., reported a risk elevation of 3.1 times (95% CI, 1.1 - 8.5) following surgical treatment of fractures below the hip in the presence of VV[263]. For knee arthroscopy, the incidence of symptomatic postoperative VTE was low (0.1 - 0.25%), and no association with VV was found[264,265].

There is no consensus on the need for preliminary surgical treatment of varicose veins to reduce the risk of postoperative VTE. Limited evidence suggests that patients with treated VV may normalize their VTE risk after THA and TKA[259,266]. This risk may be mitigated by VTE prophylaxis, although current studies on VTE prophylaxis for orthopaedic procedures did not analyze the efficacy of preventive measures in this small subgroup of patients with VV and hence no conclusion can be drawn. The intervention for VV can increase VTE risk by itself[267], and the risk of symptomatic PE remains elevated for up to 18 weeks[268]. The minimal time interval between intervention for VV and orthopaedic surgery has not yet been determined; however, it seems prudent to defer elective surgery at least 3 months.

SVT is an inflammatory process that obstructs the superficial veins of the lower extremities. SVT can extend into the deep veins and lead to PE. Thrombosis of superficial veins provoked by chemical and mechanical injury of the vascular wall, such as surgical trauma, is usually benign and self-limited[269]. Conversely, spontaneous SVT is considered a benign self-limited disorder, but has been shown to be associated with the risk of concomitant DVT and PE in 18% and 7% of non-surgical patients, respectively[270]. Superficial thrombosis is most likely to affect patients with VV, accounting for up to 90% of all cases of SVT[271]. Thrombus usually propagates in the deep veins through saphenous vein junctions and/or perforating veins[272]. However, up to 42% of all patients have a DVT that is not contiguous with SVT, particularly on the contralateral limb in 17%, hence suggesting SVT may be an underlying indicator of thrombophilia[272,273].

VTE risk is greatest during the first 3 months following diagnosis, but remains significantly increased compared to controls even after 5 years[274]. Current evidence suggests an underlying thrombophilia that requires anticoagulation prior to elective surgery, although duration of treatment and period of increased VTE risk have not been established. In practice, it may be preferable to defer elective orthopaedic surgery by at least 3 months from the time of SVT diagnosis. The same recommendation was developed for interventions to remove VV after SVT[275]. In patients with VV and a history of SVT, removal of varicosities prior to orthopaedic surgery could be considered.

A past history of SVT is an independent risk factor for future DVT or PE[274]. Recurrent SVT is associated with a 2.3 - 2.5-fold increased risk of further VTE[276,277]. The risk of VTE recurrence is equivalent to that after proximal DVT[278], with an OR of 5.5 (95% CI, 4.8 – 6.4) compared to controls[279]. VTE risk increased to 9.3 times when combined with an additional mild thrombotic risk factor, 31.4 times when combined with a strong risk factor, and increased to 42.5 times (95% CI, 10 - 118) with surgery[279].

For lower limb orthopaedic surgery, the estimated increase in VTE risk is 5 - 10 times in patients with a history of spontaneous SVT[262,263]. A history of SVT was hence included in the Caprini risk assessment model version of 2010[280] and needs to be assessed in tandem with the presence of VV in order to calculate individual risk for postoperative VTE.

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10 - (A) Do oral contraceptive medications increase the risk of VTE? (B) If so, should they be stopped prior to orthopaedic procedures?

Response/Recommendation: The incidence of postoperative venous thromboembolism (VTE) is increased in women who use oral contraceptives pills (OCP), as compared to women who do not. Cessation in all users is not recommended. However, OCP use should be taken into account when assessing the patient's and the procedure's estimated risk and hence, form a basis for decisions on thromboprophylaxis.

Strength of Recommendation: (A) Strong; (B) Limited.

Delegates vote: Agree 94.66% Disagree 1.94% Abstain 3.40% (Strong Consensus).

Rationale: It is well established that women who use OCP have an increased risk of VTE as compared to women who do not. On the whole, their risk is about 3- to 4-fold increased but, considering that the absolute VTE risk in pre-menopausal women is low (~ 1 in 10,000 women per year), this does not lead to a substantially high-risk (~ 3 - 4 per 10,000 per year; 0.03 - 0.04% per year)[281,282].

It is also well known that the risk of VTE is increased after orthopaedic surgery, where the size of this risk, in addition to the presence or absence of patient-related risk factors, depends strongly on the duration of the procedure, the amount of tissue damage and the length of immobilization. Hence, overall, the VTE risk is lower, for example, after knee arthroscopy (~ 0.8% in the following 3 months) than after knee replacement (~ 1.5 - 2%)[283,284].

The question regarding whether the risk of VTE is additionally increased in women who undergo orthopaedic surgery and take OCP as compared to women who have the same surgery but do not use hormonal contraception, has been studied previously. Most of these studies confirm an increased risk for these women for all types of surgery. Maletis et al., performed a retrospective cohort study of elective arthroscopic knee procedures using the administrative database of a large health maintenance organization. On the basis of the international classification of diseases version 9 - clinical modification (ICD – 9) - (CM) procedure codes, 20,770 patients undergoing knee procedures were identified. The incidence of VTE in female patients was found to be higher if they had been prescribed OCP at 0.63% compared with 0.30% in female patients with no such prescription[285]. In another large, routinely collected dataset, of almost 65,000 female patients between the ages of 16- and 40-years undergoing knee arthroscopy or anterior cruciate ligament (ACL) reconstruction, Traven et al., found that patients taking OCP had a 2-fold increased risk of a VTE compared with non-users, where the procedural subgroup (ACL reconstruction or simple knee arthroscopy), did not make a strong difference in risk[286]. Van Adrichem et al., found in a large case-control study in 4,000 VTE cases and 6,000 control subjects, out of whom 127 had undergone knee arthroscopy, that after this procedure the risk in women using OCP was 13 times higher than in women not using this treatment[287].

In patients undergoing foot and ankle surgery, a similar picture emerges. Richey et al., performed a retrospective

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observational cohort study of 22,486 adults in whom an overall incidence of VTE was found to be 0.9%. In a nested case-control study within this population, they identified.

Four risk factors for an increased VTE risk, of which use of hormone therapy or OCP was associated with an 8.9-fold increased risk[288]. For arthroscopic shoulder surgery, however, Stone et al., evaluating 924 female patients found no significant difference in the incidence of VTE in patients taking vs. not taking OCP (2 [0.22%] vs. 150 [0.57%], respectively; p = 0.2). Still, the risk was more than doubled, and the fact that the relation was not significant is likely to have been due to the low number of cases (insufficient power)[289]. The same holds true for hip arthroscopy. Khazi et al., identified 9,477 patients who underwent hip arthroscopy from an administrative claims database in whom the 90-day incidence was 1.14%. Multivariable analysis identified several risk factors for VTE in these patients, but OCP use was not one of them, which was again most likely due to low numbers[290].

A following question that results from this conclusion is how to reduce VTE risk in women taking OCP who need to undergo elective orthopaedic surgery. An obvious solution would be to advise them to stop taking this treatment for a couple of weeks or months, until the VTE risk due to the procedure has passed. However, let's consider the numbers: if we take the risks as described by Maletis et al., as a basis (i.e., 0.63% with and 0.30% without OCP)[285], we would have to let 303 (100/[0.63 - 0.30]) women stop taking the OCP to prevent one VTE (number needed to treat). Furthermore, should this for some reason fail, the consequences of an unplanned pregnancy are enormous. In a useful study to quantify the size of this problem, Dale et al., studied 78 healthy women in whom OCP were stopped prior to elective orthopaedic surgery. Five pregnancies in 73 women in whom complete outcome data were available were reported, giving a pregnancy rate of 6.8%[291]. If we apply this rate to the calculation above, about 21 pregnancies would occur (6.8% of 303 women) in an attempt to prevent one VTE. Even if the pregnancy rate could be reduced, this does not seem a viable option.

An alternative approach would be to quantify an individual's VTE risk based on the risk associated with the procedure and other surgical risk factors, in combination with the presence or absence of patient-related risk factors, of which OCP would be one. Several studies have shown that the risk increases with the total number of risk factors present (such as higher age, higher body mass index (BMI), family history, presence of other comorbidities, etc.)[292,293]. A recent prediction score that was developed to estimate an individual's risk after knee arthroscopy, the Leiden-thrombosis risk prediction for patients after knee arthroscopy (L-TRiP[ascopy]) score showed good performance, which also persisted after external validation[294]. Targeted thromboprophylaxis based on a patient's risk estimate would then be the next step but this option needs further study.

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11 - Do oral hormonal therapy, used for cancer management, increase the risk of post-operative VTE in patients undergoing orthopaedic procedures? If so, should they be stopped prior to surgery?

Response/Recommendation: Hormonal therapy used in cancer management, like tamoxifen, increases the risk of venous thromboembolism (VTE) in patients undergoing orthopaedic procedures. We suggest they should be suspended at least 7 days before surgery, a degree of individualization of approach is needed based on risk factors and clinical settling (type of cancer, etc.).

Strength of Recommendation: Weak.

Delegates vote: Agree 92.08% Disagree 2.97% Abstain 4.95% (Strong Consensus).

Rationale: Cancer patients have a hypercoagulable state due to the presence of all components of Virchow's triad. There is evidence of platelet activation along with elevated levels of inflammatory cytokines (vascular endothelial growth factor,

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tissue factor), tumor mass effect compressing adjacent veins and damage to the endothelium[295].

The rate of VTE in orthopaedic oncology patients has been reported to be between 1% and 28%[295].

Following orthopaedic lower limb surgery, pulmonary embolisms (PE) are less likely to occur in association with a deep venous thrombosis (DVT) when patients receive prophylaxis with an anticoagulant agent (8% vs. 42%)[295].

Hormonal therapies are a mainstay of treatment for prostate and breast cancers. Androgen deprivation therapies, which include gonadotropin-release hormone agonists, oral antiandrogens, and estrogens, have also been reported to increase the risk of VTE[296].

In the case of androgenic hormones such as testosterone and methyltestosterone (used for the treatment of hypogonadism in men and advanced breast cancer in women), and oxymetholone (used for the treatment of cancer-associated anemia), the literature has not demonstrated an association between perioperative VTE events and androgenic hormone use[297].

The use of selective estrogen receptor modulators (SERM), such as tamoxifen, is a known risk factor for VTE, namely DVT and PE[298]. Indeed, tamoxifen is a risk factor for VTE and the estimates of the risk ratio for VTE, ranging from 1.3 - 7.0[296].

Nevertheless, there is a paucity of information in the literature about the management of tamoxifen in this population, with merely a suggestion that tamoxifen should be stopped as the risk of developing VTE during the perioperative period[298].

A consensus of the Mayo clinic indicates that we should continue SERM before and on the day of surgery if taken for breast cancer prevention or treatment but consider potential for increased wound complication and VTE risk if continued. If SERM are taken for other indications and additional patient or surgery specific risk factors for VTE are present, we should stop SERM at least 7 days before surgery[297]. Thus, a degree of individualization of approach is needed.

It is imperative to balance between the continuous cytostatic effect, by continuing tamoxifen; against the reduction of VTE risk, by stopping tamoxifen for a finite period perioperatively. The half-life elimination of tamoxifen is between 5 and 7 days[298].

The National Institute for Health and Care Excellence (NICE) guidelines stipulate that tamoxifen may need to be stopped for up to 6 weeks prior to elective surgery, without further details on risk stratification nor specification of the duration of stopping tamoxifen[298].

Salvador Oscar Rivero Boschert, José J. Aguilar Ramírez, Gregory Y.H. Lip

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12 - Are patients, who traveled on airplanes or had long car rides prior to surgery, at an increased risk of VTE? If so, what is the optimal interval between travel and surgery?

Response/Recommendation: It is well established that travel on airplanes, especially 'long-haul flights', is a major risk factor for development of venous thromboembolism (VTE). Individuals with preexisting risk factors for VTE appear to be at greatest risk. There is a paucity of literature examining the influence of long-distance travel prior to surgery on the risk of postoperative VTE. Similarly, while it is commonly accepted that airplane travel in the acute postoperative period should be avoided due to an increased risk of VTE, there is limited evidence supporting this notion. Lastly, due to limited literature on the optimal strategy for VTE risk mitigation in patients who engage in long-distance travel either pre- or post-operatively, the choice of prophylactic agent should be individualized, taking into account the relative risks and benefits of different pharmacological and non-pharmacological options for each patient.

Strength of Recommendation: Limited.

Delegates vote: Agree 96.10% Disagree 1.46% Abstain 2.44% (Strong Consensus).

Rationale: Although air travel and orthopaedic surgery, especially joint replacement surgery, are both well documented risk factors for the development of VTE, neither the American Academy of Orthopaedic Surgeons (AAOS), nor the American College of Chest Physicians (ACCP) have published guidelines regarding the safety of flying in the early postoperative period. The Center for Disease Control and Prevention (CDC) noted that there are "combined effects observed between these established risk factors and different forms of travel", but also do not provide an evidence-based justification of this recommendation, largely due to the dearth of literature on this subject[299].

Air travel and risk of venous thromboembolism (VTE): A large body of literature on the topic of air travel as a risk factor for VTE currently exists, dating back to the early 1950's when VTE was first termed "economy class syndrome" by John Homans[300,301]. One meta-analysis found that air travel was associated with a nearly 3-fold increased risk of VTE, with a dose-response relationship of 18% higher risk for each 2-hour increase in travel duration[302]. Another meta-analysis of 14 studies involving over 4,000 episodes of deep venous thrombosis (DVT) demonstrated a relative risk of 2.8 (95% confidence interval [CI] 2.2 - 3.7) for long duration flights[303]. A study in the New England Journal of Medicine corroborated this finding, noting that a greater distance traveled was a significant risk factor for pulmonary embolism (PE), with an

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incidence of 4.8 cases/million for those traveling more than 10,000 km compared to 1.5 cases/million for those traveling greater than 5,000 km, and 0.01 cases/million for those traveling less than 5,000 km[304]. In a case control study on the topic of long-haul flights (> 8 hours), the relative risk of VTE was found to be 2.8 (95% CI 1.46 - 5.49) for travelers, although the authors noted that all flight-associated thromboses occurred exclusively in passengers with at least one established risk factor for venous thrombosis[305]. In one of the largest population-based case-control studies the Multiple Environmental and Genetic Assessment (MEGA) study, the authors found that traveling increased risk of VTE 2-fold (odds ratio [OR] 2.1, 95% CI 1.5 - 3.0), and the risk of flying was similar to the risk of traveling by car, bus or train. There was also an additive risk for those with predisposing factors for VTE, as it was found that travel led to an even higher risk of VTE in individuals with Factor V Leiden (OR 8.1, 95% CI 2.7 - 24.7), those with a body mass index (BMI) of > 30Kg/m^2 (OR 9.9, 95% CI 3.6 - 27.6) and those who were taking oral contraceptive pills (OCP) (OR > 20)[306]. It was also shown that the risk of developing VTE increased by almost 20 times among passengers who had recently undergone surgery when compared to passengers who had not (OR 19.8)[303]. The extent of additional risk contributed by these different risk factors, however, was not clear.

Cooper et al., performed a retrospective cohort study of 1,465 consecutive total joint arthroplasty (TJA) patients, which comprised 220 patients (15%) who took a flight home at a mean of 2.9 days after surgery (range, 1 - 10 days) and a control group of 1,245 patients (85%) who did not. The authors found no difference in the rate of DVT, PE, or VTE between the groups, with the caveat that all patients received appropriate risk stratified VTE prophylaxis after surgery[299]. Another retrospective review examined 608 patients who had extended travel for an average of 1,377 miles and 6.5 days after total hip arthroplasty (THA) and received appropriate DVT prophylaxis. There were no deaths or symptomatic PE in the study, and only 5 (0.82%) symptomatic DVT and 9 (1.5%) bleeding complications occurred[307].

Timing: Regarding the timing of diagnosis of VTE in relation to travel, the abovementioned MEGA study found that of the 233 events that occurred within 8 weeks of travel, 29% were diagnosed in the first week, after which the incidence gradually decreased[306]. This pattern was also described in a separate study from Australia, thus supporting a causal relation[308]. Two additional studies found that the majority of VTE occurred within the first 2 weeks after landing, with a mean interval of 4 days, although the risk was present for up to 8 weeks[303,309,310]. In the single paper that examined the impact of preoperative travel on the risk of VTE in patients who were scheduled to receive a TJA, Citak et al., compared 155 patients (87 THA, 68 total knee arthroplasties [TKA]) to 187 patients (92 THA, 95 TKA) without bus, air, or car travel for longer than 30 minutes. The study found that patients with preoperative air travel were not at higher risk of VTE compared to patients without preoperative air travel who underwent TKA (hazard ratio [HR] = 0.95; 95% CI = 0.14 - 6.52)[311].

Prophylaxis: The ninth edition of the ACCP guidelines from 2012 suggested the following preventive measures for patients deemed to be at risk of VTE on long-haul flights: walking, calf muscle exercises, and aisle seating (evidence level 2C)[312] cited in[313]. A recent Cochrane review of 11 randomized studies with a total of 2,906 patients (1,273 high-risk patients) on flights lasting more than 5 hours concluded that there was high-quality evidence demonstrating a reduction in the incidence of asymptomatic DVT, and moderate-quality evidence demonstrating a reduction in superficial venous thrombosis following the use of graduated elastic compression stockings[314]. Furthermore, the ACCP guidelines suggested that passengers on long-haul flights who are at risk of VTE should wear below the knee compression stockings providing 15 - 30 mmHg of pressure at the ankle during the flight (evidence level 2C).

No consensus has been reached in regards to pharmacologic prophylaxis, and this should be prescribed on a case-by-case basis. Antiplatelets did not prove to be an effective prophylactic agent for primary or secondary long-haul flight-related VTE[309,315], cited in[313,316]; cited in[317]. While the LONFIT-3 study suggested that the risk of VTE could be eliminated by taking low-molecular-weight heparin (LMWH), there is still a lack of evidence supporting its widespread use in this situation[315,318], cited in[313]. Direct-oral anticoagulants (DOAC) have theoretical benefits given their short half-lives, rapid onset of action and oral administration. In a retrospective review of over 600 patients flying an average of 6.5 days after THA, who were prescribed anticoagulants such as enoxaparin, dalteparin, fondaparinux or warfarin, no deaths or symptomatic PE were reported, and only 5 (0.82%) symptomatic DVT and 9 (1.5%) bleeding complications occurred[307].

Conclusion: Extended travel, whether by air, car, or train, has been associated with a higher risk of VTE in the general population because of the limited movement in a seated position, which may lead to positional lower extremity venous stasis. This risk is further exacerbated in comorbid conditions such as obesity and Factor V Leiden deficiency. Long-haul travel beyond 6 - 8 hours is associated with a dose-response increase in the rate of VTE because of a prolonged reduction in venous outflow. Similarly, joint replacement surgery is associated with an elevated risk of VTE in the postoperative period. Notwithstanding, there is no conclusive evidence to suggest that these independent risks are additive when the two exposures temporally related (i.e., extended travel before or after lower extremity arthroplasty surgery). Studies have suggested that a greater protection against VTE is afforded with the use of more potent anticoagulants in favor of antiplatelet agents when long-haul travel occurs within 6 weeks after surgery. The overall recommendation is therefore to individualize the VTE prophylaxis strategy in patients who choose to undergo extended travel in the perioperative period, and surgeons should consider the use of oral anticoagulants in patients who carry additional thrombotic risk factors.

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13 - Do all orthopaedic procedures have the same risk profile for DVT?

Response/Recommendation: Orthopaedic procedures carry variable risk profiles for deep venous thrombosis (DVT). They have been classically stratified according to the incidence of venous thromboembolism (VTE) events, with total hip arthroplasty (THA) and total knee arthroplasty (TKA) being the highest risk alongside with hip fracture fixation.

Strength of Recommendation: Limited.

Delegates vote: Agree 98.52% Disagree 0.49% Abstain 0.99% (Strong Consensus).

Rationale: Orthopaedic procedures do not have all the same profile risk for DVT. Risk for DVT arises from patient-related factors, the nature of the injury, the extent of the orthopaedic intervention or the resulting immobility. The complex interaction of these risk factors has been termed thrombotic potential[319].

Procedure-related factors such as surgery time-length, type of anesthesia, extent of tissue injury or trauma, site of surgery, and surgical technique[320], are variables that may determine the variance in the prevalence of DVT from different surgical procedures. General anesthesia, for example, could favor an over-physiological muscle relaxation that produces a slower blood flow resulting in endothelial hypoxia, leukocyte adhesion, and the accumulation of activated coagulation factors[321].

Traditionally, overall surgical procedures have been categorized as low-, intermediate-, high-, and very high-risk according to the incidence of symptomatic VTE[322-324]. The incidence of DVT after an orthopaedic procedure depends on the detection method used to assess the presence of thrombi. Although there is controversy about the relevance of asymptomatic DVT, it has been associated with recurrent VTE and post-thrombotic syndrome[325].

THA and TKA, open reduction and internal fixation of hip fractures, and surgery due to major trauma are among the orthopaedic procedures with the highest DVT risk. With contemporary surgical protocols the prevalence of VTE after THA has been reported to be up to 22%, using venography as a diagnostic method, even with the use of pharmacological prophylaxis[326]. THA has shown asymptomatic DVT events in 33% of patients, either with pharmacological, mechanical prophylaxis or both[325].

For non-major orthopaedic surgery in the lower limb, included achilles tendon repair, surgery involving the tibial plateau or femoral diaphysis, tibial or ankle fractures or tibial osteotomy, arthrodesis of the knee, ankle, or hindfoot, among others, symptomatic DVT rates have resulted in 0,66% with the use enoxaparin or rivaroxaban[327].Acetabular or pelvic reconstruction in a major trauma has an overall symptomatic DVT rate of 4% using low-molecular-weight heparin (LMWH)[328].

For the upper extremity, data suggests that the greatest risk for DVT relates to personal or family history of thromboembolic events, active malignancy, prothrombotic disorders and the presence of a central venous catheter[329], instead of a patient undergoing a surgical procedure[330].

Interestingly, certain surgeries are performed on patients with a demographic profile that adds risks factors for VTE unrelated to the procedure, but indirectly carries non-modifiable elements that magnifies the procedure's risk. An example of this is the TKA, a procedure commonly performed on patients with advanced age, obesity, certain degree of post-operative immobilization, and the indication of general anesthesia. Injury site influences the DVT risk for lower limb fractures, even before the added risk of fracture fixation[331]. Around the knee, around the hip, femoral shaft, tibiofibular, and ankle fractures have a DVT prevalence of 8.67%, 6.32%, 5.7%, 2.09%, and 1.97%, respectively[331].

Recent studies have shown a decrease in symptomatic rates of VTE events as well as overall rates of surgical complications in the last decades[332,333]. This may be attributed to a combination of improvements in surgical techniques and

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perioperative care, including unicompartmental surgery, shorter operative procedure times, greater use of regional anesthesia, more effective analgesia, faster postoperative mobilization, increased use of day-case procedures, shorter duration of hospitalization, and more consistent use and/or longer duration of prophylaxis[334].

The challenge of the quantification of the risk for DVT due to each intervention as an independent risk factor remains unresolved. A substitute for this void, is the integral assessment of the thrombotic potential, an explicit declaration of adherence to a formal DVT prevention guideline aligned with the institutional value proposition, and a detailed informed consent[335].

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14 - Does the duration of surgery influence the incidence of postoperative VTE?

Response/Recommendation: Surgical duration is directly associated with an increased risk of venous thrombosis (VTE). When intraoperative complications or surgical complexity affect the length of surgery, VTE risk should be reevaluated.

Strength of Recommendation: Moderate.

Delegates vote: Agree 98.07% Disagree 0.48% Abstain 1.45% (Strong Consensus).

Rationale: Understanding of the relationship between VTE risk and surgical duration is important for surgical planning and management. Risk stratification could help refine chemoprophylaxis strategies for surgeons, perioperative care physicians and anesthesiologists, and better inform patients of the potential hazards associated with prolonged surgery.

Multiple studies in general[336-338], plastic[339,340], vascular[341], gynecological[342], and neurosurgical[343] literature have found an increased risk of VTE with longer operative time. This association has been shown even in patients undergoing outpatient procedures[344]. In the context of orthopaedic surgery, conflicting evidence has been reported. While the majority of studies have identified increased operative time as a risk factor for VTE[345-352], some studies did not[353-358]. It is also possible that this risk may not apply to all orthopaedic procedures[359,360]. In a systematic review of Level-I and Level-II studies, Zhang et al., concluded that surgery time > 2 hours increased the risk of VTE[349]. A separate systematic review of randomized control trials also found that the incidence of deep venous thrombosis (DVT) in patients undergoing elective total knee arthroplasty (TKA) declined with the average duration of surgery (124.3 minutes in 1996 - 97.3 minutes in 2003)[361]. Using routine venography to assess for DVT on the third to ninth postoperative day, Zhang et al., found that 173 of 963 patients with a venography confirmed DVT had a greater operative duration compared to those who did not[348]. This association has also been reported in the Asian population[350,362]. Won et al., found that the relative risk was 1.6 times higher in the group with ≥ 105-minute surgery time compared to those with < 105-minute surgery time[361]. Using a national database in Japan, Nagase et al., found that patients who underwent a longer period of anesthesia (≥ 180 minutes) had more than twice the risk (odds ration [OR] 2.13) of postoperative pulmonary embolism (PE) compared to patients with a shorter period of anesthesia (< 180 minutes)[363]. Consistent with these findings, Jaffar et al., analyzed institutional data of 4,075 postmenopausal women undergoing primary major joint replacement and found that a threshold of 3.5 hours (210 minutes) increased the odds of VTE substantially (OR 3.83)[352]. This relationship was shown after controlling for multiple confounders and persisted even when patients with distal DVT were excluded.

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In spite of the abundant literature on the topic, few studies were sufficiently powered or utilized multi-institutional data. To overcome these shortcomings, Kim et al., performed a comprehensive analysis across surgical specialties and institutions using a generalizable database[364]. Using the National Surgical Quality Improvement Program (NSQIP) database from 2005 - 2011, the authors studied 1'432,855 patients who underwent surgery under general anesthesia across 9 surgical disciplines, performing the analysis at the specialty and procedural level while adjusting for differing surgical and patient complexity. Compared with a procedure of average duration, patients who underwent the longest procedures experienced a 1.27-fold increase in the odds of developing a VTE, whereas the shortest procedures demonstrated an OR of 0.86. Importantly, the incidence of VTE increased with increasing quintiles of surgical duration in all 9 surgical specialties in the subgroup analyses.

Despite the broad consensus on the association between VTE risk and operative time, an exact cutoff time that significantly increased the risk of this complication could not be identified. While some studies examined a threshold of 120 minutes or more[344,362], different cutoffs such as 80 mins[346], 105 mins[351], 180 mins[363], and even up to 3.5 hours[352] have been identified. Due to the heterogeneity in procedure type, anesthesia techniques, follow-up duration, and method for calculating operative time, a precise cutoff would be extremely difficult to ascertain.

The explanation for the relationship between surgical duration and VTE risk is likely multifactorial. In accordance with the pathophysiologic basis of VTE (also known as "Virchow's triad"[365(p198)]), immobility resulting from long surgical procedures can result in blood stasis, hypercoagulability and endothelial damage caused by vessel wall distension[352,366-369], thus increasing the risk of VTE development. Venous stasis and ischemia can promote DVT formation via the upregulation of P-selectin and local prothrombotic microparticles[369,370]. The hypercoagulable state as well as the inflammation and endothelial damage that occurs during surgery can similarly initiate the clotting cascade and increase the risk of thrombus formation.

With such a large volume of surgeries performed annually, the adjusted risk difference of - 0.12% - 0.23% as suggested by Kim et al., could translate into a substantial burden of VTE attributable to surgical duration[364]. Consequently, the relationship between operative time and the incidence of VTE should be strongly considered in the postoperative assessment of VTE risk. Widely used risk stratification tools such as the Rogers score do not take surgical duration into account[371], whereas the Caprini score distinguishes only between operations shorter or longer than 45 minutes for the sake of defining "major surgery"[372]. In view of these limitations, future development of risk assessment scoring systems should also factor in the length of surgery to guide prophylactic measures. Overall, a greater understanding of the relationship between VTE and surgical duration will help direct surgical planning, target chemoprophylaxis strategies, and better inform patients and clinicians when deciding to proceed with combined or longer operations.

Emanuele Chisari, Graham S. Goh, Javad Parvizi

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15 - Does the volume of intraoperative blood loss influence the incidence of post-operative VTE in patients undergoing orthopaedic procedures?

Response/Recommendation: There is no concrete data related to this issue. However, because of a potential association between allogeneic blood transfusion and postoperative venous thromboembolism (VTE), we recommend that strategies be in place to reduce intraoperative blood loss and the possible need for allogeneic blood transfusion.

Strength of Recommendation: Limited.

Delegates vote: Agree 97.56% Disagree 0.49% Abstain 1.95% (Strong Consensus).

Rationale: Despite contemporary advancements in blood conservation strategies, patients undergoing major orthopaedic surgery may experience significant intraoperative blood loss necessitating perioperative blood transfusions[373-377]. Notably, transfusion rates among modern cohorts undergoing complex total joint arthroplasty (TJA), spine surgery, or revision procedures may reach up to 20%[378-385]. Despite ongoing efforts to limit perioperative blood loss, it remains unclear whether the incidence of postoperative VTE is influenced by the volume of intraoperative blood loss or by the receipt of blood transfusion in the perioperative period.

While Goel et al., recently analyzed the National Surgical Quality Improvement Program (NSQIP) database and reported a significantly higher risk of VTE among orthopaedic surgery patients receiving perioperative blood transfuions[382], analyses on separate cohorts undergoing specific surgical procedures including TJA[386-395], spine surgery[396-409], pediatric trauma surgery[410], and surgery for lower extremity and pelvic fractures[411-416] have demonstrated inconsistent results.

There is some evidence from retrospective studies of patients undergoing TJA that a higher volume of blood loss and transfusion requirements may be associated with a higher incidence of VTE[387,391,393,394]. Notably, in their analysis of 1'721,806 TJA patients, Parvizi et al., identified transfusion as an independent risk factor for postoperative VTE[391]. However, these findings remain mixed in orthopaedic literature[386,388-390,392], with other studies failing to identify an association after controlling for various patient and surgical factors, such as VTE prophylaxis[390] and postoperative hemoglobin levels[386].

Two meta-analyses[399,400] evaluating the relationship between blood loss and postoperative VTE in spine surgery have presented contradictory findings. While Xin et al., identified blood loss to be associated with VTE risk among patients undergoing spine surgery, the majority of included studies primarily conducted univariate analyses without adjusting for confounding factors[400]. Additionally, while Zhang et al., did not identify a relationship between intraoperative blood loss and VTE incidence, their pooled analysis did identify transfusion as a risk factor for VTE[399]. Similar to studies evaluating TJA, literature evaluating patients undergoing spine surgery have demonstrated inconsistent results when assessing both blood loss[396-398,401-403] and transfusion[396,401,402,409,417,418].

However, there is some evidence to suggest that the region of the spine being operated on may affect these relationships, with the majority of lumbar spine studies demonstrating a higher risk of VTE among transfused patients[396,409,417,418]. Although, Aoude et al., did not find an association between transfusion and VTE incidence among thoracic spinal fusion patients, perioperative blood transfusion was associated with a significantly higher risk of pulmonary embolism (PE) and overall VTE in their lumbar fusion cohort[418].

Analyses evaluating the impact of perioperative blood loss and transfusion on VTE risk in patients with lower extremity and pelvic fractures have also demonstrated varying results. While patients suffering from postoperative VTE have been reported to have comparably higher blood loss[412-414], it is unclear whether this independently affects the postoperative risk of VTE[413,414]. Additionally, there is mixed data regarding the relationship between perioperative blood transfusion and deep

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venous thrombosis (DVT)[411,412,415,416]. However, it is important to note that other studies utilizing multivariate analyses among patients without malignancy have demonstrated a higher risk of DVT among patients receiving transfusions[411,412].

The inconsistencies demonstrated across included studies may be due to methodological limitations of the respective studies exploring this topic. Of note, a large proportion of studies failed to control for patient- and procedure-related VTE risk factors as well as variations in implemented VTE prophylaxis protocols. Similarly, variability in the use of tranexamic acid[419-421] or tourniquets[422] in certain procedures, as well as the accuracy of estimated blood loss[423,424] may contribute to these inconsistent results. Furthermore, although blood transfusion represents a surrogate measure of perioperative blood loss, there is some evidence that red blood cell transfusion itself may induce a hypercoagulable state[425-428].

Based on the available literature, there is insufficient evidence to definitively conclude that the incidence of VTE is associated with the volume of intraoperative blood loss or the receipt of perioperative blood transfusions. However, the implementation of perioperative strategies to reduce blood loss and transfusion rates remain essential given their historic relationship with other perioperative complications[375,377].

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16 - Does administration of allogeneic blood transfusion influence the incidence of post-operative VTE in patients undergoing orthopaedic procedures?

Response/Recommendation: The majority of the clinical studies, largely from total joint arthroplasty (TJA) literature, cite an association between allogeneic blood transfusions and venous thromboembolism (VTE) following orthopaedic surgery. Along with the scientific rationale, these associations are sufficient to urge surgeons to minimize the use of allogeneic blood transfusions in the peri-operative period.

Strength of Recommendation: Limited.

Delegates vote: Agree 95.10% Disagree 1.47% Abstain 3.43% (Strong Consensus).

Rationale: While several risk factors for the development of VTE have been established[429,430], others are still widely debated[430,431]. One potentially modifiable risk factor that has gained attention due to its common and unrestricted use is allogeneic blood transfusion[432-434]. Physicians and orthopaedic surgeons in particular tend to overprescribe blood transfusions[435-438]. In fact, orthopaedic surgery represents the most common reason for allogeneic blood transfusion in patients undergoing elective procedures, accounting for nearly 10% of all hospital transfused red blood cell units[436,437].

The biological mechanisms substantiating the increased thrombotic risk following blood transfusion have been well described[439,440]. Several attempts were made to assess this relationship in clinical studies. Registry data has consistently demonstrated an association between blood transfusions and VTE, although all published studies to date have utilized the same National Surgical Quality Improvement Program (NSQIP) database[432,433], rendering them susceptible to inherent limitations[441,442]. Goel et al., analyzed 750,937 patients from this database, of which 153,320 underwent orthopaedic surgery. The results of their subgroup analysis showed an adjusted odds ratio (OR) of 1.7 (95% confidence interval [CI] 1.5 - 2.0) for developing VTE following blood transfusion[432]. Acuña et al., utilized the same database and timeframe to examine the association in 333,463 patients undergoing TKA[433]. While they found an initial association between perioperative blood transfusions and deep vein thrombosis (DVT) (adjusted OR 1.32, 95% CI 1.14 - 1.53), their propensity-score matched analysis failed to confirm this association. A significant association between perioperative blood transfusions and pulmonary embolism (PE) was also not detected in both regression analysis and propensity score analysis. Aoude et al.[443], on the other hand, utilizing the same database to analyze patients undergoing lumbar fusion, showed a significant association between transfusions and DVT as well as PE (OR 2.69 and 3.55, respectively). However, an association was not found in patients undergoing thoracic fusion, whereas anterior approaches of the lumbar spine led to a significantly higher rate of VTE postoperatively, suggesting that other factors such as location and surgical approach could have influenced VTE risk in spine surgery patients.

Institutional studies have also examined the association between blood transfusion and VTE. Jiang et al.[444], studied a relatively small cohort of 715 patients undergoing TJA. While their sample size was low, a high event rate was observed (8% developed VTE), allowing the authors to demonstrate a statistically significant association between allogeneic blood transfusions and VTE (OR 3.9, 95% CI 1.8 - 8.4). These findings contradicted to those published in a large institutional database study recently[434]. Jackson et al., failed to show a

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significant association between perioperative blood transfusions and VTE following primary TJA after multivariate analyses as well as a sensitivity analysis using propensity score matching based on a VTE risk calculator (OR, 0.42; 95% CI, 0.12 - 1.39). While the study by Jackson et al., evaluated a large number of 29,000 TJA, the event rate was only 1.04% (the number of VTE in the transfused group), possibly rendering the study underpowered to detect an effect size that may be clinically meaningful. While the purpose was not to specifically assess the relationship between blood transfusions and VTE, Parvizi et al., evaluated multiple potential risk factors for VTE in an attempt to create a risk stratification calculator. In the cohort of 1'721,806 TJA patients, blood transfusions (prescribed to 21.7% of the patients) were among the top ten most important factors associated with VTE[430].

Evidence from spine surgery also suggested an association between blood transfusions and an increased risk of VTE[443,445-447]. Johnson et al.[446], reported a 4.6% rate of thrombotic events in patients who underwent spinal fusion and received allogeneic blood transfusion compared to 1.1% in those who did not receive a transfusion. This relationship remained significant after adjusting for confounders (95% CI 1.032 - 1.194, p = 0.003). Wang et al.[447], evaluated 1,346 patients undergoing spine surgery that were stratified to elective and emergent procedures. While blood transfusions were significantly associated with a higher risk of DVT following emergent procedures, no significant association was found following elective surgery.

These contradictory results are a testament to the immense difficulty in isolating a single variable association when the event rate is low, and many confounding variables exist. Possible reasons for the discrepancy among the abovementioned studies could be the difference in time periods. Changes in the perioperative care including early mobility, more aggressive rehabilitation, same-day discharge, and transition to aspirin as the chemoprophylactic agent of choice may have confounded the results as well. Other possible confounding factors include the length and complexity of the surgical procedure. Patients undergoing long and complex procedures are more likely to require blood transfusion. These patients have longer surgical times, slower recovery, and potentially, more neurological deficits. These factors have not been isolated and studied separately as possible risk factors. Future studies should further assess this relationship using granular data, taking into account the many confounders associated with blood transfusions. While current literature does not clearly show an association between blood transfusions and VTE, the possible association makes it reasonable to recommend a strict approach to minimize blood loss during surgery, reduce surgical time and discourage the liberal use of allogeneic blood transfusions in the perioperative period.

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17 - Does administration of tranexamic acid (TXA) to patients undergoing orthopaedic procedures increase the risk of subsequent VTE?

Response/Recommendation A: Administration of tranexamic acid (TXA) in patients undergoing orthopaedic procedures does not increase the risk of developing subsequent

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venous thromboembolism (VTE) in patients without prior VTE history.

Strength of Recommendation A: Strong.

Response/Recommendation B: Administration of TXA in patients undergoing orthopaedic procedures does not increase the risk of developing subsequent VTE in patients with prior VTE or equivalently elevated hypercoagulability risk.

Strength of Recommendation B: Moderate.

Delegates vote: Agree 97.06% Disagree 0.98% Abstain 1.96% (Strong Consensus).

Rationale: TXA is an antifibrinolytic agent that blocks lysin-binding sites on plasminogen, thereby preventing fibrin-plasminogen interaction and facilitating clot stabilization[448]. Administered intravenously (IV), orally, topically, or in IV-topical combinations, TXA has been shown to effectively decrease blood loss and mortality in the setting of major trauma and, over the past few decades, has seen reemerged interest in orthopaedic surgery, including adult reconstruction, orthopaedic trauma, and spine surgery[448-454]. Nevertheless, given its potency as a fibrin clot stabilizer, theoretical concerns exist regarding elevated VTE risk following TXA administration.

At this time, strong evidence supports that TXA is not associated with elevated VTE risk in orthopaedic surgery. In their recent meta-analysis of 101 orthopaedic subspecialty studies, Taeuber et al., found that IV TXA did not significantly increase the risk of subsequent VTE (TXA: 3.6%, control: 2.7%, $p = 0.64$)[455]. Among subspecialties, TXA has been most well studied in the setting of total joint arthroplasty (TJA). Fillingham et al., meta-analysis demonstrated a lack of evidence to support higher VTE rates in patients receiving perioperative IV, topical, and oral TXA in primary TJA[450]. As a result of the mounting evidence of TXA administration not leading to an increased risk of VTE, the combined clinical practice guideline of the American Association of Hip and Knee Surgeons, the American Academy of Orthopaedic Surgeons, the American Society of Regional Anesthesia and Pain Medicine, and the Hip and Knee Societies provided a strong recommendation regarding the safe administration of TXA in patients without a history of VTE[456]. Several published randomized controlled trials (RCT) have demonstrated equivalent VTE risk in patients receiving TXA in hip, knee, and shoulder arthroplasty[457-459]. No studies have demonstrated increased VTE risk associated with TXA. Routine TXA use is currently incorporated in all rapid recovery protocols in arthroplasty practices and has been proved safe and effective in reducing blood loss and the need for blood transfusions[459].

TXA administration has also been shown to reduce blood loss without increasing VTE risk in orthopaedic trauma. In a meta-analysis of RCT, Reale et al., demonstrated that VTE risk is not increased in patients receiving TXA for non-arthroplasty lower limb orthopaedic procedures such as hip fractures and knee arthroscopy[460]. This is particularly relevant in hip fracture surgery where mortality risk is sharply affected by perioperative blood loss and transfusion requirements for fragile patients and thus TXA may be quite beneficial with prudent use[461,462]. TXA use in spine surgery has also recently emerged, with an interest in its use for single-level fusion for degenerative spine conditions and adult deformity surgery where blood loss may be substantial[452,463]. In their meta-analysis of RCT, Cheriyan et al., found that IV TXA administration did not increase the risk of VTE or local hematoma in patients undergoing cervical and lumbar spine surgery[463]. Reasonable theoretical concerns on the balance between blood loss and epidural hematoma formation exist.

Though most published studies on TXA specifically exclude patients with prior VTE, moderate quality data exists and supports this recommendation in high-risk orthopaedic patients with prior VTE or other hypercoagulable risk-equivalent medical condition (e.g., atrial fibrillation, coronary artery disease [CAD], cerebrovascular accident, cancer). In a matched retrospective series of 1,262 patients with prior VTE undergoing primary TJA, Sabbag et al., found that the risk of VTE recurrence was not significantly greater in patients who received perioperative IV TXA administration[464]. When matched-comparison analysis was performed on the 31 patients in their cohort who experienced a recurrent VTE, IV TXA was not independently associated with increased risk. Using the American Society of Anesthesiologist (ASA) status ≥ 3 as a surrogate for high VTE risk, Fillingham et al., found in meta-regression that high-risk patients were at no higher risk of subsequent VTE following TXA administration[450]. This analysis is supported by a retrospective chart review of 38,220 TJA patients, where Porter et al., concluded that high-risk patients that receive TXA are not associated with an increase in adverse outcomes. Similar VTE risk profiles have been noted in orthopaedic patients with comorbid CAD and cancer patients undergoing endoprosthetic reconstruction for primary bone sarcoma or metastatic carcinoma to bone[465,466]. The decision to utilize TXA must not be solely based on the theoretical risk of VTE, but instead must weigh all risks and benefits to the medication. It is important to note that patients with higher comorbidity burden (e.g., prior VTE, CAD, ASA ≥ 3, malignancy) are known to have a higher risk of complication following significant blood loss and blood product transfusion and, as such, indirectly benefit from routine TXA usage where there is lack of evidence to suggest harm from TXA administration.

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18 - Does tourniquet applied to the lower extremity influence the incidence of post-operative VTE?

Response/Recommendation: There is inadequate evidence to link the use of lower extremity tourniquet during orthopaedic procedures and postoperative venous thromboembolism (VTE).

Strength of Recommendation: Limited.

Delegates vote: Agree 91.58% Disagree 4.95% Abstain 3.47% (Strong Consensus).

Rationale: The systematic review conducted identified a few studies related to the use of torniquet and VTE or embolization. Historical reports examined emboli using echocardiograms immediately following release of a lower limb tourniquet[467-469]. In one particular prospective comparative study of 24 patients undergoing total knee arthroplasty (TKA), there was a 5.33 fold increase in large venous emboli with the use of a pneumatic tourniquet[467]. There is anecdotal evidence of patient mortality caused by exsanguination of a limb and inflation of a pneumatic tourniquet[468,469].

More recently, higher-level evidence has failed to demonstrate a significant relationship between tourniquet use and VTE[470-473]. The three prospective randomized studies evaluating tourniquet use in TKA, all failed to show a significant difference in symptomatic VTE[471-473]. Moreover, systematic review and meta-analysis of foot and ankle procedures demonstrated limited evidence for increased risk of VTE with the use of a tourniquet[474].

Despite limited overall evidence for use of a tourniquet as a risk factor for VTE, tourniquet duration has been associated with VTE. Two retrospective and one prospective study have examined this topic[475-477]. A registry study of 577 primary TKA patients demonstrated increased risk of complications, including deep venous thrombosis (DVT) with tourniquet time over 100 minutes[475]. It is worth noting that the relationship between tourniquet time and operative time is difficult to separate. One retrospective comparative study of a single surgeon who routinely used a tourniquet and another who did not demonstrated significantly higher rate of VTE with the use of a tourniquet. However, a major confounding variable was surgical time, 72 vs. 36 min. Systematic review of many studies on the topic over the last ten years shows a strong relationship between longer operative time and the risk of postoperative VTE[478].

To further complicate matters, there are other factors that have impeded definitive research on the topic. For one, modern DVT prophylaxis and early ambulation has greatly reduced the incidence of symptomatic VTE[479]. Although variably reported, one large series showed an incidence of VTE following primary TKA to be less than 0.31%[480]. Moreover, the timing of tourniquet use is widely variable between surgeons. Some surgeons have advocated use of a tourniquet during cementation for TKA while others may use tourniquet for the entire duration of the procedure. A prospective randomized controlled study of half course vs. full course tourniquet with 64 patients demonstrated no difference in symptomatic or asymptomatic VTE between groups[481]. High quality randomized data with adequate power is needed to further characterize the relationship between torniquet use and VTE, but this may prove impractical. One contemporary study hypothesized that a total of 3,400 patients would be needed to provide 95% power and 5% significance, assuming a baseline symptomatic VTE event rate of 1% and minimally clinically important difference of 1%[479].

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19 - Does tourniquet applied to upper extremity influence the incidence of post-operative VTE?

Response/Recommendation: There does not appear to be a high rate of venous thromboembolism (VTE) after the use of tourniquets for upper extremity surgery.

Strength of Recommendation: Limited.

Delegates vote: Agree 96.55% Disagree 0.49% Abstain 2.96% (Strong Consensus).

Rationale: Arterial tourniquets are commonly used to achieve a bloodless operative field. While there is some data to suggest an increase in the rates of VTE in lower extremity surgery, this type of data does not exist in the upper extremity. The body of literature related to tourniquet use in the upper extremity focuses on an assessment of pain, and post-operative complications, such as hematoma and limb ischemia. Most data are from level IV case series or level III comparative studies[482]. No study demonstrates an increase in symptomatic VTE with the use of tourniquet in the upper extremity; however, no study also specifically evaluated the possible association between VTE and the use of upper extremity torniquet. There is one randomized controlled trial comparing minor hand procedures performed with or without the use of a tourniquet[483–485]. Similarly, the authors did not specifically evaluate VTE, and do not report any difference based on tourniquet use.

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20 - Is intraoperative heparin effective and safe to prevent postoperative VTE in patients undergoing orthopaedic procedures?

Response/Recommendation: Intravenous (IV) administration of intraoperative heparin to patients undergoing total hip arthroplasty (THA) has been investigated and found to be safe and effective in prevention of postoperative venous thromboembolism (VTE). Further studies are needed to evaluate the efficacy of this modality in other orthopaedic procedures.

Strength of Recommendation: Moderate (for hip).

Delegates vote: Agree 84.06% Disagree 8.70% Abstain 7.25% (Strong Consensus).

Rationale: There is an increased risk of VTE after major orthopaedic surgery, such as THA, total knee arthroplasty (TKA), or spine surgery[486]. The initial stimulus for thrombus formation occurs during surgery but most regimens for VTE prophylaxis start postoperatively[487]. In a randomized controlled trial (RCT) comparing low-molecular-weight heparin (LMWH) started within 2 hr. before surgery vs. 4 hr. after surgery vs. warfarin for THA, the risk of bleeding was highest in patients started on preoperative LMWH[488]. During surgery, particularly THA, there is activation of coagulation, measured as increased levels of thrombin-antithrombin complex, prothrombin fragment 1 + 2, fibrinogen peptide A and D-dimer after reaming of the femur during the insertion of the femoral component of the prosthesis[489]. These findings led to the evaluation of administration of intraoperative heparin to reduce the thrombus formation in the early stage. Unfractionated heparin (UFH) was used because there was experience from intravenous administration of heparin during cardiac bypass surgery. Furthermore, UFH can be effectively reversed with protamine in case of increased bleeding.

Three RCT have been published, comparing intraoperative IV UFH with placebo; two in THA[490,491], and one in total knee arthroplasty (TKA)[492]. In the THA trials all patients received aspirin 650 mg daily for 11 – 30 days postoperatively, which could have attenuated the effect of intraoperative heparin. The UFH regimens differed. In the study by Sharrock et al., 1,000 units UFH before surgery plus 500 units every 30 min during surgery was administered[490]. In the study by Westrich et al., 15 units/Kg of UFH was administered at the end of acetabular reconstruction[491], and in the study by Giachino et al., 100 units/Kg of UFH was administered before tourniquet

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inflation during TKA and the UFH was reversed later with protamine[492]. In the study by Sharrock et al., there was a reduction of the composite of deep venous thrombosis (DVT) detected on screening with venography and pulmonary embolism (PE) in the UFH group but also increased intraoperative blood loss[490]. In the study by Westrich et al., there were similar outcome in the two groups regarding VTE, intraoperative blood loss and postoperative drainage[491]. The study by Giachino et al., evaluated embolic material, interpreted as mainly fat emboli, in the right atrium after release of the tourniquet without detecting any difference between the groups[492]. One additional study included 26 patients undergoing THA who were randomized into two groups (one group receiving UFH and another group receiving none) and found that the level of D-dimer and other coagulation parameters were reduced in the group receiving UFH[493].

Several prospective cohort studies have been performed, comparing different regimens of intraoperative UFH for THA[494], or comparing two small cohorts with or without UFH intraoperatively for THA[495], or for TKA[496] without any difference in outcome, or comparing with historical studies that did not use intraoperative UFH but without any clear difference in symptomatic VTE[497]. The exception is for one of the cohorts (adjusted dose heparin) in the study by Huo et al., for which in comparison with a historical control group there was a reduction in VTE ($p = 0.37$)[494]. Another prospective study in TKA was a single arm cohort without any comparator[498]. A prospective cohort study in patients with lumbar spine surgery compared UFH 50 - 75 units/Kg with control without any difference in VTE or blood loss (after adjustments for confounders)[499].

A retrospective chart review of two very large cohorts with THA and TKA receiving 1,000 iu of UFH at skin incision and 500 units intraoperatively did not find significant differences in the incidence of fatal PE vs. historical controls[500]. Finally, a retrospective review of patients with a history of VTE and undergoing THA with UFH 10 units/Kg before preparation of the femoral canal had inconclusive results, since there was no comparator and postoperatively different antithrombotic regimens were used[501].

Regarding safety, with the exception of the study by Sharrock et al.[494], there was no study that showed significantly increased bleeding with intraoperative heparin (after adjustments, when applicable), and the aforementioned study used repeated doses of 500 units heparin every 30 minutes during surgery, which added up to more heparin than any subsequent regimen.

It should be noted that almost all studies in patients with THA used regional anesthesia, which contributes to a reduction in the VTE incidence and may have been a confounding variable.

Despite the demonstration of activated coagulation during major orthopaedic surgery, there is no high-quality clinical evidence to support the benefit of intraoperative UFH for all orthopaedic procedures. The only potential benefit of intraoperative administration of UFH may be in patients undergoing THA.

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21 - Does the type of anesthesia administered influence the risk of VTE in orthopaedic surgery?

Response/Recommendation: The use of neuraxial anesthesia is associated with a reduced risk of venous thromboembolism (VTE) after lower extremity joint arthroplasty and should be considered as part of a multimodal prophylaxis regimen when feasible.

Strength of Recommendation: Moderate.

Delegates vote: Agree 94.58% Disagree 2.46% Abstain 2.96% (Strong Consensus).

Rationale: Many orthopaedic procedures performed on the extremities are amenable to regional (neuraxial and/or

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peripheral nerve blocks) instead of or in addition to general anesthesia. This approach has been linked to better pain control, sympathectomy-mediated vasodilatation, and reduction in the overall stress response[502]. Despite the many reported benefits of regional anesthesia in mitigating the risk of perioperative complications, data on the impact of regional anesthesia on the risk of thromboembolic events are available almost exclusively for total joint arthroplasty. Here, recent consensus group work by the International Consensus Group on Anesthesia Related Outcomes after Surgery (ICAROS), which was based on an extensive review and analysis of the literature, suggested that the use of neuraxial vs. general anesthesia was associated with a 48% and 37% reduction in the risk of deep venous thrombosis and pulmonary embolism for total hip arthroplasty (THA), and a 33% and 21% reduction in the risk of the same endpoints for total knee arthroplasty (TKA), respectively[503]. This benefit was also noted when the analysis was restricted to studies wherein chemoprophylaxis was routinely used. Conclusions remained unaffected by the analysis of: 1) studies published after 1995 to reflect more contemporary practice, and 2) only randomized controlled trials as supposed to the inclusion of observational data. Additionally, when combining regional techniques with general anesthesia, additional benefit was observed, thereby suggesting an intrinsic benefit of neuraxial anesthesia that was separate from the avoidance of a general anesthetic approach.

There is a paucity of literature on the impact of regional anesthesia on thromboembolic risk in other types of orthopaedic surgery. However, the choice of anesthetic and analgesic technique should also take into consideration additional adverse outcomes (i.e., risk of infection, pulmonary and cardiac compromise, etc.), many of which are substantially reduced with the use of regional anesthetic approaches. Further, the impact of anesthetic and analgesic techniques on VTE should be continually reassessed in light of recent advances such as those related to Early Recovery After Surgery (ERAS) pathways.

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22 - Does the use of PMMA cement during orthopaedic procedures influence the risk of subsequent VTE?

Response/Recommendation: Although polymethyl methacrylate (PMMA) cement and its component parts have not been demonstrated to be thrombogenic *in vitro*, the use of PMMA cement does influence the risk of subsequent embolization, some of which may be labeled as venous thromboembolism (VTE).

Strength of Recommendation: Moderate.

Delegates vote: Agree 84.77% Disagree 9.64% Abstain 5.58% (Strong Consensus).

Rationale: PMMA bone cement is widely used across a variety of clinical applications in orthopaedic surgery including for implant fixation purposes, cranial surgery, and spinal fixation[504]. Bone cement consists of two component parts. Typically, the powder is composed of the polymer, an initiator, and a radio-opacifier. The liquid consists of the monomer, accelerator, and the inhibitor[505].

An *in vitro* study by Blinc et al., found that the surface of aged or fresh bone cement did not exhibit thrombogenicity, and that the liquid component of bone cement inhibited both platelet aggregation and plasma clotting, but not at concentrations that would be expected *in vivo*[506]. Similarly, Cenni et al., evaluated the compatibility of methacrylate-based bone cement on plasma, cultured human endothelial cells, and an erythrocyte suspension. That study found no effect of cement on the plasmatic phase of coagulation, did not induce the expression of endothelial cell procoagulant activity, and had no hemolytic effect on erythrocytes[507]. A follow-up study by the same group involving the testing of seven different bone cements found no induction of hemolysis nor any activation of the intrinsic coagulation pathway in vitro[508]. Animal studies, using a dog model, supports the *in vitro* findings and do not implicate the monomer as playing a role in cardiopulmonary/vascular events[509-511].

Clinical observations, however, have identified embolic phenomenon associated with the use of PMMA bone cement. The spinal surgery literature is rich with reported complications of non-thrombotic pulmonary cement embolism due to intra-vascular extravasation of pressurized liquid cement during percutaneous vertebroplasty (PVP) and balloon kyphoplasty (BKP) procedures[512-515]. Embolization of the pulmonary circulation with small amounts of cement is often asymptomatic and frequently identified incidentally on plain film radiography as well as computer tomography (CT) of the chest[516-520]. The incidence of pulmonary cement embolization ranges from 3.5 to 23% based on imaging and is felt to underestimate the true incidence of cement extravasation into the pulmonary circulation[514]. Several techniques have been introduced to successfully reduce the risk of pulmonary cement embolism either by intensive monitoring using CT fluoroscopy[521-523] or by reducing the pressure in the vertebral body before/during cement injection[524-527]. No evidence-based guidelines exist regarding the therapeutic management of patients with pulmonary cement embolism although approaches range from observation in asymptomatic patients to anticoagulation for 3 - 6 months in symptomatic individuals[514].

Embolic and thrombotic events in association with the use of PMMA bone cement have been observed from the earliest days of arthroplasty involving both the hip and knee, as well as in the shoulder and in oncologic procedures[504].

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Prospective studies involving the use of transesophageal echocardiography (TEE) document fat and marrow emboli during bone preparation, cementing and implant insertion[528-530]. Clinical manifestations of this embolization range from transient hypoxia, loss of consciousness, to acute respiratory distress syndrome (ARDS), and even death[531,532]. The development of this clinical entity has been variously described as bone cement implantation syndrome (BCIS) or fat embolism syndrome (FES) both of which are incompletely understood entities occurring as rare non-thrombogenic complications in patients following total hip arthroplasty (THA) and total knee arthroplasty (TKA). An prospective study by Morda et al., on patients with fractures of the femoral neck did not identify alterations in coagulation based on thromboelastographic studies as playing any role in the development of BCIS[533]. Treatment of both BCIS and FES centers on supportive care, fluid resuscitation, possible corticosteroid use, and respiratory support in the face of ARDS[534].

With regard to the risk of venous thromboembolism, a meta-analysis by Li et al., compared the efficacy and safety of cemented and uncemented hemiarthroplasty in the treatment of elderly patients with fracture of the femoral neck. That meta-analysis involved eight randomized control trials (RCT) encompassing 1,577 hips. The incidence of pulmonary embolism (PE) was statistically significantly higher in the cemented group[535]. Conversely, however, Liu et al., found no difference in cardiovascular complications — including PE — in their meta-analysis of 15 RCT encompassing 3,790 patients comparing cemented vs. cementless hemi-arthroplasty for elderly patients with a displaced femoral neck fracture[536].

In association with THA, fat and marrow emboli that have been demonstrated to occur in association with cementing were found to be reduced when using changes in surgical technique involving such methods such as bone-vacuum assistance[537,538]. Marrow contents are felt to be activators of the coagulation cascade when introduced into the intravascular space[539]. In a prospective RCT by Pitto et al., a reduction in fat and bone marrow embolization demonstrated via TEE using a bone-vacuum technique resulted in a statistically significant reduction in VTE events compared to standard cementing[540]. With regards to TKA, limited information is available regarding the VTE risk and fixation. In a retrospective review by Hitos et al., cemented TKA was associated with a rate of deep venous thrombosis (DVT) that was statistically significantly higher than cementless TKA[541]. An RCT with venographic endpoints by Clark et al., comparing cementless TKA, cemented TKA, and cemented THA found an increased length of the thrombus with cemented TKA but no difference in incidence of DVT among the three groups[542]. Two prospective cohort studies that were underpowered found no effect of cement vs. cementless fixation on DVT rate following TKA[543,544].

Surgical technique, anatomic location and patient selection appear to play important roles in the mitigation of VTE risk when using PMMA cement.

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23 - Does the intra-operative positioning of a patient undergoing orthopaedic surgery influence the risk of subsequent VTE?

Response/Recommendation: While surgical positioning may influence the venous thromboembolism (VTE) risk after some orthopaedic surgical procedures, there are no high-quality studies addressing this issue. We recommend that surgeons base these decisions on optimal surgical site access/exposure as well as their technical expertise rather than as a strategy to reduce VTE risk.

Strength of Recommendation: Consensus.

Delegates vote: Agree 97.04% Disagree 0.49% Abstain 2.46% (Strong Consensus).

Rationale: Intraoperative patient positioning has been shown influence operative time, blood loss and VTE risk in a variety of surgical procedures[545]. Surgical positioning, which is inextricably related to surgical site approach, may affect all three components of Virchow's triad. For example, the prone position often leads to reduced venous return due to abdominal compression and compression of femoral veins[545]; intraoperative hip and knee extension may also decrease venous drainage from the legs[546]. Therefore, patient positioning has been proposed as a potentially modifiable risk factor for VTE in orthopaedic patients. However, data on this topic is extremely limited and is too heterogenous to allow the determination of VTE rates with different intraoperative positions for any given orthopaedic procedure. More important surgical risk factors include the surgical approach as well as type of procedure.

Shoulder: Open or arthroscopic shoulder surgery can be performed either with the patient positioned in the lateral decubitus or the beach-chair position[547]. Although the risk of VTE is very low after shoulder surgery, some reports have suggested that deep venous thrombosis (DVT) of the upper or lower extremity is more common following the lateral decubitus position[548-550]. However, due to the paucity of studies on this issue, it is still premature to conclude whether or not patient position affects VTE rate after shoulder surgery.

Spine: The prone position during spine surgery may significantly increase intra-abdominal pressure, reduce venous return and increase bleeding rates compared to other positions[551,552]. In a population database that included 357,926 spine surgeries, VTE was recorded in 0.9% of patients operated in the supine position and 1.6% after a procedure in the prone position (hazard ratio [HR] = 1.8)[553]. However, the rate of VTE was more affected by the underlying diagnosis and type of procedure. The recent 2019 Congress of Neurological Surgeons evidence-based guidelines on treatment of thoracolumbar spine trauma did not address intraoperative positioning and did not recommend a specific surgical approach[554].

Pelvic fracture repair: Various surgical approaches in pelvic fracture repair may be associated with different rates of DVT; however, there were no high-quality studies assessing the impact of patient positioning on the risk of VTE following this procedure[555,556].

Hip fracture repair: A randomized trial that allocated 120 elderly patients with intertrochanteric hip fractures to the lateral decubitus or supine intraoperative position reported only one DVT after surgery[557]. Similarly, another study of 102 patients undergoing intertrochanteric hip fracture repair found no significant difference in any postoperative complication, including VTE, between supine and lateral positioning, although surgical time and blood loss were greater in the supine group[558].

Total hip arthroplasty (THA): Using intraoperative venography or Doppler ultrasound, previous studies have shown that posterior and lateral approaches to the hip may result in obstruction of the common femoral vein[559,560]. However, femoral vein compression was not seen with anterior approaches[561]. No cases of VTE were reported in a randomized trial of 100 patients undergoing THA using an anterior or lateral approach[562]. In a small, retrospective, before-after study, Kawano et al., utilized a lateral approach for THA performed in the lateral decubitus position and then switched to an anterior

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approach in the supine position[563]. Surprisingly, asymptomatic DVT based on routine screening with either computer tomography (CT) or ultrasound two weeks after surgery was found in 5% of the 80 patients in the lateral decubitus group and 19% of the 36 patients in the supine group. However, DVT was more common in earlier cases in the supine group compared to later cases (33% vs. 6%), suggesting that surgical experience had a greater impact on DVT incidence compared to surgical approach or patient position.

Total knee arthroplasty (TKA): A Doppler ultrasound study conducted intraoperatively before a TKA procedure found that calf venous blood flow was significantly reduced with knee flexion of at least 90º, and that postoperative DVT (especially proximal DVT) occurred more commonly in patients with the lowest preoperative venous flow velocity after knee flexion[564]. The authors concluded that marked knee flexion during TKA reduced venous blood flow and may have increased DVT risk. However, two meta-analyses of randomized control trial (RCT) in TKA patients found that postoperative knee flexion following TKA was not associated with a significant difference in VTE rate compared to knee extension[565,566].

Other orthopaedic procedures: A study on 68 patients undergoing elective achilles tendon repair reported no VTE events in patients who underwent surgery in the prone and lateral decubitus positions[567].

Conclusion: There appears to be a difference in VTE rates with different intraoperative patient positions following certain orthopaedic procedures such as spine surgery. However, any observed differences were small compared to the risk associated with the procedure itself. Consequently, it is recommended that intraoperative patient positioning should be based on considerations such as optimal access to the surgical site as well as the technical proficiency of the surgeon, rather than VTE risk. Regardless of patient positioning, other important factors that may decrease VTE risk include careful intraoperative positioning and padding, avoidance of dehydration, prevention of increased intraabdominal pressure, use of regional anesthesia, minimally invasive procedures, rapid postoperative mobilization, and adequate postoperative pain control[568]. When excessive venous stasis is anticipated to occur, intraoperative use of sequential compression devices should be considered alongside risk-appropriate pharmacologic thromboprophylaxis[569].

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24 - Is there a validated risk stratification scoring system that can be used for determining VTE risk of a patient undergoing orthopaedic procedures?

Response/Recommendation: There is currently no validated risk score that can be used across all orthopaedic subspecialties. Most of the studies concerning risk scores have originated from joint replacement literature and generally use similar risk factors that classify patients as either high- or low-risk. Unfortunately, none of these scores have been properly externally validated. They also lack any assessment of major bleeding events. Furthermore, the impact of these risk scores on patient outcomes and decision-making remains unknown. Additional studies are required to address these major limitations.

Strength of Recommendation: Moderate.

Delegates vote: Agree 99.52% Disagree 0.00% Abstain 0.48% (Strong Consensus).

Rationale: There are numerous risk factors for the development of venous thromboembolism (VTE) after an orthopaedic surgical procedure. These can be generally classified as either host- or surgery-related[570-578]. While it is important to know the individual risk factors associated with VTE, this alone does not always contribute to clinical decision-making and overall risk stratification. In the era of personalized medicine, individualized risk scores are increasingly needed, especially when taking into consideration the many existing pharmacological and non-pharmacological options for VTE prophylaxis. Improved risk stratification could help to better target these prophylactic measures for individual patients.

An ideal risk stratification model should include the following key components:

1. Risk scores that are derived from data that is both granular and contemporary, taking into account recent changes in orthopaedic procedures as well as enhanced recovery protocols.
2. Procedure-specific risk scores, which consider risk factors that are unique to each orthopaedic subspecialty.
3. Account for modifiable factors such as unilateral vs. bilateral procedures, type of anesthesia, and the use of tranexamic acid[579].
4. Include the modifying effect that different antithrombotic agents have on the overall risk. It is often assumed that patients with multiple risk factors and deemed to be high-risk based on risk calculators would benefit from more potent chemoprophylaxis. However, recent studies have suggested otherwise[580].
5. Be easy to use and interactive, allowing the clinician to assess how a patient's individual risk can be modified.
6. Predict major bleeding events (including wound-related issues), which are influenced by the type of chemoprophylaxis chosen.
7. Make a clear distinction between pulmonary embolism (PE), proximal deep venous thrombosis (DVT) and distal DVT, as each may have different risk factors as well as different implications with regard to treatment.
8. Include external validation, ideally in a global context, in multiple consistent studies and across various subspecialties. For example, the exponential increase in thrombotic risk with the presence of multiple comorbidities has been shown in other specialties but needs to be investigated in the arthroplasty population. Machine learning tools may be used to identify the interactions between multiple risk factors.

A systematic review of the literature was performed that included only papers concerning the development or validation of a risk stratification model. Papers that involved non-surgical treatments were excluded. Papers were also excluded if only preoperative VTE was assessed. Our literature search resulted in 513 potentially relevant papers. Of those, 426 were excluded on the basis of titles/abstracts and 87 full text articles were reviewed. Of these 87 articles, only 10 studies met the abovementioned criteria; eight articles involved total joint arthroplasty (TJA) patients, one article involved lower extremity trauma patients, and one article involved foot and ankle patients. No randomized controlled trials were identified. Only one study evaluated patients prospectively. The number of component variables in a single risk score ranged from 5 - 25. Seven different risk scores or institutional protocols were identified. The number of patients included in the studies ranged from 217 - 1,721,806. Our assessment of these current risk stratification models (Table III) was performed in comparison to the abovementioned ideal.

In general, the majority of the risk scores identified similar risk factors associated with VTE. While they differed in the relative weight given to each variable in the scoring system, all scores were similar in their attempt to stratify patients into risk groups under the assumption that this should guide the choice of chemoprophylaxis. The specific threshold that was chosen ultimately affects the performance (i.e., sensitivity and specificity) of the individual risk score. The Caprini risk score represents an excellent example. While this score has served the medical and surgical community for many years and has had great success outside of orthopaedics, it is not widely accepted in orthopaedics as the original threshold score of 5 would automatically place all orthopaedic patients in the high-risk group. This would obviously result in capturing all VTE events (i.e., high sensitivity), but at the cost of extremely low specificity. Acknowledging this issue, a recent study investigated the optimal threshold (maximizing sensitivity and specificity) for stratifying patients and found a score of 10 to be ideal, thus improving specificity at the expense of sensitivity. Choosing this threshold for prophylaxis would result in prescribing warfarin or other non-aspirin alternatives to nearly 40% of patients. Other scoring systems identified different, and at times arbitrary, thresholds defining "high-risk" patients, resulting in 1.8% to 9.3% of patients being included in this category. This affects the interpretation of each risk score and does not allow a direct comparison of their performance across different studies. Establishing an acceptable common threshold above which patients should be considered "high-risk" may

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TABLE III Studies included in the systematic review

Study (Country, Year)	Data source	Population (Sample size)	Predictors	External validation	Includes procedure-specific risk factors	Chemoprophylaxis included in the model	Endpoint that was statistically assessed	Key findings
Dauty (France, 2012)[589]	Institutional data (at least 4 centers; both public and private)	TKA (primary/ revision not mentioned) (n = 272)	RAPT score	No	No	No	Symptomatic DVT	RAPT score < 6 was associated with a 3.0 relative risk for DVT
Saragas (South Africa, 2013)[586]	Single institution	Foot and ankle surgeries (n = 216)	Caprini score	Yes	No	No	Any documented DVT or PE	No significant difference in number of risk factors in the VTE and non-VTE groups. 90.9% of patients in the VTE group and 73.7% of patients in the non-VTE group had a total risk factor score of ≥ 5 (no statistical comparison provided)
Parvizi (USA, 2014)[571]	Single institution	TKA and THA (primary and revision) (n = 26,391)	Knee surgery, CCI, atrial fibrillation, postoperative DVT, COPD, anemia, depression, BMI	No	Limited	No	Symptomatic PE	Patients were classified into low- (0.35%), medium- (1.4%), and high- (9.3%) risk categories
Nam (USA, 2015)[587]	Single institution	THA (Primary and revision) and hip resurfacing (n = 1,859)	Institutional protocol: Age (> 70), previous DVT, active cancer, hypercoagulability, multiple comorbidities, morbid obesity, family history of VTE, immobility.	Yes (Prospective)	No	No	Symptomatic DVT or PE	75.4% were categorized as routine risk and 24.6% as high risk. The cumulative rate of VTE was 0.5% in the routine and 0.5% in the high-risk cohort within 6 weeks postoperatively (p = 1.00). Patients in the routine risk cohort had a lower rate of major bleeding (0.5% vs. 2.0%, p = 0.006) and wound complications (0.2% vs. 1.2%, p = 0.01)
Parvizi (USA, 2016)[572]	Nationwide Inpatient Sample	TKA and THA (primary and revision) (n = 1'721,806)	VTEstimator	Yes. On institutional data. (n = 25,775)	Limited	No	Any documented DVT or PE	A score above 75 was provisionally chosen to dichotomize patients into low- and high-risk. Above this threshold, the rate of VTE in the NIS group was 1.68% and 3.85% in the validation group

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TABLE III (*continued*)

Study (Country, Year)	Data source	Population (Sample size)	Predictors	External validation	Includes procedure-specific risk factors	Chemoprophylaxis included in the model	Endpoint that was statistically assessed	Key findings
Bohl (USA, 2016)[581]	American College of Surgeons National Surgical Quality Improvement Program	Primary TKA and THA (n = 118,473)	Age, sex, BMI, preoperative hematocrit, knee surgery.	Yes. On institutional data. (n = 17,384)	No	No	Symptomatic PE	Patients with a score between 9 and 12 had an increased risk of PE in the validation group (2.6%)
Bateman (USA, 2017)[585]	Single institution	Primary TKA and THA (n=363)	Caprini and VTEstimator	Yes	No	No	Symptomatic PE and DVT	Mean Caprini and VTEstimator scores were not different between those who did and did not develop VTE
Dashe (USA, 2019)[584]	Single institution	Lower extremity fractures grouped into "low-" risk (isolated foot and ankle) and "high-" risk (pelvis and acetabulum)	Caprini score	Yes	No	No	Any documented DVT or PE before or after surgery.	Caprini score was not different between "low-" and "high-" risk fractures. The cutoff that best-predicted VTE events based on receiver-operating curves was 12 (c = 0.74) in the high-risk group, 11 (c = 0.79) in the low-risk group.
Krauss (USA, 2019)[582]	Single institution	TKA and THA (n = 1,078)	Institutional protocol and Caprini score	Yes	No	Reported but not statistically evaluated	Symptomatic PE and DVT	Patients were dichotomized based on a threshold score of 10. 7/394 in the high-risk group developed VTE compared to 1/684 in the low-risk group.
Gold (USA, 2020)[583]	Single institution	Primary TKA and THA (n = 2,155)	Caprini score	Yes	No	Taken into consideration for validation	Symptomatic PE and DVT	Higher Caprini scores (continuous and dichotomized with a threshold of 11) were not associated with increased VTE risk when controlling for VTE chemoprophylaxis

TKA=Total knee arthroplasty; RAPT=Risk Assessment and Prediction Tool; DVT=Deep venous thrombosis; PE=Pulmonary embolism; VTE=Venous thromboembolism; THA=Total hips arthroplasty; CCI=Charlson comorbidity index; COPD=Chronic obstructive pulmonary disease; BMI=Body mass index; NIS=Nationwide inpatient sample.

help to standardize these risk scores. Notwithstanding, the assumption that "high-risk" patients may require more aggressive anticoagulation is still contentious, as recent studies have suggested that aspirin may be appropriate for higher-risk groups[580]. With advances in the field of machine learning and taking into account that current institutional data includes "high-risk" patients receiving aspirin, a more personalized approach to risk stratification may be feasible. Instead of classifying patients into groups, it may be possible to report the specific VTE probability for individual patients and allow

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clinicians to make their own decision with regard to the optimal chemoprophylaxis based on their assessment of what is an "acceptable" risk.

External validation was lacking for all studies. The included studies could be broadly subdivided into studies in which scoring systems were formulated and evaluated within the same cohort or a holdout of patients[572,581], and other studies that set out to validate an existing score or protocol[582-587]. The majority of studies that showed encouraging results with external validation were conducted by the same authors that developed the score, thus leading to concerns with regard to reproducibility and generalization. Nam et. al.[587], were the only group that prospectively evaluated their institutional protocol and thus were able to take into account the influence of chemoprophylaxis in their evaluation. Using a simple protocol, they categorized patients into either "routine-" (75.4%) or "high-" (24.6%) risk groups and showed a 0.5% VTE rate in both groups. Whether their protocol simply did not capture all "high-risk" patients or whether the VTE rate was affected by the use of more aggressive anticoagulation in the "high-risk" group remains debatable. The Caprini score was the only score to be evaluated by external groups and across fields other than joint replacement, aside from one external study[585] that also evaluated the VTEstimator score. Bateman et al.[585], retrospectively evaluated the Caprini and VTEstimator score in a group of 363 total knee arthroplasty (TKA) and total hip arthroplasty (THA) patients. They failed to show an association between mean scores and VTE risk. However, the study suffered from many methodological issues including the small sample size and low event rate (only 10 VTE), an inability to assess the scores adequately due to missing data, and the evaluation of scores as a continuous variable as opposed to a categorical variable for risk stratification[588]. Krauss et al.[582], compared a departmental protocol with the Caprini score and showed that using a threshold of 10, the latter was able to capture 7 out of 8 VTE compared to only 1 event that was captured using the former. Notably, this threshold of 10 was chosen to optimize the results of the Caprini score within that specific cohort (using the Youden index), and therefore does not reflect a true external validation of the score. More recently in a cohort of 2,155 TJA patients, Gold et al.[583], failed to find an association between high Caprini scores (when evaluated continuously and categorically using 11 as the threshold) and VTE risk when taking into account chemoprophylaxis in a multivariate analysis. Outside of joint arthroplasty, two studies have evaluated the Caprini score. Saragas et al.[586], failed to show the utility of the Caprini score in a heterogeneous group of foot and ankle patients; however, they used the original 5-point threshold for stratifying patients and the sample size was too small to perform statistical analysis. Dashe et al.[584], examined a group of lower extremity fractures. The Caprini score was no different between "low-" (isolated foot and ankle) and "high-" (pelvic/acetabular) risk fractures, although the latter cohort was more prone to VTE. While the optimal cutoff to predict VTE was 11 - 12, the actual performance of the score could not truly be evaluated. Furthermore, the group studied included both preoperative and postoperative VTE, thereby making it difficult to interpret the results.

Another major limitation of all but two of the current risk scores is the inclusion of PE and DVT (proximal and distal) as one combined outcome. Some studies also included asymptomatic and isolated distal DVT, the importance of which remains unknown. Additionally, there is evidence suggesting that PE and DVT are two distinct entities, and hence individual risk factors may need to be weighed differently with respect to each entity. In a cohort of 1,078 patients, Krauss et al.[582], were able to capture 7/394 VTE in the "high-risk" patients, while only 1/684 "low-risk" patients had a VTE. Interestingly, only 1 of the 7 "high-risk" patients had a PE, while the single patient in the "low-risk" group had a PE as well. If one were to consider PE as the primary outcome, the occurrence of PE would in fact be a sporadic event, and no association with any of the risk scores would be found. On further analysis, the PE patient in the low-risk group was later found to have a congenital thrombophilic factor that would have placed the patient in the high-risk category.

Finally, one inherent limitation to all of the current scoring systems is the failure of these scores to account for major bleeding events or wound complications. The sensitivities and specificities of the different scores affect the overall number of patients receiving aggressive anticoagulation, as mentioned above. Not only may this have a financial impact, but there may also be a direct effect on the number of major bleeding events or wound complications that could complicate VTE prophylaxis. Predicting these adverse events may be as important as predicting VTE risk. Nam et al.[587], reported on the treatment of 75.4% "routine-risk" patients with aspirin and 24.6% "high-risk" patients with warfarin. While VTE rates were 0.5% in both groups, patients in the former cohort had a lower rate of major bleeding (0.5% vs. 2.0%, $p = 0.006$) and wound complications (0.2% vs. 1.2%, $p = 0.01$) compared to the latter cohort. It is clear that decisions which modify a patient's VTE risk may also affect bleeding risk, and contemporary risk assessment tools should ideally take this into account. As such, future VTE risk scoring systems should also incorporate the risk of major bleeding events and wound complications.

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25 - Is there a risk stratification system for predicting major bleeding events following orthopaedic procedures?

Response/Recommendation: There is no formal risk stratification system available for predicting major bleeding events following orthopaedic procedures. A recent consensus statement limited to patients on chronic oral anticoagulation undergoing specific surgical procedures does stratify the risk of bleeding events (high, low/moderate, and minimal).

Strength of Recommendation: Consensus.

Delegates vote: Agree 98.07% Disagree 0.48% Abstain 1.45% (Strong Consensus).

Rationale: Bleeding is a common adverse consequence following elective and trauma orthopaedic procedures. Major blood loss can occur which may result in further surgery, cardiopulmonary morbidity, infection, coagulopathy, hypothermia, increased hospital stays and costs, or even mortality[590-592]. Allogeneic blood transfusions may be required to manage major blood loss but are also associated with risks including viral transmission and incompatibility[593]. Blood loss after orthopaedic surgery is multifactorial, and likely related to a number of patients, surgeon, and procedural factors. Two large cohort studies compromising a total of almost 4,500 patients reported the risk of major bleeding after orthopaedic surgery to be up to 5.4%[594,595]. The frequent use of chemical venous thromboembolism (VTE) prophylaxis for many orthopaedic procedures may also increase the risk of major bleeding[596].

If the risk of major bleeding following orthopaedic procedures could be reliably predicted preoperatively and/or intraoperatively, then it may be possible to implement strategies to reduce blood loss and associated adverse events. We performed a systematic review of the literature (see Appendix # 25 for search strategy) to answer the research questions "Is there a risk stratification system for predicting major bleeding events following orthopaedic procedures?"

Presently there is no general formal risk stratification system available for predicting major bleeding events following orthopaedic procedures. Additionally, many of the studies concerning major bleeding following orthopaedic procedures explore surgical risk factors and do not discuss the impact of anticoagulant agents for VTE prophylaxis.

A recent consensus statement from the International Society on Thrombosis and Haemostasis does stratify the risk of procedural bleeding in a subset of patients on chronic oral anticoagulation pre-operatively into three groups (high, low/moderate, and minimal). The risk stratification is limited due to being based solely on the specific surgical procedure performed[597]. High bleeding risk orthopaedic procedures, defined as a 30-day risk of major bleeding greater than 2%, include (i) major orthopaedic surgery, including shoulder replacement, (ii) major surgery with extensive tissue injury, (iii) spinal surgery, and (iv) any major operation lasting greater than 45 minutes. Low/moderate bleeding risk orthopaedic procedures, defined as a 30-day risk of major bleeding of up to 2%, include arthroscopy, foot, and hand surgery. No orthopaedic procedure is defined within the minimal bleeding risk category. In a cohort of 3,082 patients undergoing hip, knee, or spine surgery which were predominantly elective, Oberweis et al., identified the procedure type as an independent predictor of major bleeding[595]. Multivariate analysis showed that spinal surgery was associated with the highest risk of major bleeding, with the risk of major bleeding being 81% and 65% lower in patients undergoing knee and hip surgery respectively compared to spinal surgery.

A number of studies have investigated predictors of major bleeding following specific elective and trauma orthopaedic procedures. In these studies, the outcomes assessed were most frequently blood transfusion requirements and/or the volume of blood loss measured in a variety of ways. Importantly, as a result of the increased risk of VTE following many orthopaedic procedures, patients are administered VTE prophylaxis to lower their risk. However, these anticoagulant agents are associated with an increased risk of major bleeding events in the postoperative period. Several studies have

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highlighted the differences in major bleeding event risk across prophylactic agents[598-603].

Most studies investigating predictors of major bleeding following orthopaedic procedures have included patients undergoing primary total hip arthroplasty (THA) and total knee arthroplasty (TKA). Studies have reported an increased risk of blood transfusion following primary THA and TKA with a lower pre-operative hemoglobin concentration, lower patient body weight or body mass index (BMI), older age at surgery, female sex, longer operative times, and in patients with a history of cancer, coronary artery disease, or chronic obstructive pulmonary disease, and patients undergoing bilateral TKA[595,604-614]. Studies also found a reduced risk of allogeneic blood transfusion in patients receiving topical tranexamic acid following primary THA[605], and in patients receiving re-infused blood collected from cell salvage following primary TKA[615]. Additionally, many studies have analyzed the impact VTE prophylaxis has in major bleeding events following joint procedures. Lindquist et al., retrospective cohort study, which analyzed the impact of VTE prophylaxis on major bleeding rates following TKA, found patients on aspirin (ASA) and enoxaparin to be associated with a lower major bleeding risk than patients on rivaroxaban[602]. While Lassen et al., study comparing rivaroxaban and enoxaparin demonstrated no significant difference in postoperative bleeding events[601], Anderson et al., reported no difference between major bleeding events in patients undergoing total joint arthroplasty between ASA and rivaroxaban[598]. Additionally, a study by Jacob et al., identified clopidogrel, an antiplatelet, to incur a greater bleeding risk postoperatively[600].

Revision THA and TKA are associated with increased blood loss compared with primary procedures[604]. In a cohort of 210 patients undergoing revision THA, independent predictors of allogeneic blood transfusion were low pre-operative hemoglobin concentration, low patient body weight, operating theatre blood loss, and the absence of perioperative cell salvage[616]. In another cohort of 146 revision THA, blood loss and transfusion risk were associated with patient factors, such as male sex, older age, low pre-operative hemoglobin concentration, and were also associated with surgical factors, including femoral component and dual-component revisions (compared with acetabular only revisions), and revision of cemented components[617].

In studies assessing patients undergoing idiopathic scoliosis surgical correction, greater blood loss was associated with larger preoperative total Cobb angles, increasing number of vertebral levels fused, increasing number of screws inserted, and longer operative times[618-620]. One study of 311 patients undergoing posterior spinal instrumentation and fusion for adolescent idiopathic scoliosis reported that the variable most strongly associated with blood loss was the number of levels fused; the fusion of 12 or more levels had a probability of greater than 10% of major haemorrhage[619].

Following 169 periacetabular osteotomies performed for acetabular dysplasia, longer duration of surgery correlated with increased blood loss, whilst other factors such as patient age, BMI, arthrotomy, and anesthesia used were not associated with blood loss[621]. Blood loss increased by 11.1% per hour of surgery.

In a cohort of 546 patients undergoing surgery for acute hip fracture, independent predictors of blood loss were type of surgery, pre-operative use of ASA, intra-operative hypotension, and gastrointestinal bleeding or ulceration[622]. In terms of the type of surgery performed, compared to dynamic hip screw, intramedullary nailing was associated with increased blood loss. The use of screw/pin fixation and the use of arthroplasty were both associated with reduced blood loss compared to dynamic hip screw fixation[622].

In a study of 212 patients undergoing shoulder replacement for either trauma or elective indications, the predictors of blood transfusion were preoperative hemoglobin levels less than 12.15 g/dL, and postoperative day one hemoglobin levels less than 10.0 g/dL[623].

While many of these focus on the importance of identifying risk factors for major bleeding events, most studies do not focus on the incidence of major bleeding as a result of differences in both patient risk factors and VTE prophylactic agents. Beyer-Westendort et al., analyzed the differences in the bleeding rates between rivaroxaban and fondaparinux in patients undergoing major orthopaedic surgery, identifying rivaroxaban to be associated with decreased bleeding risk[599]. Additionally, Nurmohamed et al., meta-analysis found no significant difference between the risk of bleeding between low-molecular-weight heparin (LMWH) and standard heparin following orthopaedic surgery[603]. Unfortunately, the literature of bleeding risk stratification is limited to discrete comparisons between a subset of anticoagulants. No study has been able to thoroughly investigate the risk for major bleeding events across the variety of anticoagulation agents available for patients undergoing orthopaedic surgery. Due to differences in patient demographics, it is important to identify the relationship between risk factors and clinical variables, such as VTE prophylaxis, to properly predict and stratify patient risk preoperatively.

Future research should focus on developing and validating a risk stratification system for predicting major bleeding events following both elective and trauma orthopaedic procedures that places a larger emphasis on VTE prophylactic agents. Any risk stratification system should consider patient and procedural factors as well as postoperative anticoagulation and should aim to be generalizable to the population of interest rather than limited subsets.

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26 - Is there a role for stratification of patients undergoing orthopaedic procedures for risk of bleeding? If so, should VTE prophylaxis be altered based on bleeding risk profile?

Response/Recommendation: Given the incidence and severe outcomes of major bleeding events following orthopaedic procedures, there is definite need for risk stratification prior to surgery. While much attention has been put into identification of venous thromboembolism (VTE) risk factors and multiple guidelines exist attempting to mitigate this risk, major bleeding events (MBE) are serious complications that received less attention. Unjustifiably, MBE is often examined as a secondary outcome and therefore cohorts are too small to allow adequate statistical power for examining this issue. While current literature cannot support one chemoprophylaxis agent over the other in terms of MBE risk, it is important to consider that any potential benefit in terms of VTE risk reduction should be weighed against a potential increase in bleeding risk.

Strength of Recommendation: Limited.

Delegates vote: Agree 97.21% Disagree 0.93% Abstain 1.86% (Strong Consensus).

Rationale: MBE are potential and serious complications following orthopaedic procedures. In a recent systematic review, the rate of clinically important bleeding was 3%, which was much higher compared to VTE event rate[624]. This raises the question of whether our focus has been too much on VTE at the expense of bleeding complications. MBE have been shown to increase the risk for blood transfusion and have been associated with increased cost, longer length of stay, allergic reactions, and increased rates of deep venous thrombosis (DVT), surgical site infections and mortality[625,626]. Therefore, blood loss

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prevention strategies including use of tranexamic acid, spinal anesthesia, early mobilization, same-day discharge, use of compression devices, and transition to aspirin (ASA) for prophylaxis have gained popularity in the last decade and may have a beneficial effect.

Personalized medicine and patient optimization including risk stratification models have gained popularity in recent years and there are currently several VTE stratification strategies available[627,628]. The work done in the field of VTE has taught us that different patient characteristics, co-morbidities and genetic factors all play a role in the overall risk for event. As such, risk stratification for MBE may lead to better preoperative workup and optimization as well as induce intraoperative and postoperative modalities to avoid this increased risk. Identifying high-risk patients for MBE is therefore paramount prior to orthopaedic surgery.

To minimize bleeding and prevent VTE adequately, it is important to identify patients that are at high risk for MBE. Some previous studies have shown several significant risk factors for MBE after total joint arthroplasty (TJA). In their study, Prasad et al., suggested that there is a significant perioperative blood loss in males, as well as with increased tourniquet time and surgical time after total knee arthroplasty (TKA)[629]. Another study by Pugely et al., demonstrated lower blood transfusions rates when spinal anesthesia was compared to general anesthesia in patients undergoing TKA[630]. Frisch et al., suggested that female gender, age, higher body mass index (BMI), creatinine level, procedure type (TKA compared to total hip arthroplasty [THA]), increased surgical time, intraoperative blood loss, preoperative hemoglobin and intraoperative fluids may be associated with postoperative blood transfusion rates[625]. Type of chemoprophylaxis may also play a significant role in MBE risk. In their study Zufferey et al., found that the risk of MBE with fondaparinux thromboprophylaxis is highest in the first days after the operation. The authors have suggested that male sex, lower BMI, and increased duration of drug exposure may increase the risk for major bleeding as well. Since fondaparinux is eliminated through kidneys, in case of moderate renal impairment lowering the dose of the drug may reduce the risk of major bleeding[631].

The International Society on Thrombosis and Hemostasis (ISTH) defines major bleeding as blood transfusion ≥ 2 units within 1 day of surgery[632]. In the coronary artery disease (CAD) population, the incidence of both thrombotic and bleeding events is higher than in the non-CAD population. In arthroplasty literature, "major bleeding" term contains intracranial bleeding, gastrointestinal bleeding, bleeding that requires ≥ 2 units of blood transfusion, and hematoma formation which requires reoperation[633]. Oberweis et al., reported that procedure type (Spinal surgery > THA > TKA), active cancer, female sex, CAD and chronic obstructive pulmonary disease (COPD) are independent risk factors for MBE[634]. Previous perioperative bleeding and active cancer are known as risk factors for MBE after surgical procedures[635,636] In a recent study, Tafur et al., found that hypertension is also a risk factor for perioperative bleeding[637]. In a systematic review performed by Borre et al., in a patient group with 322,010 patients, patients with chronic kidney disease are at increased risk for MBE (moderate strength of evidence)[638]. An international normalized ratio (INR), age, prior stroke, presence of heart disease, diabetes mellitus, sex, cancer, race/ethnicity and cognitive impairment also suggested as risk factors for MBE, however, the evidence was not enough to support these conclusions[638].

Numerous anticoagulant drugs are begin used for VTE prophylaxis. However, these drugs especially potent anticoagulants may increase the risk of bleeding[639-641] which may result in periprosthetic joint infection (PJI), extended length of hospital stays, and higher costs[642,643]. The 2011 American Academy of Orthopaedic Surgeons (AAOS) guidelines on VTE prophylaxis recommend that a balance must be obtained to minimize bleeding while providing adequate VTE prevention[644]. Although the risk of VTE is well defined, the risk factors that may result in MBE in patients undergoing orthopaedic procedures are not well defined. Identifying bleeding risk factors and staying away from potent anticoagulants may help patients from bleeding and transfusion-related complication. Rivaroxaban, a highly selective oral Factor Xa inhibitor was found to be effective in preventing VTE and is not highly associated with MBE[645]. In a study comparing ASA and rivaroxaban in a cohort of 3,424 patients, the rate of MBE was 0.47% in the ASA group and 0.29% in the rivaroxaban group. There was no clinical significance regarding bleeding between these two drugs[646]. In a pool-analysis of phase III randomized clinical trials (RCT), Nieto et al., compared dabigatran, rivaroxaban and apixaban (new direct oral-anticoagulants [DOAC]) vs. enoxaparin regarding thromboprophylaxis and bleeding complications. MBE rates were similar in patients treated with DOAC (0.8%) compared to those treated with enoxaparin (0.8%). In the same study, the rivaroxaban group was more likely to have increased MBE rates compared to the enoxaparin group. In the other trials apixaban favorably, and equally, dabigatran, were superior to enoxaparin regarding bleeding episodes[647]. In a study by Vulcano et al., they found the percentage of bleeding, minor bleeding, and MBE as 0.3%, 0%, and 0.3% respectively for patients who received ASA and 1.6%,0.9%, 0.7% respectively for patients who received warfarin. Although not statistically significant, ASA tends to be safer than warfarin[648]. In 2017 a systematic review comparing low-molecular-weight heparin (LMWH) with the control group, warfarin and dabigatran has been performed by Suen et al., the risk for surgical site bleeding episodes was increased in LMWH group in contrast to the control, warfarin, and dabigatran group. And this difference was statistically significant in both groups[639]. Several studies have shown a higher incidence of MBE with warfarin use compared to ASA[640-642].

Our search results showed that there are no high-level studies with a primary outcome aimed to define risk factors for bleeding in patients undergoing TJA. Studies on possible risk factors for MBE are retrospective cohorts. Furthermore, these risk factors are mostly reported as secondary outcome values. With the available data, possible risk factors for bleeding after orthopaedic procedures are listed in Table IV.

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TABLE IV Risk factors associated to MBE

Older age
Gender (Female)
Active cancer
Surgical procedure type (Spine > THA > TKA)
Anesthesia type (General > Spinal)
Intraoperative blood loss
Increased creatinine level
Preoperative hemoglobin level
Increased surgical time
Increased tourniquet time
Hypertension
History of previous bleeding

MBE=Major bleeding event; THA=Total hip arthroplasty; TKA=Total knee arthroplasty.

To summarize, MBE occur at a similar and even increased rate compared to VTE events[624,646]. There is therefore an urgent need for MBE risk stratification models for patients undergoing orthopaedic procedures. RCT with adequate power are called for the identification of risk factors associated with MBE. Furthermore, developing a risk score calculator for bleeding risk is necessary for better patient optimization, blood loss prophylaxis and reducing blood transfusion-related complications.

Ömer Serdar Hakyemez, Ibrahim Azboy

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27 - Is Thromboelastography (TEG) useful in predicting the risk of VTE in patients undergoing orthopaedic procedures?

Response/Recommendation: Although previously validated in other surgical subspecialties to predict venous thromboembolism (VTE), thromboelastography (TEG) has not been adequately trialed in patients undergoing orthopedic procedures. However, limited studies suggest that TEG is a useful adjunct for assessing orthopaedic hypercoagulopathy and VTE after traumatic injury and/or surgical intervention based upon a maximal amplitude (MA) > 65 mm.

Strength of Recommendation: Moderate

Delegates vote: Agree 89.74% Disagree 1.54% Abstain 8.72% (Strong Consensus).

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Rationale: VTE prevention continues to be a high priority for orthopaedic surgeons. However, VTE is not always preventable despite administration of various chemical and/or mechanical prophylaxis measures, especially in the context of no universal gold standard protocol (i.e., specific medication and duration[649-652]).

Viscoelastic hemostatic assays (VHA), like TEG or rotational thromboelastometry (ROTEM), offer the most comprehensive method of assessing individual patient coagulopathy. VHA globally assess coagulopathy by providing a graphical representation of the entire clotting cascade from clot initiation through fibrinolysis. Serial TEG of the severe trauma patient demonstrates the transition from index hypocoagulability to postinjury or postsurgical hypercoagulability also validating VTE prevention[653,654]. Stutz et al., describe the value of VHA assessing the "safe zone" for anticoagulation where patients are neither undertreated and unprotected from VTE or overtreated and at risk for undesirable postoperative hemorrhage and/or wound complications[655].

TEG has demonstrated mortality benefit over conventional coagulation tests (CCT: (activated partial thromboplastin time [aPTT] and prothrombin time [PT]/ international normalized ratio [INR]) when guiding initial blood product transfusion for the seriously injured polytrauma patient[656]. In tandem, orthopaedic literature on the use of VHA also surrounds trauma resuscitation and severe hemorrhage. Modified TEG with platelet mapping demonstrated a reduced ratio of fresh frozen plasma (1 unit) to packed red cells (2.5 units) and platelets (2.8 units) during massive transfusion of severe pelvic fractures[657]. In a different study, TEG reaction time (R-time) > 6 min was found to be an independent risk factor for death in patients with pelvic fractures (odds ratio [OR] 16; 95% confidence interval [CI] 5.4 - 53, $p = 0.0010$) with no significant association with CCT[658]. Another retrospective review of perioperative transfusions during orthopaedic spine procedures, fracture, and total joint arthroplasty (TJA) surgery found TEG-guided transfusion therapy reduced and optimized blood components ($p < 0.05$) with improved coagulation function ($p < 0.05$) and decreased hospital length of stay ($p < 0.001$) as compared to CCT. The risk of bleeding and thrombosis was not specifically studied[659].

The progression towards a hypercoagulable state has been shown to occur early in the traumatic or postoperative phase. A prospective cohort polytrauma study found admission TEG hypercoagulability in 582/983 patients, with a doubled rate of deep venous thrombosis (DVT) despite prophylaxis when compared to hypocoagulable TEG patients ($p = 0.039$)[660]. In a systematic review of 31 studies using TEG in orthopaedics, 17 studies cited MA as a significant predictor of VTE among a total of 6,348 patients[661]. Within this review, Brown et al., performed a selected meta-analysis of 5 studies with 3,180 patients to determine if an MA > 65 mm predicted VTE; they found an insignificant OR of 1.31 (95% CI, 0.74 - 2.34, $p = 0.175$). Notably, the cutoff MA value to define hypercoagulability remains inconsistent within the literature and a limiting factor to its predictive value. However, this analysis found TEG consistently demonstrated hypercoagulability beginning soon after surgery[661]. The study by Gary et al.[662], and Cotton et al.[663], were omitted from this meta-analysis despite being the initial studies indicating that an admission MA > 65 mm was a useful threshold for VTE prediction in orthopaedic trauma patients. In a retrospective cohort of 1,818 trauma patients stratified by extremity abbreviated injury severity scores ≥ 2 (ORTHO group) and < 2 (non-ORTHO group), an admission MA > 65 mm constituted an OR of 3.66 for developing VTE, and MA > 72 mm increased the OR to 6.70[662]. In the prospective The Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial, there were early (< 12 days) and late (> 12 days) VTE events in trauma patients, with the preponderance of early events occurring within 72 hours of hospital admission and increased risk for patients with pelvic and/or femur fractures[664].

Fibrinolytic shutdown, which describes the hypercoagulable state associated with the posttraumatic period, has been studied as a VTE prognosticator following orthopaedic trauma. Nelson et al., found fibrinolytic shutdown via TEG on initial assessment of pelvic fractures was not predictive of VTE[665]. The absence of correlation was not surprising in that the definition of fibrinolytic shutdown was only during the index presentation. It is more likely that prolonged shutdown over a series of hours or days (vs. initial fibrinolysis shutdown) is a better predictor of thrombotic risk[665,666]. Future studies on serial VHA over a period of months following major orthopaedic trauma/ surgery might validate the duration of VTE prophylaxis.

The value of serial TEG assays has demonstrated an improved understanding of coagulopathy during the perioperative phase. In a small study of 10 total knee arthroplasty (TKA), 10 total hip arthroplasty (THA) and 10 other lower extremity surgery controls, Okamura et al., found increased MA and coagulation index values 24-hours after TKA and THA surgery as compared to before anesthesia, indicating the early hypercoagulable state that can occur after TJA[667]. Kim et al., found intraoperative TEG tracings demonstrated increased hypercoagulable findings with decreased R-time and increased alpha angle and MA values ($p < 0.05$) during a review of 45 elderly patients (age > 65) undergoing major orthopaedic surgery. These levels trended towards normal postoperatively when compared to preop TEG[668]. Finally, serial TEG found hypercoagulability in 250 patients with femoral neck fractures as measured in the preop, immediate postop, and 6-week postop timepoints, validating a correlation with the development of VTE[669].

In general, there is a sparsity of orthopaedic literature on the routine use of TEG as an adjunctive test to direct perioperative care when compared to counterparts in other surgical subspecialties. VHA have expanded into more reproducible and less operator-dependent cartridge systems with rapid results. Future orthopaedic controlled trials are necessary to determine the effective role of VHA in predicting patient risk for VTE and their value in assessing the effectiveness and

duration of VTE prophylaxis. Orthopaedic surgeons must become increasingly familiar with the tenants of VHA as they pertain to assessing the spectrum of coagulopathy and individualizing surgical care.

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28 - Does lower extremity deep venous thrombosis arising after total joint arthroplasty propagate to cause pulmonary embolus?

Response/Recommendation: Deep venous thrombosis (DVT) propagation, causing pulmonary embolus (PE), has been described in patients with unprovoked clots, and attributed to the prothrombotic phenotype of the individual. While it is recognized that a PE may arise from a DVT, a direct relationship between DVT propagation and a PE does not appear to exist for patients undergoing orthopedic procedures, in particular total joint arthroplasty (TJA).

Strength of Recommendation: Moderate.

Delegates vote: Agree 90.59% Disagree 5.94% Abstain 3.47% (Strong Consensus).

Rationale: Understanding the natural history, prognosis, and implications of venous thromboembolism (VTE) occurring as a consequence of orthopaedic procedures is imperative. Despite DVT rates falling to as low as 0.4% post total hip arthroplasty (THA), and 0.8% post total knee arthroplasty (TKA), consensus is lacking regarding the risk of propagation of distal DVT to the lungs[670-673]. Much of the literature pertaining to the natural history of VTE reports on unprovoked DVT or those provoked in the setting of prothrombotic risk factors, the pathophysiology of which differ from the provoked postoperative DVT[674-676]. A causal relationship between DVT and PE has not been proven in patients undergoing lower limb TJA)[670,677,678].

Surgery has been reported as a major, but transient, trigger for VTE[679-681]. Local activation of the clotting cascade begins intraoperatively following endothelial injury and the release of tissue thromboplastin, which promotes an inflammatory feedback loop involving procoagulant proteins and fibrin strands[682,683]. This transient prothrombotic environment, encompassing distal venous valve pockets that provide a nidus for clot formation, predispose orthopaedic patients to a higher rate of ipsilateral DVT than those undergoing major non-orthopaedic procedures[676,682,684]. Amongst surgical specialties, however, retrospective research has shown that PE rates in the arthroplasty cohort are no higher than those undergoing gastrointestinal, vascular or gynecological procedures[685]. If a DVT was to consistently propagate to cause a PE post arthroplasty, the literature would appreciate a significantly elevated PE incidence compared to other surgical specialties, in proportion to that of DVT rates, however this is not the case.

PE are thought to most commonly arise by way of an established distal thrombus becoming dislodged, travelling within the returning circulatory system to the lungs, obstructing arterioles

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within the pulmonary vasculature and causing ischemia[674]. Thrombosis can also arise directly within the pulmonary vasculature. Patients at risk of in-situ pulmonary artery thrombosis display a pronounced prothrombotic phenotype, with contributions from abnormal fibrinogen variants, family history, autoimmune disease, endocrine dysregulation, and active cancer[674,686,687]. Separate to both hematological pathophysiological pathways, increased intramedullary pressure during arthroplasty procedures has been shown to embolize prothrombotic fat, bone marrow and cement fragments through systemic veins into the pulmonary vascular system[682,688,689]. Activation of extremity and pulmonary thrombogenesis, by way of thromboplastin exposure, has been hypothesized to contribute to DVT and PE rates following TJA, however intraoperative steps have been taken to mitigate this process[682,689]. Manifestation of symptomatic PE is a complex, multifactorial process, with multiple pathophysiological pathways likely coexisting in genetically susceptible patients, however propagation of an extremity thrombus does not appear to consistently contribute to the burden of arthroplasty-related PE disease[690-692].

Little exists in the literature to clarify the evolution of incidental asymptomatic DVT, as evidenced by the lack of consensus within published guidelines[676,693-695]. Observational studies have confirmed that the majority of isolated deep DVT display an uneventful clinical course, without embolization[696]. Half of such thrombi arise at the time of surgery and resolve spontaneously within the first 72 hours postoperatively[696]. Whereas unprovoked, proximal DVT are concerning given their tendency to propagate to cause a PE, and risk of recurrence[696-701]. In the provoked postoperative setting, however, PE rates do not appear to correlate with the observed incidence of proximal DVT, which have been identified in 27% of all DVT post THA, and 15% of all DVT post TKA[702,703]. An increased proximal DVT rate in those undergoing THA has not translated into a heightened burden of PE compared to those post TKA[691,704].

Perioperative prophylaxis and early mobilization have made significant progress in the fight against VTE, which can be appreciated via the falling incidence of post-arthroplasty DVT[675,705,706]. In contrast, due to radiological advancements, and the ability to now discern even smaller emboli, the incidence of PE has been seen to increase the last two decades[707,708]. Highly sensitive multi-detector row computer tomography (CT) pulmonary angiography scanning allows for the detection of clinically insignificant disease in the postoperative setting, arising within the periphery of the pulmonary vasculature[708-710]. Despite prophylaxis and enhanced recovery pathways, the rate of clinically significant PE persists between 0.2 - 1.1% of all arthroplasty patients[691,711-713]. The proportion of TJA patients at risk of PE development has remained consistent over the past two decades, regardless of compliance with guidelines directed towards reducing the venographic evidence of DVT[676,713].

Whilst unprovoked lower extremity DVT carries a risk of propagation, this has not been proven to occur in the provoked perioperative orthopaedic setting[670,673]. PE are thought to arise via multiple interacting pathophysiological processes, most likely within genetically susceptible patients undergoing TJA. Robust scientific evidence, investigating the propagation tendencies of the provoked postoperative DVT, is lacking. Carefully designed, prospective research will play a vital role in clarifying our understanding of perioperative VTE as a disease, most notably its natural history and prognosis in the arthroplasty patient.

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29 - How should patients with post-operative proximal (popliteal or supra-popliteal) DVT be managed?

Response/Recommendation: In line with the current guidelines, we recommend that consideration should be given to treat proximal deep venous thrombosis (DVT), affecting popliteal or suprapopliteal vessels, arising acutely in patients undergoing orthopaedic procedures.

Strength of Recommendation: Moderate.

Delegates vote: Agree 98.54% Disagree 0.97% Abstain 0.49% (Strong Consensus).

Rationale: Venous thromboembolism (VTE) is a well-recognized complication following lower limb orthopaedic surgery[714,715]. Peak onset of DVT is within postoperative weeks two and three[716,717], with the risk remaining elevated for 6 - 12 weeks, falling gradually thereafter until 4 - 6 months postoperatively[718-721]. Asymptomatic proximal DVT, affecting popliteal and suprapopliteal vessels, have been reported to constitute 27% of all DVT occurring following total hip arthroplasty (THA), and 15% of all DVT post total knee arthroplasty (TKA)[722,723]. Unprovoked proximal DVT are a cause for concern given their tendency to firstly recur[724-729], and secondly to have a higher potential to propagate and cause pulmonary embolus (PE)[724-729]. Although such causal relationship for patients undergoing orthopaedic procedures has not been proven[730-732]. Relating to unprovoked DVT, consensus exists amongst the published guidelines stipulating that proximal DVT should be treated to avoid progression and prevent a potentially fatal PE. A causal relationship between the provoked postoperative DVT and PE has yet to be clearly demonstrated in the orthopaedic setting, however despite the serious risks associated with administration of anticoagulation, treatment is currently recommended within the published guidelines, whilst awaiting clarification by way of formal investigation[718,732-735].

There are, however, guidelines by various organizations related to this subject matter. The American College of Chest Physicians (ACCP), the European Society of Cardiology (ESC) and the American Society of Hematology (ASH) suggest that acute postoperative proximal DVT should be treated with an anticoagulation agent, preferably a direct oral anticoagulant (DOAC)[733,736-738]. The guidelines also stipulate that some DOAC, namely dabigatran and edoxaban, should be administered after 5 - 10 days of parenteral low-molecular-weight heparin (LMWH)[733,737,738]. The ACCP suggests that a vitamin K antagonist should be favored as second line over that of LMWH therapy, following appropriate bridging, with a recommended international normalized ratio (INR) target of 2.0 - 3.0 for the duration of treatment[718,737-739]. In patients with active cancer, and a confirmed acute postoperative DVT, the ACCP and ESC

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suggest LMWH as the first line given its favorable profile in reducing recurrent episodes of VTE in such patients[733,737,740].

The above guidelines recommend that the anticoagulation should be continued for three months[718,733,737,738]. The decision for extended treatment beyond three months must be based on the risk-benefit ratio for each individual patient[733].

Regarding the suspected postoperative DVT, patients post lower limb orthopaedic surgery almost certainly attain a Well's score of at least 2, until the twelfth postoperative week. The published guidelines suggest commencing treatment with parenteral anticoagulation in situations where a diagnostic Doppler ultrasound may be delayed longer than 4 hours[718,733,741]. Current healthcare services cannot guarantee a Doppler ultrasound within this timeframe, most notably when patients present acutely over a weekend. Given the heightened risks of anticoagulation-associated hematoma, wound drainage, and surgical site infection (SSI) in the perioperative setting, orthopaedic surgeons have reservations about commencing therapeutic anticoagulation before confirming the diagnosis[732-735]. Perhaps, in the setting of a suspected DVT, when a Doppler cannot be performed within 4 hours, patients post lower limb orthopaedic surgery should continue on their VTE prophylaxis regimen, unless considered to be of significantly high risk by way of a history of thrombophilia or active cancer, in advance of organizing an urgent scan the next day.

Anticoagulation is suggested in favor of catheter directed thrombolysis, systemic thrombolysis and operative venous thrombectomy, in the setting of non-limb-threatening acute postoperative proximal DVT[718,733,737,738,742,743]. Adjuvant catheter directed thrombolysis may be considered in patients with acute iliofemoral disease, with symptoms less than 14 days, and a life expectancy greater than 1 year[733]. Inferior vena cava (IVC) filters are suggested only for patients with contraindications to anticoagulation therapy, and routine use of IVC filter in addition to anticoagulation is not recommended[718,737,738,744-747]. Ambulation is recommended, although severe pain and swelling may require deferral[718,733]. Compression stockings are not routinely recommended in the setting of an acute provoked postoperative proximal DVT, unless providing symptomatic relief, as the literature has not proven any benefit in preventing the onset of post thrombotic syndrome[733,737,738].

Whilst guidelines suggest anticoagulation therapy based on population characteristics, the optimal treatment choice for each individual must be ascertained, based on a careful risk assessment, incorporating the preferences of both the patient and their family, following informed consent and shared decision making.

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30 - How should patients with post-operative distal DVT be managed?

Response/Recommendation: In the absence of concrete evidence, the opinion of this workgroup is that patients with isolated distal deep venous thrombosis (DVT), can be monitored without treatment or treated by aspirin (ASA).

Strength of Recommendation: Limited.

Delegates vote: Agree 79.70% Disagree 14.85% Abstain 5.45% (Strong Consensus).

Rationale: It is commonly accepted that patients with a postoperative proximal DVT (at or above the popliteal vein) or pulmonary embolism (PE) need to be anticoagulated[748,749]. It is not, however, known if patients with a distal DVT (infrapopliteal) need to be treated or merely monitored for progression.

The main concern with the presence of DVT is that the emboli may mechanically propagate to the prximal veins and pulmonary vasculature, resulting in pulmonary dysfunction and possible fatal outcome[748]. Based on older literature, the rate of progression of DVT varies between 0 to 44%[749-751]. Two recent systematic reviews of mixed nonsurgical and surgical patients demonstrated that around 9.0% of distal DVT were found to extend proximally[749,752]. In a randomized controlled trial (RCT) of patients with symptomatic distal DVT presenting to the emergency room, Horner et al., found that the propagation including proximal DVT, and PE was 11% in the conservatively treated group vs. 0% in the anticoagulated group[753]. Similarly, in their systematic review of mainly nonsurgical patients, Lim et al., concluded that the risk for recurrence of DVT (odds ratio [OR] 0.16, $p = 0.01$) or the extension of the distal DVT in a proximal deep vein (OR 0.29; $p < 0.004$) was higher when a no treatment approach was performed compared with treatment with an anticoagulant drug[754]. Of note, the anticoagulation regimens in the included studies were heterogeneous in nature, including a variable combination of intravenous heparin, coumadin, or low-molecular-weight heparin (LMWH) (dalteparin, enoxaparin, or nadroparin).

Other studies have suggested that isolated distal DVT present a low risk for causing PE and may be clinically insignificant. They also question the value of aggressive treatment and even the need for any treatment[755,756]. Palareti et al., adopted a surveillance approach in 65 patients with distal DVT and mixed risk factors including active malignancy, immobilization, or major surgery[755]. Untreated isolated distal DVT had a clinically uneventful course at 3-month follow-up, with a 3.1% rate of DVT extension into the proximal veins. Fleck et al., retrospectively reviewed 102 patients diagnosed with distal DVT, of which only 33.3% had recent undergone surgery[756]. Despite most of their cohort being treated with anticoagulation, no cases of PE were seen in the treated vs. untreated patients. Relatively high rates of new proximal DVT propagation were reported in their untreated patients with distal DVT (3/14; 21.4%), however the study population had significant comorbidities including active malignancy in approximately one third of patients, thereby limiting generalizability to orthopaedic patients. Those who advocate for monitoring the patients with distal DVT rather than treatment, cite the perils of administration of anticoagulation drugs, such as bleeding, as a disincentive for treating these patients. Development of hematoma, persistent wound drainage, and subsequent periprosthetic joint infections have all been associated with administration of anticoagulation, with ASA posing the lowest risk[752,757-759].

The Cochrane Library recently collated a systematic review pertaining to management of distal DVT. Kirkilesis et al., evaluated 8 RCT involving both nonsurgical and surgical patients which included 1,239 participants with distal DVT who were randomized to treatment with anticoagulation with vitamin K antagonists or no anticoagulation[752]. There was no difference with respect to development of PE (relative risk [RR] 0.81, 95% confidence interval [CI] 0.18 – 3.59) between the treatment groups. The anticoagulation group showed a reduced risk of recurrent VTE (RR 0.34, 95% CI 0.15 – 0.77), which was defined as any DVT recurrence in the calf veins, or progression of DVT to proximal veins, or PE development within 3-months. Recurrence of local distal DVT and propagation to proximal veins was also reduced (RR 0.25, 95% CI 0.10 – 0.67). The authors also found that ≥ 3 months reduced the incidence of recurrent VTE to 5.8% as compared with

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13.9% in participants treated only for 6 weeks. While there was no statistical difference in major bleeding between the groups, there was an increase in clinically relevant non-major bleeding events in the group treated with anticoagulants (RR 3.34, 95% CI 1.07 – 10.46). Righini et al., conducted a randomized, double-blind, placebo-controlled trial of mainly nonsurgical patients examining treatment of symptomatic distal DVT using LMWH. They reported LMWH was no better than placebo in reducing the risk of proximal extension or VTE events (3% vs. 5%, p = 0.54) in low-risk patients with symptomatic calf DVT but increased the risk of bleeding (risk difference 4.1, 95% CI 0·4 – 9·2, p = 0.025). Notably, this study was underpowered at publication due to early termination of enrollment[760].

Multiple retrospective studies have also shown relatively low rates of propagation of distal DVT, regardless of treatment approach. Li et al., evaluated 310 consecutive patients after vascular surgery and found 33 with distal DVT[761]. These 33 patients were randomized into full dose or half dose anticoagulation with LMWH and no progression of DVT was reported in either group. Parisi et al., reported on 171 patients with distal DVT treated with LMWH and showed 2.9% of patients had propagation to the proximal veins[762]. It is important to mention that the majority of patients with propagation had a history of unprovoked DVT in this study. More recently, Tsuda et al., followed 742 consecutive patients after THA with postoperative Duplex imaging[763]. The incidence of postoperative DVT was 33%. All the postoperative distal DVT that occurred in the calf veins (n = 232) were not treated and remained benign postoperatively, with no cases of progression to the proximal veins seen during follow-up, and furthermore 93% of distal DVT disappeared on serial imaging.

ASA is well studied as an effective VTE prophylaxis following total joint arthroplasty (TJA)[764], yet its efficacy as an antithrombotic therapy following TJA is less clear in the orthopaedic patient. Becattini et al., showed a 42% reduction in the incidence of recurrent DVT in a multicenter randomized double-blind clinical trial of 402 nonsurgical patients with prior unprovoked VTE when prophylaxis with ASA was compared to placebo[765]. In another study, Brighton et al., also showed that low-dose ASA was effective in preventing recurrent VTE (hazard ratio [HR] 0.66, p = 0.01) in a randomized placebo-controlled trial of 822 nonsurgical patients following their first episode of unprovoked VTE[766]. Omari et al., retrospectively reported on 486 patients with distal DVT after TKA who were treated with ASA 325 mg twice daily[767]. Follow-up doppler ultrasound was performed on 459/486 cases (94.4%) and demonstrated resolution of distal DVT in 445/459 (96.9%) cases. Doppler diagnosed propagation to a proximal vein occurred in 10/459 (2.2%) cases. One patient with a distal DVT developed a PE at 6 weeks postoperatively. The authors concluded that there was a low rate of distal DVT propagation in patients managed with ASA. Additionally, no significant bleeding episodes, wound-related complications, or other adverse events were noted from ASA therapy.

The majority of the literature evaluating treatment of distal DVT is in non-orthopaedic and non-surgical patients. These populations often include mixed diagnoses and levels of comorbidity, including malignancy, which continue to confound our understanding and provide limited evidence to guide management[768]. Distal DVT can either be treated immediately upon diagnosis (with anticoagulation) or be monitored (by holding anticoagulation and only treating progression to proximal veins or if PE is identified)[752]. Data suggesting that anticoagulation is indicated for distal DVT are limited, and such a strategy entails a risk of over-treatment when weighed against the risks of anticoagulation in the postoperative setting.

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31 - How should a patient with a soleal vein thrombosis detected after an orthopaedic procedure be managed?

Response/Recommendation: There is little high-quality literature available regarding treatment of soleal vein thrombosis after orthopaedic surgery. The rate of propagation of soleal vein thrombosis to proximal veins is very low. Thus, these patients may be managed by close monitoring, which may include repeat imaging, and possible administration of aspirin (ASA).

Strength of Recommendation: Limited.

Delegates vote: Agree 89.11% Disagree 6.93% Abstain 3.96% (Strong Consensus).

Rationale: Venous thromboembolism (VTE) of the soleal vein has been considered to be the most commonly involved vein in VTE of the distal lower extremity[769,770]. Soleal VTE is part of a group known as muscular calf VTE, which also includes VTE of the gastrocnemius vein. Muscular deep venous thrombosis (DVT) comprises up to half of distal VTE, and VTE of soleal vein has been associated with proximal VTE and fatal pulmonary embolism (PE) in a number of postmortem studies[771-774]. Specifically, propagation rates of muscular calf VTE to more proximal DVT vary from 1.2% - 25% and progression to PE is reported from rare to 20.7%[770-772,775-782]. Mortality rates in muscular calf VTE are more limited with a single study reporting a rate of 0.5% secondary to PE[783].

There is a paucity of orthopaedic literature on patients with an isolated soleal VTE as a high percentage are found in concurrence with VTE of adjacent veins. This is further complicated by inconsistencies in the current literature with regards to the optimal method of how to manage both soleal and muscular calf DVT. Several studies directly compare therapeutic anticoagulation vs. prophylaxis to mechanical treatment. A prospective cohort study compared patients who had acute muscular DVT treated with therapeutic low-molecular-weight heparin (LMWH) and compression therapy vs. compression therapy alone. They found that LMWH significantly lowered thrombus progression to deep calf veins (95% confidence interval [CI] 11.5 - 43.4%)[784]. Other retrospective studies substantiate the aforementioned findings by showing that therapeutic doses of anticoagulation significantly decrease the risk of PE, the time to vein recanalization after DVT, and VTE recurrence in patients with both muscular and distal DVT[778,780,785,786]. These studies also argue that a therapeutic dosage is more effective than prophylactic dose of anticoagulants[780,786].

There are also several studies that argue against the use of therapeutic anticoagulation for the treatment of soleal and muscular calf VTE. A randomized controlled study of 109 patients diagnosed with muscular calf vein thrombosis compared therapeutic LMWH and calf stockings to calf stockings alone. Therapeutic LMWH did not decrease the rate of clot propagation[779]. Likewise, there are a number of retrospective studies and systematic reviews that examine the conflicting evidence of treating muscular calf DVT. Conclusions of these articles mostly favor compression therapy, prophylactic chemoprophylaxis, and doppler monitoring[777,787-790].

The use of high doses of anticoagulation in the prevention of VTE is associated with adverse events and should be approached with caution. Therapeutic anticoagulation results in an increased bleeding risk which is associated with its own postoperative complications[791-793]. Many studies demonstrate that lowering postoperative bleeding may decrease post-operative surgical infections[794-797]. Furthermore, patients receiving more aggressive does of anticoagulation had an increase in postoperative wound complications but no change in overall VTE rates[798].

In knee and hip arthroplasty, ASA has an increased safety profile and current evidence has demonstrated its non-inferiority to more aggressive forms of VTE chemoprophylaxis. In an institutional registry study comparing warfarin and ASA, no difference was observed in VTE rates while warfarin was associated with increased rates of mortality and infection[799,800].

Conclusion: Recommendations for the treatment of soleal VTE remains unclear. There is a paucity of clinical studies in the orthopaedic literature to support standardized guidelines. Most existing studies arise from the vascular field and thus there is a lack of external validity due to inherent differences in patient populations. Furthermore, there is a paucity of literature examining outcomes solely related to soleal vein VTE. Due to these concerns, chemoprophylaxis anticoagulation should be based on stratification of risk of thrombus propagation vs. bleeding in the immediate postoperative period. The American Academy of Orthopaedic Surgeons (AAOS) clinical practice guidelines on VTE prophylaxis also recommends early mobilization as a consensus recommendation for patients at high-risk of VTE when appropriate. The use of ASA has been shown to be effective for patients with distal DVT[800], and may be considered in patients with soleal vein thrombosis[800]. Finally, the use of repeat imaging after initial diagnosis has proven to be beneficial in guiding further management. This would balance patient safety by avoiding both the risks of VTE propagation and generation of postoperative complications, such as bleeding, arising from administration of aggressive anticoagulation. High-quality studies are needed to further guide treatment recommendations.

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32 - When do venous thromboembolism (VTE) episodes occur after orthopaedic procedures?

Response/Recommendation: The most critical period for venous thromboembolism (VTE) development is within the first month after orthopaedic surgery, but the risk of VTE may persist for longer.

Strength of Recommendation: Limited.

Delegates vote: Agree 97.56% Disagree 0.98% Abstain 1.46% (Strong Consensus).

Rationale: The ideal duration of thromboprophylaxis after orthopaedic surgery is not clear and understanding the timeline of VTE episodes following orthopaedic procedures remains essential for optimizing VTE prophylaxis. Physicians must balance the efficacy of anticoagulation against its safety profile[801]. Limited data on the time course of VTE episodes following orthopaedic surgery exists. Of the available literature, the majority of studies focused on VTE following joint arthroplasty[802-807] and spine[808-811] procedures as these subspecialties are known to be associated with a higher risk of VTE.

Many studies have analyzed the timeline of VTE episodes following total joint arthroplasty (TJA) and other major joint procedures. It is well established that the risk of VTE continues long after discharge and approximately 50% to 75% of cases of VTE manifest post-discharge. In a retrospective database study, White et al., found that the median number of days to VTE following total knee arthroplasty (TKA) was 7 days, while the median following total hip arthroplasty (THA) was 14 days[802]. In their analysis of 19,586 THA and 24,059 TKA, 76% of the VTE diagnoses were after discharge for THA and 47% were after discharge for TKA. The findings of a retrospective study by Shohat et al., on the time to VTE following TKA were similar, with a median time to VTE of 8 days[803].

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Nevertheless, a prospective study by Dahl et al., found that the onset of deep venous thrombosis (DVT) symptoms occurred at an average of 17 days following TKA, 27 days following THA, and 36 days following hip fracture surgery[804]. Bjørnaråa et al., reported similar timelines to Dahl et al., for TKA, THA, and hip fracture surgery, while also noting that symptomatic pulmonary embolism (PE) occurred earlier than DVT following TKA and hip fracture surgery. The median time to clinical VTE after hip fracture surgery was 24 days for DVT and 17 days for PE; for total hip revision (THR), this was 21 days and 34 days, respectively; for total knee revision (TKR), this was 20 days and 12 days, respectively[806]. Hu et al., focused on the timing of PE in patients following TJA and reported a median day of diagnosis of 3 days[807]. Parvizi et al., similarly found that 81% of events in patients on warfarin occurred within 3 days after TJA and 89% of events occurred within one week[805].

While the reported numbers of days post-operation may vary, these studies demonstrate that the majority of VTE occurred after hospital discharge, but PE symptoms surfaced earlier compared to DVT. Plante et al., retrospectively investigated risk factors in 346 patients undergoing TKA and reported a mean time to VTE diagnosis of 5.6 days[812]. Campbell et al., evaluated the effectiveness of different prophylactic agents following hip fracture surgery in a large cohort[813]. In this study, most VTE events were seen in the first two weeks after surgery. However, despite different thromboprophylaxis methods, VTE continued to occur throughout the first 90 days. Arcelus et al., reported results of patients with VTE after major orthopaedic surgery in a multicenter, prospective study[814]. The mean time from surgery to VTE was 22 ± 16 days and the percentage of patients who developed VTE during the first 15 days after surgery was 47%. Fukuda et al., evaluated patients 5 days after TKA using an ultrasonography probe, detecting postoperative DVT in 81.3% and symptomatic PE in 1.7% of cases[815]. Senay et al.[816], aimed to assess the incidence of symptomatic VTE after discharge in patients who underwent TJA. They showed mean time from surgery to symptomatic VTE of 20.4 days (range, 5 - 84 days), while mean time from surgery to PE was 29.7 days (range, 9 - 84 days). Warwick et al., suggested a longer duration of prophylaxis in view of their results[817]. The mean times to VTE were 21.5 days for THA, and 9.7 days for TKA in that study. Kang et al., evaluated East Asian patients who underwent elective THA and reported that symptomatic DVT developed an average of 21 days (range, 10 - 47 days) after the operation[818]. In another observational study of 45,968 consecutive procedures, Lapidus et al., reported symptomatic VTE in orthopaedic surgery[819]. The median time to DVT was 16 days (range, 0 – 42 days) after surgery with 85% diagnosed after hospital discharge, whereas the median time to PE was 23 days (range,0 – 42 days) with 80% diagnosed after discharge.

Several studies also examined the time course to VTE in spine procedures. Cloney et al., studied the time to VTE following 6,869 cumulative spine surgeries in a single institution. The study showed that the rate of VTE increased linearly in the first two weeks following a spine procedure before reaching a plateau[808]. Li et al., performed a time-to-event analysis of VTE in patients undergoing spine surgery and identified a peak incidence in the first postoperative week[811]. More specifically, McClendon et al., analyzed the time to VTE in patients following spinal fusion greater than or equal to five levels[809]. They determined a mean time-to-event of 15 days following the operation. Additionally, the study by De le Garza Ramos et al., on the time course of postoperative complications following adult spinal deformity surgery reported a mean time to VTE of 12 days[810]. With similar time to VTE reported, these studies demonstrate that the majority of VTE events following spine procedures occur within the first two postoperative weeks.

While the time to diagnosis for PE may be earlier compared to the time to diagnosis for DVT, these studies suggest that the majority of VTE events following orthopaedic procedures occur after hospital discharge. By understanding the timeline of VTE events following orthopaedic procedures, physicians and patients can be made aware of critical high-risk periods that may focus efforts for mitigating VTE-related morbidity and mortality. Based on the current literature, the most critical period for VTE ranges from 3 - 27 days after orthopaedic surgery, but the risk for VTE may persist for longer than expected. It remains difficult to predict outcomes as the literature does not report homogenized results in terms of prophylaxis, diagnostic and treatment methods, as well as symptomatic and asymptomatic VTE.

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33 - Should a patient with active lower extremity DVT undergo an orthopaedic procedure?

Response/Recommendation: There is limited scientific evidence to support the safety of orthopaedic surgery in a patient with an active deep venous thrombosis (DVT) or pulmonary embolism (PE). Thus, the management of these patients must be individualized based on the patient history, procedure, extent of the DVT/PE, physiologic parameters, and the risk of bleeding during and after surgery.

Strength of Recommendation: Limited.

Delegates vote: Agree 95.61% Disagree 2.44% Abstain 1.95% (Strong Consensus).

Rationale: Acute or active venous thromboembolism (VTE) in the form of DVT or PE may be present in a patient undergoing both elective and emergent orthopaedic procedures. While no formal cutoff exists, studies have often utilized 21 days from the onset of symptoms to define acute VTE[820]. When VTE occurs prior to surgical intervention, the need for anticoagulation or other intervention to treat the VTE and to avoid further associated morbidity must be incorporated into the perioperative orthopaedic management.

If the surgical intervention is not time-sensitive, then it should be delayed for as long as possible until the DVT/PE is treated and/or resolved. When a patient undergoing elective surgery develops VTE prior to surgery, due to a recurrence rate of nearly 40% within the first 4 weeks, surgery should be delayed at least one month[821]. The longer surgery can be delayed, the lower the risk for VTE recurrence[822-824].

Patients undergoing elective orthopaedic procedures, such as hip or knee arthroplasty are already at high risk for venous thromboembolism[825]. The American Academy of Orthopaedic Surgeons (AAOS) guidelines report that a history of VTE significantly increases the risk in patients undergoing elective arthroplasty, and several studies cite additional risk factors such as: middle or old age, trauma, body mass index (BMI), cholesterol, high-density lipoprotein, apolipoprotein A, malignancy, prolonged surgery or contraceptive use, hormone therapy and pregnancy in women[826-828]. The risk of DVT is also increased in patients undergoing spinal surgery. Zervos, et al., reported that patients with a history of DVT who underwent elective spinal surgery have a higher risk of developing symptomatic DVT postoperatively[829].

However, the surgical intervention may be time-sensitive and/or emergent. For example, patients with hip fractures have optimal outcomes and decreased morbidity and mortality when operative intervention is delivered within the first 24 - 48 hours[830-833]. Patients with hip fracture are known to have an incidence of DVT ranging from 9 - 13% preoperatively[834]. It may be necessary to surgically treat the hip fracture in the face of an active/acute DVT/PE. Another group of patients with time sensitive surgical issues are those with open fractures and orthopaedic infections. Interestingly, fractures and infections both trigger an inflammatory cascade which may make patients prone to developing DVT[835,836].

Sixty percent of DVT occur in the proximal venous system and 40% occur distally[837]. Distal DVT that occur in the gastrocnemius or soleal veins have a low probability of propagating proximally or developing into a PE[838,839]. The evidence on whether to treat a distal DVT varies[840] and the use of anticoagulants for isolated distal DVT in otherwise low-risk patients may not be superior to either a placebo or non-treatment[841-843]. With no treatment, close observation with ultrasound at two weeks is suggested[844]. Proximal DVT, however, have a higher association with PE[845-847]. In addition to the increased risk of developing PE (6% - 32%) as an acute complication or post-thrombotic syndrome (25% - 38%) and venous ulceration (9.8%) as chronic complications[848-851]; progression may also be associated with increased morbidity with mortality rates up to 40%[852-854].

In patients with acute VTE, various agents can be utilized to achieve therapeutic anticoagulation to prevent further clot development. Warfarin and newer direct-acting oral anticoagulants (DOAC) have limited utility. Warfarin anticoagulation would need to be bridged with heparin perioperatively while DOAC have limited anticoagulation reversal options. Treatment with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) may be more useful for patients with acute VTE requiring non-elective surgery[855]. In the setting of an acute or active DVT or PE, stopping UFH or LMWH treatment for a period of time for a patient to undergo surgery is feasible and carries low risk[856,857]. To limit undesirable anticoagulant effects intraoperatively, LMWH should be held for 24 hours or reduced by 50% the evening prior to surgery[822,855] while UFH should be discontinued 4 - 6 hours prior to procedure[858]. All patients should receive mechanical prophylaxis prior to and during surgery which can decrease the

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risk of VTE by up to 60%[823,859]. However, mechanical compression should be avoided in a limb with a DVT due to the potential risk of embolizing a clot[860]. Postoperatively, patients are at increased risk of bleeding, and anticoagulation is often restarted once post-procedural hemostasis is ensured. Data related to the optimal start time of prophylaxis is limited[855]. Based on the findings of the PROSPECT trial, a multicenter prospective study of 260 patients, restarting enoxaparin 12 - 24 hours postoperatively resulted in bleeding in 20% of patients undergoing major surgery[861]. Patients may be bridged with UFH or LMWH to warfarin or DOAC, beginning 24 - 72 hours after major surgery and 18 - 14 hours after minor surgery[855,862-865].

Use of an inferior vena cava (IVC) filter should be considered when a patient has contraindications to anticoagulation or a history of recurrent VTE on prophylaxis[823]. Although controversial, the utilization of IVC filters has increased over the years, especially with the advent of percutaneous insertion[866,867]. IVC filters in high-risk patients with an acute proximal DVT have been shown to initially prevent acute PE[868], and can capture a thrombus in up to 13% of patients postoperatively[869]. Although rare, complications associated with IVC filters increase after 30 days and include filter migration, fracture, vena cava perforation, and vena cava occlusion[870-872].

If immediate intervention is required in an unstable patient with cardiac strain identified by echocardiogram, the benefits associated with more invasive options such as thrombolysis or embolectomy may outweigh the risks to a surgical patient[847,873-875]. Systemic thrombolysis may significantly increase the risk of bleeding, however thrombolysis may prevent further hemodynamic decompensation from VTE[876-878]. While no specific studies exist about performing thrombolysis in orthopaedic patients, a few studies[879-881] show the safety of thrombolysis in post-surgical patients with one report suggesting the use of a thigh tourniquet to prevent surgical site hemorrhage until the thrombolytic agent was no longer active[882]. Another option in patients with pulmonary embolism is catheter-directed thrombolysis which has demonstrated effectiveness in improving right ventricular strain and pulmonary artery pressure with no risk of major bleeding[883-885].

While there is limited high-level evidence to support definitive general recommendations, patients with DVT or PE are not advised to undergo elective surgery due to the high surgical risk associated with increased mortality. However, its management prior to an emergent orthopaedic procedure varies based on individual patient factors with perioperative implications of each clinical scenario.

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34 - How long after a diagnosed DVT and/or PE can a patient undergo elective orthopaedic procedure?

Response/Recommendation: In the absence of definitive evidence, the opinion of this workgroup is that elective orthopaedic surgery should be delayed by 6 months in patients with a recently diagnosed deep venous thrombosis (DVT) and/or pulmonary embolism (PE).

Strength of Recommendation: Consensus.

Delegates vote: Agree 88.61% Disagree 7.43% Abstain 3.96% (Strong Consensus).

Rationale: Patients with active or recently diagnosed DVT or PE may be at a higher risk of developing another episode of venous thromboembolism (VTE). The objective of this systematic review was to determine when it would be safe to subject such a patient to elective orthopaedic procedure. There is a dearth of literature related to this subject matter. A few studies exist that support delaying non-orthopaedic elective surgery for three months while on anti-coagulation for DVT treatment[886]. A longer time interval between a DVT and subsequent surgery may decrease the risk of recurrence, but no specific time frame has been reported in the orthopaedic literature[887]. If surgery must be performed, bridging therapy can be considered, and in those who have received less than one month of anti-coagulation, placement of an inferior vena cava filter may be recommended[886,888]. For minor procedures with minimal anticipated blood loss, one study suggests patients may continue with anti-coagulation through the peri-operative period[889]. Another study concluded that most patients on long-term warfarin may discontinue the use five days prior to an elective surgery, and most do not require heparin bridging in the peri-operative period[890]. The optimal peri-procedural management of patients taking direct-oral anticoagulants is determined on an individual case basis[891,892].

To our knowledge, no literature exists that provides a definitive answer to the posed question. However, given the fact that patients with a recent diagnosis of VTE may be on anti-coagulation treatment and are also at increased risk of subsequent VTE, the opinion of this workgroup is that elective orthopaedic procedure should be delayed for a minimum of three months and preferably for six months. This period of waiting allows for the patient to be treated for the diagnosed VTE and also may provide opportunity to determine the cause of VTE. In patients in whom surgical procedure is emergent or urgent, the period of waiting could be shortened.

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35 - Are there adverse consequences of not treating acute lower extremity DVT in patients undergoing orthopaedic procedures?

Response/Recommendation: Available data suggests that patients with proximal (above knee) lower extremity deep venous thrombosis (DVT) may be at higher risk of pulmonary embolism (PE). From the limited evidence, it appears that the majority of patients with distal DVT may be left untreated with no adverse consequences.

Strength of Recommendation: Limited.

Delegates vote: Agree 82.94% Disagree 14.69% Abstain 2.37% (Strong Consensus).

Rationale: DVT is a common post-operative complication among patients undergoing orthopaedic procedures[893]. Compared to other surgical specialties, orthopaedic procedures are associated with a disproportionally high risk of DVT[894]. Although the incidence of DVT vary between orthopaedic procedures, highest rates of mortality are observed in patients with fractures compared to elective procedures, proximal lower limb as compared to distal and post-operative immobilized and non-weightbearing compared to mobilized and early weightbearing[895]. Even with thromboprophylaxis the rate of symptomatic venous thromboembolism (VTE) may be as high as 12% after internal fixation of pelvic fractures, 3.8% after proximal tibia fracture and 3.7% after total knee arthroplasty (TKA)[895]. Common complications of symptomatic DVT include a risk of PE, post-thrombotic syndrome and chronic venous insufficiency as well as recurrence of DVT and PE[896-898]. Although DVT proximal to the popliteal vein, as compared to distal DVT, have been thought to exhibit an increased risk of PE, older studies from the 1980's have shown equal risk between the two[899,900]. Despite these findings post-surgical venographic or ultrasonographic screening for DVT are not recommended by the American Academy of Orthopaedic Surgeons guidelines as it has not been associated with lower complication or readmission rates[901]. For patients with confirmed above knee DVT, anticoagulant therapy is generally recommended[902].

Although perioperative thromboprophylaxis has been widely incorporated into orthopaedic clinical routine, the clinical course of untreated DVT is scarcely documented, especially in Western populations. Moreover, findings are conflicting when compared to studies from Asian populations.

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In a randomized control trial (RCT) by McKenna et al., from 1980, 46 patients undergoing TKA were randomized to receive aspirin vs. placebo for VTE[903]. Nine of these 12 patients in the placebo group who did not receive any prophylaxis developed DVT shown on ^{903}I-fibrinogen scanning and confirmed with phlebography. Three of the four patients who had calf DVT had a PE, one of the two with a popliteal DVT had a PE and none of three patients with femoral DVT developed a PE.

In three prospective studies by Grady-Benson & Oishi et al., from the 1990's patients undergoing TKA or total hip arthroplasty (THA) were screened with duplex ultrasonography to detect DVT[904-906]. While all patients with proximal DVT were treated with anticoagulants, distal DVT were left untreated. It was not stated whether the DVT were asymptomatic or not. DVT not diagnosed in the screening procedure but presenting symptomatically at a later point were treated in all three studies. Outcomes from the three studies were conflicting. In one study, no patients with distal DVT presented with either proximal DVT or PE[904]. In the two other studies, 20% of untreated distal DVT patients propagated to become proximal DVT[905,906].

In contrast, a prospective study by Solis from 2002 et al., screened 201 patients from Australia undergoing foot and/or ankle surgery with calf duplex ultrasound at the first postoperative visit[907]. Patients who were not treated with perioperative anticoagulants, and patients with prior VTE or prior on-going anticoagulant treatment due to other medical conditions were excluded. In total, 7 asymptomatic patients screened positive for DVT and were left untreated. Although the duration of the subsequent follow-up of the patients with DVT was not stated, none had evidence of progression on ultrasound or symptoms consistent with thrombosis or PE.

Several studies on Asian populations have documented untreated distal DVT without any severe adverse events[908,909].

In a study by Tsuda et al., from 2010 on a South Korean population 185 patients undergoing THA were screened for preoperatively and postoperatively[910]. Nine patients (5%) with asymptomatic distal DVT were identified, all resolved at 6-months follow-up despite not being treated with anticoagulants.

A subsequent study by the same group followed 742 patients from South Korea undergoing elective THA and recorded 237 postoperative asymptomatic DVT of which 231 were located in calf veins, 5 in popliteal veins and 1 extending from calf to femoral vein, all left untreated[911]. One of the 5 patients with popliteal vein DVT developed symptomatic non-fatal PE, two of the other four resolved at 6 months follow-up. Of the 231 distal DVT, 93% resolved at 2 years and none developed symptomatic or fatal PE or were readmitted for VTE.

Kim et al.[912], reported on 200 Korean patients operated with unilateral THA or one-staged bilateral THA and were screened with venograms postoperative day 6 or 7 and lung perfusions day 7 or 8. They identified 72 patients with DVT out of which 42 (58%) had DVT at or proximal to the popliteal vein. No patients were treated with anticoagulants, and none developed PE or had other adverse effects. All DVT were completely resolved on follow-up venograms after 6 months.

There is limited recent literature available documenting untreated DVTs in patients undergoing orthopaedic procedures. The outcomes differ between study populations where findings from Western populations show higher (though inconsistent) rates of DVT progression compared to studies from Asia. Although data exist to improve patient VTE risk assessment based on factors such as age, body mass index, malignancy, genetic coagulation deficiency and previous VTE, the exact individual risk stratification for adverse consequences and propagation of established DVT is difficult. Repeated duplex ultrasonography or treatment is sometimes recommended for distal DVT, while for proximal DVT antithrombotic therapy is commonly recommended. The risk of adverse consequences for individuals with DVT that are left untreated after orthopaedic procedures is highly variable and mostly inconclusive from current studies.

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36 - Should venous thromboembolism (VTE) screening be performed in asymptomatic patients undergoing orthopaedic surgery?

Response/Recommendation: Venous thromboembolism (VTE) screening with ultrasound is not recommended for asymptomatic patients before or after major orthopaedic surgery.

Strength of Recommendation: Moderate for post-operative screening and Limited for pre-operative screening.

Delegates vote: Agree 97.67% Disagree 1.40% Abstain 0.93% (Strong Consensus).

Rationale: Venographic studies show that venous thromboembolism (VTE) incidence after orthopaedic surgery was higher than 40% in the absence of thromboprophylaxis[913-917]. The use of antithrombotic strategies (both mechanical and pharmacological) has significantly reduced the VTE rates.

In this context the clinical balance of treating asymptomatic VTE is still controversial, and the diagnostic yield of systematic screening is still debated.

Following the review of the literature, two randomized controlled trials (RCT) provided information about the clinical value of systematic screening post-operatively.

The RCT by Robinson et al., randomized 1,024 patients submitted to knee and/or hip arthroplasty to post-discharge systematic venous ultrasound screening (518 patients) or sham ultrasound screening (506 patients). The systematic screening arm found 13 asymptomatic (2.5%) deep venous thrombosis (DVT) events and 4 DVT events with negative screening exams. Additionally, 1 patient treated with warfarin for an asymptomatic DVT had a major bleeding event. In the sham arm there were 3 DVT and 2 pulmonary embolism (PE) events totaling 5 symptomatic patients[918]. The risk of symptomatic VTE was not decreased with systematic screening (relative risk [RR] 0.78, 95% confidence interval [CI] 0.21 - 2.89, p = 0.71) nor was the risk of symptomatic events (RR 0.98, 95% CI 0.28 - 3.35, p = 0.97).

The RCT by Schmidt et al., enrolled 346 patients that underwent hip or knee replacement and received prophylactic nadroparin for 10 days[919]. Patients were randomized to ultrasound systematic screening of DVT (with low-molecular-weight heparin [LMWH] treatment in those with asymptomatic DVT) or extended prophylaxis with nadroparin for 35 days[919]. The incidence of symptomatic VTE after screening of asymptomatic DVT (6 of 110 patients without DVT in the screening) was similar to extended thromboprophylaxis (7 of 172 patients) (RR 1.34, 95% CI 0.46 - 3.88). The major bleeding risk was not statistically different among strategies (RR 4.94, 95% CI 0.23 - 102, p = 0.30*) nor overall bleeding risk (RR 0.99, 95% CI 0.25 - 3.88, p = 0.99).

Regarding bias risk, both studies samples' sizes smaller than those required to evaluate symptomatic VTE at the rates found in the studies which led us to consider the studies to have a moderate quality§[920,921].

Thus, the best available evidence did not show improvements of clinical outcomes with systematic DVT screening after major orthopaedic surgery. Additionally, Tsuda et al., followed patients after elective total hip arthroplasty and found that asymptomatic distal DVT which developed post-operatively could be treated without anticoagulation. All DVT remained benign and 93% of them ultimately resolved[922]. Similarly, Wang et al., found that following total knee arthroplasty (TKA), DVT in the calf disappeared spontaneously with time[923]. In patients undergoing elective shoulder surgery, asymptomatic VTE occurred in 5.7% of patients but all were asymptomatic[924].

Regarding pre-operative screening of VTE, there were not any RCT. However, Watanabe et al., evaluated prospectively 71 patients who underwent preoperative computerized tomography (CT) scans of pulmonary and lower limb vessels before having a TKA[925]. About 9% had a preoperative asymptomatic VTE (1 patient had PE [1%] and 7 had DVT [8%]), without any clinical symptoms. In the remaining 64 patients the surgery was performed. These patients were evaluated for post-operative VTE and 51% had CT evidence of thrombosis (8 patients DVT plus PE; 2 patients with PE; and 22 with DVT)[925]. Observational studies with ultrasound screening showed lower rates of pre-operative VTE (approximately 3%)[926,927], and an interrupted time-series study showed that the period of systematic VTE ultrasound screening was not significantly different from the non-systematic period regarding post-operative thromboembolic complications[927].

Overall, the frequency of post-operative VTE is much higher than pre-operative VTE, and some of the "postoperative" DVT reported in systematic screening studies may represent undetected preoperative VTE. The current data does not inform us robustly if therapeutic anticoagulation and/or surgery postponement can avoid clinically relevant VTE events, and therefore no recommendation can be made for systematic pre-operative VTE screening.

*Zero major bleeding events in the extended prophylaxis arm. RR, 95% CI and p-value calculated using the 0.5 correction for the zero-events arm.

§For example, Schmidt et al., trial showed the highest relative risk differential among arms and the higher rate of symptomatic VTE (5.5%). Using these data, which are conservative for sample size estimation and a power of 80% the adequate sample size would be 5,946 patients[919].

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37 - Are there specific clinical findings that are indicative of lower extremity DVT?

Response/Recommendation: The clinical diagnosis of lower extremity deep venous thrombosis (DVT) is nonspecific and individual clinical findings are of limited value in diagnosing DVT.

Strength of Recommendation: Moderate.

Delegates vote: Agree 96.73% Disagree 2.34% Abstain 0.93% (Strong Consensus).

Rationale: Patients with lower extremity DVT may show swelling, cramping, pulling discomfort, warmth, palpable cord, and prominent venous collaterals[928,929]. One meta-analysis estimated the likelihood ratio (LR) of individual clinical features of lower extremity DVT[930]. According to the results of this study, the LR (95% confidence interval [CI]) for each individual sign was as follows. Calf pain: 1.08 (0.96 - 1.20), calf swelling: 1.45 (1.25 - 1.69), difference in calf diameter: 1.80 (1.48 - 2.19), Homan's sign: 1.40 (1.18 - 1.66), warmth: 1.29 (1.07 - 1.54), tenderness: 1.27 (1.11 - 1.45), erythema: 1.30 (1.02 - 1.67), edema: 1.35(1.05 - 1.74)[930]. The meta-analysis concluded that individual clinical features were of limited value in diagnosing DVT[930].

However, structured clinical scoring systems may allow stratification of patients into groups according to their pretest probability of DVT. The most widely used and studied system is the Wells score[931-934], which was developed and validated in the outpatient setting.

The classic Wells score is a 9 point score, giving one point for each clinical presentation (active cancer / paralysis, paresis or recent immobilization of the lower extremities / recently bedridden > 3 days and/or major surgery within 4 weeks / localized tenderness along the distribution of the deep system / thigh and calf swollen / calf swelling > 3 cm compared to the asymptomatic side / pitting oedema / collateral superficial veins / history of DVT) and two negative points if an alternative diagnosis is possible. The Wells score allows patients to be categorized into high (≧ 3 points), moderate (1 - 2 points) and low (< 1 points) risk with a prevalence of DVT of 75%, 17% and 3%, respectively[933]. A dichotomized categorization (high- and low-risk only) was also validated.

One meta-analysis elucidated that a high Wells score was associated with a markedly increased probability of DVT (LR, 5.2), whereas a low Wells score was associated with a markedly reduced probability of DVT (LR, 0.25)[930].

One systematic review reported that the Wells score had median positive LR for patients with high pretest probability being 6.62 (range, 1.9 - 17.6)[935]. For those in the moderate pretest probability category, the median positive LR was 1 (range, 0 - 1.4)[935]. The positive LR for those in the low pretest probability was consistently below 1[935]. These findings suggest that patients classified as having a high pretest probability of DVT have a high likelihood of the disease, those in the moderate pretest category have no increase in the likelihood of the disease, and those with low pretest probability have a low likelihood of having the disease[935].

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38 - Are there any serological biomarkers for the diagnosis of DVT/PE?

Response/Recommendation: There are makers that can be used for detecting the presence of deep venous thrombosis/ pulmonary embolism (DVT/PE). The most commonly used serological biomarker is the D-dimer. However, there are some other markers that are also available such as: PAI-1, SF, FDP, TAT and PF 1 + 2.

Strength of Recommendation: Grade-B. Fair evidence (Level II or III studies with consistent findings) for using serological markers.

Delegates vote: Agree 88.26% Disagree 8.45% Abstain 3.29% (Strong Consensus).

Rationale: DVT and PE together referred to as venous thromboembolism (VTE), are a major contributor to the global burden of disease, with high morbidity and mortality[936]. VTE are associated with serious short- and long-term complications including recurrence, post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension, and death[937]. As an estimated 20% of patients with PE will die on or before the first day after diagnosis, timely diagnosis is critical[938]. Clinical features that are suggestive of DVT (symptoms, signs, clinical risk factors) cannot be used individually to confirm or exclude the diagnosis of VTE. However, when incorporated in the diagnostic work up and individualized pre-test probability of DVT can aid decision-making strategies. The diagnosis of DVT requires a multifaceted approach, based on clinical features, a pre-test probability scoring system (such as the Wells or modified Geneva score), laboratory tests and results of the imaging studies tests (such as compression ultrasound for DVT and computer tomography (CT) or ventilation/ perfusion lung scan for PE)[939]. Our systematic review aimed to find serological markers other than D-dimer in diagnosing DVT/VTE in orthopaedic patients.

D-dimer is the most commonly used serological marker for diagnosing VTE, it's a split product from the cross-linked fibrin clot, but it has low specificity of VTE since many other conditions such as cancer, inflammation, and pregnancy are associated with elevated D-dimer levels. D-dimer has also the important drawback of being affected by anticoagulant treatments[937]. However, a negative D-dimer can be of more value due to its high negative predictive value. The test is mainly used as a rule out screening tool. A patient with a positive D-dimer test, however, would require further investigations to confirm or refute the diagnosis.

Numerous serological markers have been studied for diagnosing VTE. We identified 50 such markers[940-989], out of these Plasminogen activator inhibitor-1 (PAI-1), soluble fibrin (SF), fibrinogen degradation product (FDP), Thrombin antithrombin-III (TAT) complexes, Prothrombin fragment 1 + 2 (PF) 1 + 2 and fibrinogen have been frequently used in patients with orthopaedic conditions. These serological markers can be classified according to the pathophysiology of DVT or thrombotic disease, one is coagulation markers, such as D-dimer, Factor VIII, thrombin generation (TG), and fibrin monomer (FM), while the other is inflammatory markers, including P-selectin, inflammatory cytokines, microparticles (MP) and leukocyte count[990].

PAI-1 is a single chain glycoprotein, which inhibits the plasma fibrinolytic activity. It is a good marker for early diagnosis of DVT/VTE on a postoperative day one after joint replacement surgeries. It has a sensitivity of 78% and specificity of 72% at a cut-off value of 53.5 ng/mL (Normal range 2.5 – 80 ng/mL). The area under the curve (AUC) on a receiver operating curve (ROC) range from 0.79 - 0.84[942,945,950,955,963,977,982].

SF is regarded as an indicator of acute fibrin formation and a precursor of fibrin thrombi. The advantage of measuring soluble fibrin is the considerably longer half-life in the circulation. It is also a marker for early diagnosis with sensitivity ranging from 67.9% - 98.5% and specificity ranging from 38.2% - 80.1% at different cut-off values (Normal range < 7.0 μg/ml). The AUC on a ROC range from 0.67 - 0.73[940,943,945,948,963,969,974,982,983].

FDP are generated when fibrinogen, soluble fibrin, or cross-linked fibrin is lysed by plasmin. It has a sensitivity ranging from 31.3% - 98.6% and a specificity of 68.1% - 74.3. The AUC on a ROC range from 0.61 - 0.71[952,953,963,973,974,977,981,991].

TAT is induced by thrombin and is a sensitive parameter of the latent activator of the clotting pathway. It has a sensitivity ranging from 71% - 79% and a specificity of 27% - 41%. The AUC on a ROC is 0.82[944,945,950,959,960,966,981].

PF 1 + 2 is cleaved from the amino-terminal end of human prothrombin when the zymogen is activated by Factor Xa to yield thrombin. It has a sensitivity ranging from 73% - 86% and specificity of 31% - 44%[944,959-961,966,967,977,989].

Fibrinogen is a soluble protein in the plasma that is broken down to fibrin by the enzyme thrombin to form clots. It has a sensitivity of 62% and specificity of 46% at a cut-off value of 3.2 g/L (Normal range 2.0 – 4.0 g/L). The AUC on a ROC range from 0.42 - 0.59[945,953,954,956,967,970,971,978].

In the diagnosis of acute-phase VTE using Fibrin-related markers (FRM), plasma FDP, D-dimer and SF levels were significantly high in the patients with acute VTE, as previously reported. These findings suggest that FRM are useful for the diagnosis of acute VTE. Meanwhile, both FDP and D-dimer were significantly higher in the patients with chronic VTE than in the patients without VTE, but SF levels were not, suggesting that SF is not useful for diagnosing subclinical VTE. This is because the half-life of SF which has been reported to be within 1 day is not sufficiently long to diagnose subclinical VTE[952,992].

Studies have reported that elevated levels of Factor VIII (above 230 - 250%) are associated with an increased risk of VTE. Additionally, there is evidence that levels are associated with an increased risk of a VTE recurrence. Factor VIII levels are increased as part of the acute phase reaction and higher

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levels are found in individuals with a non-O blood group. Although Factor VIII is a good biomarker of primary and recurrent VTE no interventional trials have been performed to guide clinicians[936].

Newer markers like miRNA's had reported to good have sensitivity and specificity with AUC result 0.959 - 1.00[949]. However, number of studies are less to draw any conclusions on newer markers like granule membrane protein (GMP-140), elastase-derived cross-linked fibrin degradation products (e-XDP), microparticle-tissue factor (MP-TF), urinary PF 1 + 2 and tissue plasminogen activator inhibitor complex (t-PAIC).

The levels of these serological markers may be affected by the chemoprophylactic drug is given to patients for example defibrase can significantly reduce plasma D-dimer levels[993]. rivaroxaban results in a smaller increase in PF 1 + 2 and TAT levels as compared with enoxaparin[943].

Combining these marker values using a mathematical model may provide a better diagnostic tool with good sensitivity and specificity. The cut-off values of these markers may be specified as per the indicated use and timing in the disease process.

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39 - What is the optimal imaging modality for detection of upper and lower extremity DVT for patients undergoing orthopaedic procedures?

Response/Recommendation: The optimal imaging modality for the detection of upper and lower extremity deep venous thrombosis (DVT) is venous compression ultrasonography (CUS). The choice between proximal leg, whole-leg, and serial CUS should be guided by an assessment of clinical pretest probability.

Strength of Recommendation: Strong.

Delegates vote: Agree 97.67% Disagree 1.40% Abstain 0.93% (Strong Consensus).

Rationale: The risk of venous thromboembolism (VTE) in major orthopaedic surgery is among the highest of all surgical specialties (4.3% approximated baseline risk of symptomatic VTE without prophylaxis for total hip or knee arthroplasty, or hip fracture surgery). Consequently, VTE is a major cause of morbidity, mortality, and increased healthcare costs following orthopaedic procedures[994,995]. VTE consists of DVT and pulmonary embolism (PE). The majority of DVT occur in the lower extremities. Prompt diagnosis and initiation of therapy is crucial, since more than 50% of untreated DVT will result in recurrent VTE, clot embolization to the lungs, or post thrombotic syndrome[996]. Importantly, excluding a diagnosis of DVT is essential as anticoagulant treatment entails a risk of fatal bleeding, and thus, is only indicated based on objective diagnosis. In the less likely event of upper extremity DVT, the risk of recurrence, embolization and post thrombotic syndrome are exceedingly rarer compared to DVT of the lower extremity.

The diagnostic approach to suspected DVT is based on an assessment of the clinical pretest probability. Unless the probability is low, imaging techniques are required to establish the diagnosis of lower or upper extremity DVT[997]. There are several imaging modalities available to confirm or exclude a diagnosis of DVT. In the past, contrast venography was considered to be the gold standard diagnostic modality, but the invasive nature and high cost of this test has largely limited its routine use in the diagnostic workup of suspected DVT[997]. Additional limitations include the discomfort for patients, contraindication in patients with severe chronic kidney disease or contrast medium allergy, and failure to cannulate the dorsal foot veins in 5% of patients[998-1000]. Further, inadequate visualization of a venous segment may be encountered in up to 20% of venograms[1001-1004]. Computed tomography (CT) and

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magnetic resonance (MR) venography are alternatives, although they typically also involve injection of contrast media and therefore share similar disadvantages with conventional venography. MR non-contrast thrombus imaging (MR-NCTI) is one imaging modality with the potential to replace venography as second-line diagnostic test[1005,1006]. This technique involves visualizing the acute thrombus, which appears as a high signal due to red cell methemoglobin in the clot, against a suppressed background[1007,1008]. Despite its advantages of being non-invasive and not requiring intravenous contrast agents, this MRI technique has not been sufficiently evaluated and is not routinely available in most centers.

The most common non-invasive imaging modality for suspected DVT is venous compression ultrasonography (CUS)[1009-1011]. For proximal DVT, this diagnostic test has been reported to have a sensitivity and specificity of 97% and 98%, respectively[1012]. This was echoed by a recent meta-analysis that reported a sensitivity and specificity of 90.1% and 98.5%, 94.0% and 97.3%, and 97.9% and 99.8% for proximal leg, whole-leg, and serial CUS, respectively[1013]. Sensitivity and specificity of CUS is substantially lower for diagnosing isolated distal DVT (IDDVT), which is defined as a thrombus involving any vein distal to the popliteal vein at the knee.

The choice between proximal leg and whole-leg CUS should be guided by an assessment of clinical pretest probability. Proximal leg CUS involves scanning the common femoral and the popliteal vein regions, or of all segments of the deep venous system between the groin and the calf trifurcation where the calf veins join the popliteal vein; whole-leg CUS includes additional scanning of the deep calf veins. Failure to fully compress the lumen of the veins with the ultrasound probe is confirmatory of DVT[1014]. A negative proximal CUS excludes a clinically important proximal DVT but does not exclude an IDDVT. As up to 10% of patients with IDDVT will progress to proximal DVT[1015-1017], patients with a high pretest probability and a normal proximal leg CUS should undergo a serial CUS one week later to exclude proximal extension of a distal DVT[1009-1011,1018], and anticoagulation can be safely withheld between serial ultrasounds in standard-risk patients. Although it is tempting to scan the distal veins to reduce the need for serial CUS, it is important to acknowledge the limitations of whole-leg CUS. First, it is more technically challenging compared to proximal leg CUS, and there is greater risk of false positives[1019,1020]. Second, whole-leg CUS is also more complex and takes additional time, whereas proximal leg CUS takes only a few minutes[1021]. Lastly, most institutions do not routinely perform whole-leg CUS. Furthermore, a true positive IDDVT found on whole-leg CUS has unclear significance, since over 90% of patients with IDDVT will not progress to proximal DVT or PE[1015-1017]. In higher-risk patients (e.g., thrombus in close proximity to deep venous system, extensive thrombus, history of VTE, malignancy etc.), anticoagulation is recommended over observation for IDDVT[1020]. Therefore, whole-leg CUS may be preferred over serial proximal CUS. D-dimer measurement is of limited value as elevated levels are non-specific for DVT and can be expected in all patients after orthopaedic surgery. A negative result would exclude the diagnosis of a DVT including IDDVT, but a "false negative" result due to heparin thromboprophylaxis needs to be considered particularly with the use of less sensitive assays[1016].

Upper extremity DVT (UEDVT) is a rare presentation of VTE, accounting for only 5 – 10% of venous thromboses[1022,1023]. Similar to lower extremity DVT, the imaging test of choice is CUS[1009-1011]. Notwithstanding, diagnosing UEDVT with CUS is more complex in the upper extremities due to the anatomy, particularly in the axillary and clavicular region where veins are difficult to compress. Consequently, CUS is often used together with doppler ultrasonography to evaluate a suspected UEDVT. Contrast venography is limited by the same shortcomings as stated above. Moreover, due to the infrequent use of venography, radiologists may have a limited experience diagnosing UEDVT using this imaging modality[1024]. CT venography and MR-NCTI are alternatives, although studies assessing its diagnostic accuracy in UEDVT are scarce[1006,1025].

As the signs and symptoms of DVT are non-specific, the diagnosis is only confirmed in less than 20% of patients investigated for suspected cases[1026]. Multiple imaging tools are available to assist in confirming a diagnosis, although clinicians should always consider the diagnostic accuracy, costs and potential adverse effects when selecting the optimal modality. As it is unnecessary to perform imaging in all patients in whom DVT is suspected, established diagnostic algorithms including an assessment of clinical pretest probability and D-dimer testing should be followed[1009-1011]. Further investigation for the optimal clinical prediction rules, D-dimer strategies, and imaging-first approaches in the setting of orthopaedic procedures is necessary.

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40 - Is there a role for lower extremity venograms for the diagnosis of lower extremity DVT?

Response/Recommendation 1: The use of lower extremity venograms for routine diagnosis of lower extremity deep venous thrombosis (DVT) is not recommended. For patients with suspicion of lower leg DVT requiring imaging, venous ultrasound (VUS) is recommended as the first diagnostic modality.

Strength of Recommendation: Strong.

Response/Recommendation 2: In patients with suspicion of iliac or vena cava thrombosis, as well as inconclusive or impossible to perform VUS, computer tomography venography (CTV) or magnetic resonance venography (MRV) should be performed, based on availability and center experience.

Strength of Recommendation: Moderate.

Response/Recommendation 3: In the patients with strong suspicion for lower extremity DVT and inconclusive or impossible to perform VUS, examination of the veins below the inguinal ligament should be done with CTV, MRV or contrast phlebography.

Strength of Recommendation: Moderate.

Response/Recommendation 4: In clinical trials with a study endpoint including the presence of lower leg asymptomatic DVT, the use of contrast venography may be performed as these are required by the regulatory bodies.

Strength of Recommendation: Moderate.

Delegates vote: Agree 99.07% Disagree 0.47% Abstain 0.47% (Strong Consensus).

Rationale: In the current DVT diagnostic algorithm, the initial imaging method of patients with high clinical suspicion for lower leg DVT remains the VUS[1027-1029]. High accuracy of the sonographic examination-based strategy was confirmed in several studies and meta-analyses as well as emphasized in several guideline documents[1027-1036].

Historically, traditional contrast venography, based on direct lower leg intravenous contrast injection, was used as the first objective imaging modality and for many years had been considered the "gold standard" for diagnosis of DVT[1037,1038]. Before the modern VUS era, due to limitations concerning other available diagnostic methods, including plethysmography, thermography, continuous wave Doppler examination or isotopic studies, phlebography became another standard

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diagnostic imaging method to confirm DVT[1039-1044]. The rates of diagnosed DVT by bilateral venography in orthopaedic surgery studies became the reference values for further research on DVT prophylaxis efficacy in orthopaedic surgery. Chen et at., reported a 21.9% DVT incidence (with proximal DVT rate - 4%) after arthroscopic posterior cruciate ligament reconstruction[1045]. In a study by Kim et al., 26% of the bilateral venograms turned out to be positive for DVT in patients after total hip arthroplasty (THA)[1046]. Clarke et al., in a venography-based study dedicated to hip and knee arthroplasty patients not receiving thromboprophylaxis, found a 32% DVT rate after THA (proximal DVT - 16%) and 66% DVT rate after total knee replacement (TKA) (proximal DVT - 16%)[1047]. A systematic review of the prospective clinical studies on DVT prevalence, with the use of contrast venography, in patients undergoing elective hip or knee surgery documented the presence of DVT in the operated leg in 16.7% of THA patients and in 33.8% of TKA patients. At the same time, DVT presence in the contralateral leg was noted in 4 - 5% of the cases[1048].

Contrast phlebography, together with venous thromboembolism (VTE) symptom evaluation, became another standard efficacy outcome evaluation method in a number of clinical trials including thromboprophylaxis trials in major orthopaedic surgery, as well as other specialties[1049-1052]. The common use of contrast venography in VTE prophylaxis trials reflects not only its accuracy in diagnosing DVT in the symptomatic patients, but also the possibility of diagnosing the presence of asymptomatic DVT[1053,1054].

In contrast to diagnosis oriented on the symptomatic leg, implementation of bilateral phlebography allows one to evaluate the presence of asymptomatic thrombosis in both extremities. Besides high sensitivity, including in the diagnosis of asymptomatic DVT cases, the advantages of direct contrast venography include the possibility of visualizing calf vein DVT as well as non-occlusive thrombotic changes[1055-1059].

Several studies, using contrast venography as the reference method, confirmed the efficacy of VUS in the diagnosis of DVT. However, the reported high sensitivity of the VUS shown in the femoro-popliteal segment, decreases in below the knee veins[1060-1064]. It should be mentioned that the presence of symptomatic as well as asymptomatic DVT, including below the knee and non-occlusive DVT, frequently became the endpoint for clinical trials, especially in trials dedicated to VTE prophylaxis. Barnes et al., in a study based on combined B-mode/duplex Doppler scanning and venography compared the results of routine postoperative screening for DVT in 158 THA patients. With a 12% incidence of proximal DVT (and total DVT rate of 30% including calf vein DVT), the duplex scan had a sensitivity of 79%, specificity of 98%, and accuracy of 97%, in relation to venography as the reference method[1065].

Despite the fact that phlebography was considered to be the "gold standard" for diagnosis of DVT, the possibility of inadequate results (evaluation) when using this technique remains significant, reaching as high as 6 - 20%[1066-1069]. Important points of concern include limited intra- and inter-observer agreement on venography results, as well as the lack of proper filling of the entire lower leg venous system (especially when injecting contrast into the foot vein for proximal deep vein segment visualization)[1069-1075].

The technical progress of the ultrasound (US) technology as well as an improvement in diagnostic protocols based on compression US as well as duplex Doppler examination increased sensitivity and specificity of the sonographic examination in DVT diagnosis. Simultaneously, the invasiveness of phlebography related to the contrast injection as well as significant exposure to radiation, together with an improvement in the alternative methods nowadays limits the use of phlebography in daily practice. Beside the adverse effects related to phlebography performance, potential contraindications should also be mentioned, including contrast allergies as well as potential for renal impairment[1076-1078].

Taking into account the clinical practice as well as method limitations, standard venography is now rarely used in daily clinical practice and its practical implementation in DVT patient management concerns mostly patients undergoing acute DVT catheter-directed thrombolysis or endovascular revascularization as well as chronic post-thrombotic venous obstruction treatment. In cases of proximal (including iliac) venous thrombosis suspicion and non-conclusive results of the US examination, CTV or MRV imaging is currently preferred to contrast phlebography[1079]. The use of bilateral direct contrast venography remains an interesting option in clinical trials evaluating symptomatic and asymptomatic lower leg DVT.

CTV is efficacious in the diagnosis of proximal lower leg DVT[1080]. CTV also more clearly demonstrates thrombus extension into the veins above the inguinal ligament or inferior vena cava than conventional contrast venography[1081,1082]. The costs of CTV examination, as well as its availability together with the invasiveness of the CTV study (contrast injection, radiation exposure) limit its use as a diagnostic measure to cases with diagnostic problems as well as inconclusive results of previous imaging studies, especially if proximal DVT is suspected. The use of CTV as the screening method for lower leg DVT in clinical studies on thromboprophylaxis is still rather rare[1083].

An important clinical subject related to CTV as a diagnostic method is the possibility of simultaneous lower leg CTV performance in patients undergoing computer tomography pulmonary artery angiography (CTPAA) because of pulmonary embolism (PE) suspicion. As suggested in several studies dedicated to this topic, CTV simultaneously performed with CTPAA offers limited value for detecting DVT and should not be performed as a routine screening test[1084].

Looking for less invasive and simplified diagnostic options of the venous system in patients with suspected PE undergoing CTPAA, the use of lower leg sonographic examination instead of the CTV was also proposed. In the Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) study, CTV performed after CTPAA showed that lower extremity imaging detects about 7% more patients requiring anticoagulation than CTPAA alone[1085]. In 711

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patients of the same study (PIOPED II) the accuracy of the CTV was compared with compression US. According to results, there was 95.5% concordance between CTV and sonography for DVT diagnosis or exclusion and the sensitivity and specificity of combined computed tomographic angiography (CTA) and CTV were equivalent to those of combined CTA and sonography[1085].

Despite promising results, the role of MRV in lower leg DVT diagnosis is still under evaluation. According to a meta-analysis, similar sensitivity and specificity of MRV and VUS is suggested (especially in the femoro-popliteal segment)[1086]. Due to the heterogenicity of the studies, as well as differences in magnetic resonance imaging (MRI) diagnostic protocols, the promising results of the available studies have to be repeated and confirmed in a large number of patients and diagnostic centers. Another option is an identification of DVT by means of direct thrombus imaging[1087]. MRI can also be used to assess the characteristic of the thrombosis to help differentiate between acute, subacute and chronic changes[1088]. Due to the costs as well as method availability, there is for now no argument supporting the replacement of US with MRV as a first line imagining modality in the patients with DVT suspicion. As an alternative diagnostic tool, MRV can be considered for patients in whom venous US is not possible to perform or the results are inconclusive[1089]. Similar to CTV, one of the important advantages of the MRV study is the potential for pelvic vein or retroperitoneal vein visualization, which is not always correctly seen and assessed in the VUS examination.

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41 - What is the most optimal imaging modality for diagnosis of pulmonary embolus (PE) following orthopaedic surgery?

Response/Recommendation: Advances in imaging have resulted in an increased ability to visualize emboli in the lungs, some of which may be clinically non-significant and may even not be a true pulmonary embolism (PE). The "gold standard" for diagnosis of PE is still the computer tomography pulmonary angiography (CTPA).

Strength of Recommendation: Strong.

Delegates vote: Agree 99.07% Disagree 0.00% Abstain 0.93% (Strong Consensus).

Rationale: The risk of deep venous thrombosis (DVT) and PE in patients undergoing surgery is well established. In the context of orthopaedic surgery, patients undergoing elective total hip/knee replacement are considered at highest risk for developing venous thromboembolism (VTE). Manifestation of VTE in these patients includes DVT and subsequent PE that can be fatal. Prior to rapid post-operative patient mobilization, some historical estimates have put the incidence of DVT without prophylaxis to be between 40% and 84% after total knee arthroplasty (TKA), and around 39% - 74% for patients undergoing total hip arthroplasty (THA)[1090]. Over the years, comprehensive guidelines on venous thromboembolism prevention have been established. These include measures such as prevention with effective preoperative and postoperative

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anticoagulation, to more conservative measures like early and aggressive postoperative mobilization, pneumatic compression stockings, and tools to identify high risk patients[1091]. Despite this, the National Institute of Health (NIH) projects that the number of patients needing joint arthroplasty and consequently the number of thromboembolic complications is on the rise[1092].

In the past, the gold standard for the diagnosis of suspected PE was the two-dimensional ventilation-perfusion (V/Q) scan. Sostman et al.[1093], estimated the sensitivity and specificity of a V/Q scan, when used to diagnose PE, to be around 77.4% and 97.7%, respectively. However, the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) I clinical trials showed that V/Q imaging reported an uncertain likelihood for PE in 65% of confirmed PE cases, indicating that a V/Q scan could not make a reliable diagnosis[1094]. Parvizi et al.[1095], showed that over their study period of five years, the incidence of PE rose from 0.21% when using V/Q scans to 0.98% with spiral CT and peaked at 1.72% with the introduction of multidetector CT. Newer techniques like the multidetector-row CTPA proved to be more sensitive for detecting PE. CTPA has also been shown to have exceptionally high specificity for diagnosing PE. The PIOPED II trial estimated that CTPA had a sensitivity of 83% and specificity of 96%, respectively[1096]. Despite only being introduced in 1998, by 2006 several institutions documented a 7- to 13-fold increase in the utilization of CTPA[1097-1100]. It is now considered the gold standard for the diagnosis of PE. Parvizi et al.[1095], also suggested that more advanced imaging techniques, like CTPA, have led to an increase in incidence of non-clinically significant PE. In other words, they have caused a rise in detection of abnormalities that are not harmful and cause no increase in morbidity or mortality. Previous investigators have examined trends in incidence of PE before and after the introduction of CTPA. An 81% increase in incidence of PE was noted with no significant increase in mortality. Furthermore, there was a 71% increase in complications secondary to anticoagulation[1101]. Overdiagnosis of PE resulting in unnecessary harm to patients who are anticoagulated for non-clinically significant PE is an important clinical issue. Ranji et al., reported that 25.4% of their patients had false positive CTPA findings and were subsequently treated with anticoagulants[1102]. Another benefit is that CTPA can identify the location of the emboli within pulmonary arteries. Some studies have shown that the size and location (central vs. segmental or subsegmental) of clots correlate with clinical severity. Auer et al.[1097], stated that patients with central PE were more likely to require intensive care unit (ICU) admission and had higher 30-day mortality rates. Additionally, the authors of a different study proposed that subsegmental emboli are non-clinically significant even when they are left untreated[1103]. However, Valle et al., found that there is no association between PE location and clinical severity (calculated by employing the PE Severity Index)[1104].

Outcomes in patients with VTE have significantly improved over the last two decades. Despite a recent rise in incidence of DVT and PE following orthopaedic procedures, recent studies have shown that morbidity and mortality secondary to these disorders is at an all-time low[1095]. This is due to the established international guidelines on preoperative optimization and risk stratification of patients undergoing surgery[1105]. Additionally, our ability to effectively diagnose patients with PE has substantially increased since the worldwide incorporation of the CT scan. We now know that once commonly used imaging modalities, such as V/Q scans, are not as reliable as previously believed. With constant developments in medical imaging, we must ensure judicious use of advanced imaging. Currently, CTPA appears to be the most accurate and effective imaging modality for the diagnosis of suspected PE. Given the risks posed to patients receiving anticoagulation with clinically non-significant emboli, we recommend the prudent use of CTPA only in patients with high clinical suspicion or high pretest probability of pulmonary embolus.

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42 - Do pulmonary arterial filling defects seen on cross-sectional imaging of the lung always represent a pulmonary embolism (PE)?

Response/Recommendation: Pulmonary arterial filling defects seen on cross-sectional imaging studies are not always indicative of pulmonary embolism (PE). There are several other conditions that can lead to arterial filling defects on cross-sectional imaging studies such as primary pulmonary arterial (PA) neoplasm, pulmonary vascular involvement of IgG4-related disease (IgG4-RD), Behcet's disease, Takayasu's arteritis (TA), Hughes–Stovin syndrome (HSS), and pulmonary arterial streak artifact.

Strength of Recommendation: Strong.

Delegates vote: Agree 90.95% Disagree 0.48% Abstain 8.57% (Strong Consensus).

Rationale: The most common cause of PA filling defects on either computed tomography pulmonary angiography (CTPA) or magnetic resonance imaging (MRI) is pulmonary thromboembolism. However, not infrequently, the presentation of this finding is not associated with a PE. Given high rates of morbidity and mortality, timely diagnosis is essential. Unusual or more rarely encountered etiologies must be considered when clinical manifestations and imaging findings are not consistent.

CTPA and MRI studies have become the primary methods for diagnosing PE, largely replacing the previous method of choice, pulmonary angiography or ventilation–perfusion V/Q scans. They are less invasive, faster, and less expensive[1106,1107]. A Pulmonary arterial filling defect is the major finding on CTPA that can be indicative of PE, with a reported sensitivity of 83 – 91% and a specificity of 89 – 96%[1108,1109]. However, there are other clinical conditions that may present with similar findings on CTPA (intraluminal filling defect), mimicking PE, and can lead to inappropriate diagnosis and possibly inappropriate intervention. Some of the conditions that may cause filling defects include primary pulmonary arterial neoplasm, pulmonary vascular involvement of IgG4-RD, Behcet's disease, TA, HSS, and pulmonary arterial streak artifact.

PE is the third most common cardiovascular condition with high mortality and morbidity rate after coronary artery disease and stroke[1109]. Fresh thrombus in acute PE is formed by red blood cells (RBC) and platelets binding together in a fibrin mesh, this presents on CTPA as a filling defect leading to complete or partial stenosis of the lumen.

Primary pulmonary arterial neoplasms: This is a very uncommon condition. The pathology in the majority of cases is pulmonary artery sarcoma (PAS), which has poor prognosis. On CTPA, PAS also manifests as a filling defect that resembles an acute PE. There are specific findings on CTPA that can help differentiate PAS from PE, including a filling defect involving the entire main PA or one of its principal branches, the proximal margin of the filling defect with the "lobulated sign" and the grape-like appearance of the distal PA, and a filling defect with heterogeneous enhancement[1110]. A magnetic resonance angiogram can be very helpful when there is suspicion for PAS.

IgG4-RD of PA: This is an autoimmune condition that results from chronic fibrotic inflammation. The main findings of PA IgG4-RD include massive filling defects without enhancement or PA aneurysm on CTPA. Definite diagnosis of PA IgG4-RD is only possible with an intrathoracic surgical biopsy[1111,1112].

Takayasu's arteritis (TA): TA is an idiopathic inflammatory disease that affects large vessels such as the aorta and PA. Studies reported PA involvement in approximately 63.3% of cases[1113]. When there is isolated PA involvement, vessel stenosis or complete occlusion of PA mimics PE[1114,1115]. One way to distinguish TA from PE is that on post-enhanced CTPA images, a "double-ring sign" can be seen in TA patients, which is resulted from arterial mural thickening[1114]. MRI is the alternate imaging modality that can help differentiate TA from PE.

Behcet's disease: Behcet's disease is an idiopathic syndrome characterized by vasculitis and recurrent ulcers of the oral and genital mucosa, with relapsing uveitis[1116]. Vascular involvement can be seen in 5 – 30% of cases[1117]. Aneurysms are the most common finding when there is vascular involvement. PA aneurysm is the most common finding (in up to 10% of cases) and tends to be multiple and bilateral[1118]. The pulmonary thrombosis of the aneurysm forms an in situ partial or complete filling defect that resembles PE.

Hughes-Stovin syndrome (HSS): HSS is a rare disorder with an unknown etiology[1119]. It is characterized by multiple PA and/or bronchial artery aneurysms as well as deep venous thrombosis, however, unlike Behcet's disease, it does not have mucocutaneous involvements[1120]. PA filling defects can be seen in the CTPA of patients with HSS and should be differentiated from PE events.

Pulmonary arterial streak artifact: Chronic lung diseases such as tuberculosis, interstitial lung disease, and bronchiectasis as well as conditions like pulmonary vein stenosis, systemic artery-PA shunt, and pulmonary hypertension can affect the hemodynamics of the PA and cause "streak artifact," which could mimic a PA filling defect. It is important to take patients' past medical history into consideration when interpreting CTPA results. Using a dual-phase scan protocol, a filling defect in early phase contrast-enhanced imaging, which resolves in the late phase, strongly suggests a pulmonary arterial streak artifact rather than a PE event.

CTPA and MRI studies are reliable tools for diagnosing PE events with a high accuracy[1108]. However, false-positive and false negatives are not uncommon. The presence of a filling defect is not always indicative of PE and other diagnostic tests, as well as past medical history, are necessary to confirm the diagnosis especially when there is a concern for one of the aforementioned conditions.

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43 - Do all emboli detected on cross-sectional imaging of the lung lead to the same degree of oxygenation compromise (hypoxia)?

Response/Recommendation: While current evidence suggests that not all emboli detected on cross-sectional imaging of the lung result in the same degree of hypoxia, evidence is conflicting regarding the association between emboli size and location to the degree of patient hypoxia. Providers should continue to risk stratify patients with acute pulmonary embolism (PE) by hemodynamic status and right ventricular dysfunction in accordance with the European Society of Cardiology (ESC) 2019 and the American Society of Hematology (ASH) 2020 guidelines for management of venous thromboembolism (VTE).

Strength of Recommendation: Limited.

Delegates vote: Agree 92.20% Disagree 0.98% Abstain 6.83% (Strong Consensus).

Rationale: Acute PE represents a common and potentially life-threatening medical problem for many patients worldwide[1121]. Current guidelines the ESC 2019, and the ASH 2020 for management of VTE recommend risk stratification for patients with PE based on hemodynamic status, right ventricular dysfunction, and certain laboratory markers[1122,1123]. Nevertheless, the popularity of computed tomography pulmonary angiography (CTPA) as the first line diagnostic test for PE has led to an increasing body of research attempting to correlate emboli characteristics seen on imaging to patient outcomes and prognosis[1124,1125].

A large body of literature has described the correlation between increasing hypoxia – clinically described as partial pressure of oxygen (PaO_2), percent saturation of oxygen (SpO_2), alveolar-arterial (AA) oxygen gradient – and worsening outcomes following PE, despite these measures having low sensitivity for diagnosis[1126-1130]. In established prognostic tools, such as the Pulmonary Embolism Severity Index (PESI), decreased PaO_2 upon initial presentation is a predictor for higher 30-day mortality after acute PE[1131,1132]. It has been described extensively that hypoxemia from acute PE results from ventilation/perfusion mismatch from redistribution of pulmonary blood flow, while minor contributors to hypoxemia include right ventricular failure, loss of pulmonary surfactant, and release of vasoconstrictive substances from nearby emboli[1129,1130,1133,1134].

Many studies have attempted to correlate pulmonary embolus characteristics to clinical hypoxia parameters, given the latter's correlation with mortality following PE. Most research utilizes validated "clot scoring" indices, such as the validated Qanadli score, which requires a specialist radiologist to incorporate imaging findings of clot size and location to create an "obstructive index" score[1135]. Of note, while findings are mixed as to whether embolus obstructive index is an independent predictor of PE mortality, many studies, including a 2013 meta-analysis, show no correlation between embolus obstructive index and mortality[1133,1135-1143].

A few recent retrospective studies found that an increasing pulmonary artery obstructive index (PAOI) on initial CTPA was associated with increasing AA gradients, worsening PaO_2, lower SpO_2, and lower partial pressure of carbon dioxide ($PaCO_2$)[1134-1147]. Other studies, however, did not come to the same conclusions. In three other recent retrospective studies, Lerche et al., and Rodrigues et al., found no association between the clot burden or obstructive index and PaO_2 values, while another study by Nakada et al., found no association between embolus volume and PaO_2[1148-1150].

Further research has attempted to understand the association between the location of the embolus and patient oxygenation measures. While two recent studies found that central and proximal emboli were associated with lower PaO_2 and higher AA gradients in patients compared to distal and peripheral emboli, another study found no correlation between thrombus vessel location and oxygenation parameters[1151-1153]. Interestingly, Pulido et al., in a study of 13,133 patients, found no correlation between size and location of pulmonary emboli with severity of hypoxia[1154]. The mixed results from these studies reinforce the notion that while not all emboli appear to result in the same degree of hypoxia, the association is not well understood. More prospective studies and meta-analyses are needed before further conclusions can be drawn.

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44 - Is there an association between pulmonary embolus and secondary pulmonary hypertension after major orthopaedic surgery?

Response/Recommendation: Chronic thromboembolic pulmonary hypertension (CTEPH) is strongly associated with prior pulmonary embolism (PE); however, this association has not been adequately explored following major orthopaedic surgeries. Given that PE is a known complication following orthopaedic surgery and incidence of CTEPH after PE is

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between 0.1% and 9.1%, evaluation for CTEPH after post-surgical PE should be considered to allow for early treatment, particularly pulmonary endarterectomy (PEA), and to prevent downstream sequelae and mortality.

Strength of Recommendation: Limited.

Delegates vote: Agree 88.78% Disagree 2.93% Abstain 8.29% (Strong Consensus).

Rationale: Major orthopaedic surgeries carry a high risk for venous thromboembolism (VTE) including deep venous thrombosis (DVT) and PE[1155]. Estimates suggest that in the contemporary era about 4.7% of patients undergoing major orthopaedic surgery will develop symptomatic VTE without prophylaxis[1156]. The major orthopaedic surgeries with the greatest risk for VTE include total knee arthroplasty (TKA), total hip arthroplasty (THA), and hip fracture surgery. The risk of VTE is highest in the first 2 weeks postoperatively but may extend for 3 months postoperatively, as with other major surgeries[1157].

Acute PE, an obstruction of a pulmonary artery or its branches by an embolic or in-situ thrombus, is potentially life-threatening and can result in chronic complications with generally poor prognosis[1157]. The presumed relationship between DVT (particularly proximal DVT) and PE, has resulted in thrombo-prophylaxis becoming standard of care after major orthopaedic surgeries[1158]. Long-term consequences associated with PE include recurrent VTE, post-thrombotic syndrome, and CTEPH[1159-1161].

CTEPH is an uncommon late complication of PE in patients who do not reestablish normal pulmonary artery perfusion and can present with disabling dyspnea, both at rest and with exertion[1162]. CTEPH can be occur after single or recurrent symptomatic PE or as a complication of asymptomatic PE[1163]. After 3 months of appropriate anticoagulation, the diagnosis can be made if the following criteria are met: 1) mismatched perfusion defects on ventilation/perfusion scan or specific radiologic signs for CTEPH on computer tomography (CT)-angiography, and 2) mean pulmonary artery pressure (PAP) > 25mmHg with pulmonary capillary wedge pressure (PAWP) $\leq$ 15mmHg on pulmonary angiogram. CTEPH is clinically classified within group 4 pulmonary hypertension (PH) and pathologically distinguished by pulmonary arterial obstruction from organized fibrotic thrombus, development of small vessel disease, and resultant aberrant vascular remodeling[1164,1165].

There is significant evidence supporting the specific link between VTE and CTEPH. The reported cumulative incidence of CTEPH ranges from 0.1% - 9.1%, within the first 2 years after a symptomatic PE event[1166-1169]. A large European multi-center retrospective cohort study reported history of VTE in almost 70% of patients with CTEPH compared to only 11% of patients with nonthromboembolic PH[1170]. Another large case-control study through the CTEPH registry reported an even stronger relationship, with risk of CTEPH being higher in those with clinical history of VTE compared to those history of VTE (odds ratio [OR] 49.01; $p < 0.0001$)[1171]. However, none of these studies included large numbers of post-surgical or trauma patients. Discrepancies in reported incidence of CTEPH are attributable to nonspecific or absent symptoms in early CTEPH leading to delayed or missed diagnoses (median time from symptom onset to diagnosis is 14 months), difficulty discriminating acute PE symptoms from pre-existing CTEPH, underutilization of guideline recommended ventilation-perfusion scans for screening, and different standards of practice across countries and regions[1172]. The Osiris Survey is one tool currently in development to predict risk of developing CTEPH. In a large, longitudinal, prospective cohort study of 1,191 consecutive PE patients in Spanish hospitals, test sensitivity was 85% (95% confidence interval [CI]: 67.5 - 94), specificity was 91% (95% CI: 89 - 93), and negative predictive value was 99.4% (95% CI: 98.4 - 99.8); however, further study and survey validation are still needed[1173].

Several patient, disease, and treatment-related risk factors for development of CTEPH have been identified. Large, persistent, idiopathic, and particularly recurrent PE, as well as larger perfusion defects, are all strongly associated with CTEPH[1159,1163,1170,1174]. Residual pulmonary vascular obstruction at six months after the initial PE was an independent risk factor for both recurrent VTE and CTEPH[1175]. Other potential risk factors reported include ongoing thyroid replacement therapy, age greater than 60, underlying malignancy, and inflammatory or infections conditions including osteomyelitis and inflammatory bowel disease[1159,1170,1174,1176]. Traditional risk factors for VTE, such as estrogen therapy or older age, have not been associated with CTEPH[1160]. Reports on the association of CTEPH with underlying thrombophilia have been mixed[1177]. Additionally, multiple studies have reported that subtherapeutic anticoagulation was not a risk factor for CTEPH; however, the focus of anticoagulation in these studies were vitamin K antagonists and newer anticoagulants have not been significantly studied[1178,1179].

The natural progression of CTEPH is right heart failure, with reduced life expectancy and increased risk of sudden cardiac death[1167,1172]. One study reported annual mortality of 6.0%[1180]. Early identification of CTEPH is critical as it is the only subgroup of PH that can potentially be surgically cured through PEA[1181]. Another study found considerable delay (median of 21 months) in diagnosis of CTEPH after acute PE, and that recurrent VTE was a predictor of longer delay which has detrimental effect on patient prognosis and healthcare utilization[1182]. Nonsurgical candidates are considered for PH-targeted medical therapies. However, high healthcare utilization has been reported in these patients as well, with costs largely attributed to expensive PH-targeted medications[1180]. Lifelong anticoagulation is recommended in all CTEPH patients, regardless of whether PEA is performed, to prevent recurrent PE[1172].

In conclusion, this review reported on CTEPH as an underrecognized late complication of PE occurring within 2 years of the initial diagnosis. While prevention of recurrent PE through initial and long-term anticoagulation are important, we did not find any evidence of association between type or duration of anticoagulation and incidence of CTEPH. We did not find any evidence for a specific link between major orthopaedic surgery and CTEPH. However, there are active

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registries and an ongoing prospective longitudinal clinical trial using "The United States Chronic Thromboembolic Pulmonary Hypertension Registry: Protocol for a Prospective, Longitudinal Study" that may shed more light on these issues in the coming years and may provide the necessary information to perform a formal decision analysis to assist in orthopaedic decision-making in the future[1183].

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45 - Is administration of any venous thromboembolism (VTE) prophylaxis effective in reducing the risk of fatal pulmonary embolism (PE)?

Response/Recommendation: There is no evidence that venous thromboembolism (VTE) prophylaxis reduces the risk of fatal pulmonary embolism (PE) in elective orthopaedic procedures, including lower limb joint replacement. In patients with a hip fracture, there is limited evidence that aspirin (ASA) may reduce fatal PE, but the strength of evidence does not support a recommendation.

Strength of Recommendation: Limited.

Delegates vote: Agree 91.13% Disagree 5.42% Abstain 3.45% (Strong Consensus).

Rationale: Preventing fatal PE remains a priority for both physicians and patients[1184]. The American Academy of Orthopaedic Surgeons (AAOS), the American College of Chest

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Physicians (ACCP) and the National Institute for Health and Care Excellence (NICE) have produced evidence-based clinical guidelines that aim to reduce VTE in orthopaedic patients[1185-1187]. All three documents use "reducing the rate of fatal PE" as a critical outcome. Despite this, controversy remains as to whether VTE prophylaxis is effective in reducing the risk of fatal PE.

A systematic literature review was performed; the methodology and search results are shown in the Appendix. Studies were included in this recommendation if they compared any method of VTE chemoprophylaxis with a control; a control could include mechanical VTE prophylaxis. Nineteen studies met the inclusion criteria with most focusing on total hip arthroplasty (THA) and total knee arthroplasty (TKA)[1188-1206].

The Pulmonary Embolism Prevention (PEP) trial was a large international multicenter, double-blinded, randomized control trial assessing ASA vs. placebo for VTE prophylaxis in hip fracture patients and elective THA and TKA surgery[1188]. In 13,356 hip fracture patients, ASA use was found to reduce the number of fatal PE by 58% (27 - 76; p = 0.002). There were 3 fatal PE in the 4,088 arthroplasty patients enrolled in the study, 1 in the ASA group and 2 in the placebo group (hazard ratio 0.5 [0.04 - 5.49]). The key limitation of this study is that 44% of the hip fracture patients and 37% of the arthroplasty patients also received either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) in both groups. Thus, diminishing the validity of the results of assessing the benefit of ASA compared with the placebo.

Three meta-analyses studied the rate of fatal PE in relation to VTE prophylaxis following total joint arthroplasty (TJA)[1189-1191]. Poultsides et al., identified 70 studies which encompassed 99,441 THA or TKA patients[1189]. There was no statistically significant difference in rates of fatal PE between any prophylactic regimens when compared with, "no routine chemoprophylaxis." Murray et al., included 93,000 THA patients and found no statistical difference in the rate of fatal PE between patients who received no VTE prophylaxis and those who received a chemoprophylaxis agent[1190]. This meta-analysis uses data from 1970s – 1990s and may therefore not be representative of current practice. Both studies are limited by the heterogeneity of the data and rely on the original authors' cause of death description to identify fatal PE, rather than autopsy proven events. Tasker et. al., assessed LMWH vs. placebo following THA, but with only 2 fatal PE seen in a total of 1,847 patients they were unable to statistically assess any relationship[1191].

Three retrospective reviews of prospective arthroplasty registries met the inclusion criteria[1192-1194]. In a regional UK arthroplasty registry, that included 1,893 patients who had undergone THA[1192], there was no statistically significant difference in the rate of fatal PE between patients who had received chemical thromboprophylaxis (0.24%, [0.05 - 0.71]) and patients who had not (0.15%, [0.00 - 0.84]) (p = 0.56). Khatod et al., reviewed two separate US joint registries between 2001 and 2008[1193,1194]. The control group used for the purpose of this recommendation was "mechanical prophylaxis only". From the Kaiser Permanente Joint Replacement Registry, in 17,595 patients who had undergone THA[1193], there was only 1 confirmed fatal PE, with 44 possible fatal PE using a worst-case scenario analysis. There was no significant difference between the control and any mode of chemical thromboprophylaxis for confirmed fatal PE (p = 0.757) or worst-case-scenario analysis (p = 0.712). Using the Total Joint Replacement Registry (TJRR) in 30,020 patients who had undergone a TKA[1194], 3 confirmed fatal PE occurred; in worst-case scenario analysis this gave a fatal PE rate of 0.13% (0.09% - 0.17%). There was no significant difference between the control and any thromboprophylaxis group for confirmed fatal PE or worst-case scenario fatal PE (p = 0.954). Limitations of all three registry studies include: potential for coding errors, possible under reporting of complications, risk of bias and difficulty ascertaining precise cause of death.

A further 5 randomized control trials (RCT) and 2 cohort studies looking at TJA met the inclusion criteria[1195-1201]. Across these 7 studies comparing different thromboprophylactic agents (LMWH, UFH, warfarin, antiplatelet agents) with a control group, 6 fatal PE were reported from a combined total of 6,187 patients. Due to the low number of fatal PE observed in these studies, none of the authors could determine the relationship between VTE prophylaxis and fatal PE.

The incidence of fatal PE is also low in other orthopaedic sub-specialties and therefore the strength of evidence regarding the role of VTE prophylaxis in reducing the risk of fatal PE is limited. A Cochrane review of LMWH, rivaroxaban and ASA compared with a control, "no intervention," in patients undergoing knee arthroscopy found no incidences of fatal PE in any of the 3,818 participants in any group[1202]. Hickey et. al., performed a systematic review and meta-analysis of patients treated with a below knee cast for foot and ankle trauma[1203]. In 6 studies, comparing LMWH to a control group which received no thromboprophylaxis, encompassing 914 patients receiving thromboprophylaxis and 901 patients in the control group, there were no incidences of fatal PE. A Cochrane review of LMWH vs. no thromboprophylaxis in patients being treated with a lower limb immobilization device (either plaster or brace) found no deaths due to PE in 3,111 participants included from 7 studies[1204]. A RCT by Selby et al., compared dalteparin to a placebo in lower leg fractures and found no fatal PE in either group[1205]. In a meta-analysis of VTE prophylaxis in elective spinal procedures there was 1 episode of fatal PE in 4,383 patients[1206].

In summary, there is no evidence that VTE prophylaxis is effective in reducing the risk of fatal PE in elective orthopaedic procedurs. Based on the current incidence of fatal PE in TJA, it is reported that a RCT with an 80% power would require over 67,000 patients to demonstrate a statistically significant change if fatal PE were to be the primary end point[1192,1207]. Even the current evidence from large joint registries falls short of this number; thus, the available evidence to answer this important clinical question is limited. In patients with a hip fracture, there is limited evidence that ASA may reduce fatal PE, but the strength of evidence does not support a recommendation.

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46 - What endpoint should be used to determine the efficacy of a venous thromboembolism (VTE) prophylactic agent?

Response/ Recommendation: The occurrence of symptomatic deep venous thrombosis (DVT) and pulmonary embolism (PE) should be used as an endpoint to evaluate the efficacy of a venous thromboembolism (VTE) prophylactic agent.

Strength of Recommendation: Moderate.

Delegates vote: Agree 94.63% Disagree 4.39% Abstain 0.98% (Strong Consensus).

Rationale: Patients undergoing orthopaedic procedures have an increased risk of DVT and PE, collectively referred to as VTE, due to hypercoagulability, endothelial damage of blood vessels, and venous stasis[1208]. The development of multimodal prophylactic regimens that utilize chemical and mechanical prophylaxis have significantly reduced the incidence of perioperative VTE[1209-1211]. Despite this, it remains crucial to continually evaluate the efficacy of VTE prophylactic agents since VTE can cause significant morbidity and mortality1212.

The Food and Drug Administration (FDA) stated in its clinical outcome assessment (COA) compendium that asymptomatic proximal DVT, symptomatic proximal or distal DVT, non-fatal PE, or VTE-related death, among others, should be used as efficacy and safety outcomes for VTE prophylaxis studies[1213]. The aim of this document is to provide a clinically useful endpoint for researchers when developing clinical trials, from amongst the COA listed[1213].

Many Phase III trials have been conducted in the last 20 years evaluating VTE prophylaxis in patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA)[1214-1227]. The purpose of those trials was to establish efficacy of VTE prophylaxis and monitor for adverse events[1218]. Commonly used primary outcomes included symptomatic VTE, asymptomatic VTE (as assessed by venography typically at the 5- to 14-day mark for standard therapy or days 28 - 35 for extended prophylaxis), and all-cause mortality[1214-1227].

Given that the rates of VTE are relatively low with current treatment guidelines and prophylaxis, less than 1% of primary THA and TKA and less than 1.5% of revision THA and TKA experiencing VTE occurrence[1228], it is reasonable that researchers prefer an objective measurement of an uncommon event. This has led to venographic evidence of asymptomatic DVT being used as an endpoint for determining efficacy of VTE prophylaxis. The objectivity of venographic studies is helpful to researchers since many DVT are clinically silent[1211,1229].

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To date, despite the frequent use of venography and venous duplex for diagnosis of DVT in clinical trials, routine venous duplex and venography screening following THA and TKA is not recommended by the clinical practice guidelines developed by the American Academy of Orthopaedic Surgery (AAOS) and the American College of Chest Physicians (AACP)[1230-1234].

There are numerous studies that prove routine screening by ultrasound for the presence of DVT is not warranted. In a study by Schmidt et al., patients undergoing THA or TKA received a 10-day regimen of low-molecular-weight heparin (LMWH) and randomized to receive prolonged LMWH or screening for DVT by ultrasound (with a positive screen being treated appropriately). Both groups developed similar rates of proximal DVT by day 35 postoperatively (below 9%), questioning the utility of screening ultrasound[1232]. Furthermore, a recent retrospective single-center study found that in patients who underwent total joint arthroplasty and had a duplex ultrasound, only 0.7% of them had a DVT and none of them exhibited clinical symptoms[1234]. Shahi et al., found that the rate of in-patient DVT being diagnosed has decreased significantly during the past decade, likely due to less screening of asymptomatic patients, while the rate of PE development has remained stable[1210].

Propagation of DVT leading to a PE is a feared complication[1235]. The latter is the rationale behind screening patients for asymptomatic DVT in an effort to prevent development of a PE. However, the association between a distal DVT and PE remains unproven. In addition, many distal DVT developed in the postoperative period resolve even without a treatment[1236]. It is believed that DVT and PE can arise independent of each other and in hypercoagulable states, such as the postoperative period[1234,1237]. In addition, a recent systematic review of contemporary trials of anticoagulation, the importance of asymptomatic DVT detected by mandatory screening was questioned[1238].

In this regard, using symptomatic DVT and PE as primary endpoints for studies evaluating the efficacy of a VTE prophylactic agent would provide clinicians with clinically important information that would help determine the best course of management of these patients.

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47 - What is the optimal duration of VTE prophylaxis following major orthopaedic procedures?

Response/Recommendation: Following major orthopaedic surgery venous thromboembolism (VTE) prophylaxis -initiated in-hospital- should be continued for 14 to 35 days after patient discharge.

Strength of Recommendation: Strong.

Delegates vote: Agree 94.86% Disagree 4.21% Abstain 0.93% (Strong Consensus).

Rationale: The occurrence of VTE, including deep venous thrombosis (DVT) and pulmonary embolism (PE) is a relatively major source of perioperative morbidity, mortality and healthcare cost in lower joint arthroplasty surgery[1239-1241]. Hence, numerous organizations, including the American Academy of Orthopaedic Surgeons (AAOS), have provided guidelines for prevention of VTE following total joint arthroplasty[1242]. However, a general consensus on the type and the duration of VTE prophylaxis following orthopaedic procedures remains disputed.[1240,1243,1244].

Guidelines by the American College of Chest Physicians (ACCP) recommend the use of chemo-thromboprophylaxis for a minimum of ten days after total hip arthroplasty (THA) and total knee arthroplasty (TKA) in addition to early mobilization[1245]. In previous trials, VTE prophylaxis was mostly given until hospital discharge, ranging from 7 - 14 days. Meanwhile, however, the length of hospitalization for most major orthopaedic surgeries has significantly decreased, rendering VTE prophylaxis limited to the hospitalization period insufficient[1246].

Moreover, several studies have shown a second peak in the rate of postoperative DVT incidence in the late postoperative period, after termination of chemothromboprophylaxis[1242].

This delayed thromboembolism suggests that VTE risk extends beyond the hospitalization period[1246-1249]. The underlying mechanism may be based on the assumption that surgery induced activation of the coagulation and fibrinolysis cascade at a local and systemic level persists for an extended period[1248]. While the optimal duration for VTE prophylaxis remains uncertain, it has been suggested that this second risk period may occur between the second and the fifth postoperative week[1247,1248]. Moreover, coagulation indicators in the plasma have shown that a substantial hypercoagulability is sustained until day 35 after THA, despite the verified lack of thrombosis at hospital discharge[1250,1251]. Continuation of thromboprophylaxis after discharge, however, appears to significantly reduce the incidence of DVT and PE in major orthopaedic surgery[1249,1252].

Given the growing body of evidence in support of persisting thromboembolic risk after hospital discharge in major orthopaedic surgery, we conducted a systematic review and meta-analysis on the direct comparative effectiveness of extended (versus short-term or in-hospital) VTE prophylaxis.

The current body of evidence consists of 19 randomized controlled trials (RCT) of high to moderate quality and one non-randomized study. Summaries and meta-analyses can be found in the Appendix. Pooled meta-analysis of RCT only, demonstrated that VTE prophylaxis, when extended for up to 6 weeks beyond hospital discharge, significantly reduced the risk for the occurrence of symptomatic and asymptomatic DVT compared to short-term regimens. The odds of a post-operative DVT were reduced by 64% in THA and by 28% in TKA recipients with VTE prophylaxis extended for several weeks beyond hospital discharge. Statistical heterogeneity within the study sample was low, despite individual trial differences with regards to duration of prophylaxis (2 - 6 weeks) and variations of utilized anticoagulant drugs (unfractionated heparin, low-molecular-weight heparin, and oral anticoagulants). The benefit of extended VTE prophylaxis was observed without an increased risk for major bleeding. More research is needed to establish the comparative effectiveness between individual anticoagulant medications[1253].

Notably, cohort studies arguing against the need for out of hospital prophylaxis are of low-quality evidence[1254,1255].

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48 - What is the cost-efficacy of each VTE prophylactic agent that may be used in patients undergoing orthopaedic surgery?

Response/Recommendation: Aspirin (ASA) is the most cost-effective venous thromboembolism (VTE) prophylaxis as the cost of drug is nominal, the rate of complications such as bleeding associated with administration of ASA is low, and there is no need for blood tests or other methods to monitor the agent. The cost-effectiveness of different methods of VTE prophylaxis depends mostly on the initial cost of the chemical or mechanical modality, the need for blood monitoring, rate of complications associated with administration of the modality, and the need for reversal agents. We recognize that the cost of various prophylactic agents varies widely across the globe.

Strength of Recommendation: Intermediate.

Delegates vote: Agree 92.52% Disagree 4.21% Abstain 3.27% (Strong Consensus).

Rationale: Major orthopaedic surgeries are reported to be associated with considerable risk of developing VTE. If no perioperative VTE prophylaxis is provided, these procedures can be associated with up to 44% risk of postoperative deep venous thrombosis (DVT), 3% of pulmonary embolism (PE) and 0.7% of all-cause mortality[1256]. VTE is the third most common cause of death and is considered as the most common preventable cause of death in hospitalized patients[1267]. These presumed drastic consequences have resulted in thromboprophylaxis to become standard of care after major orthopaedic surgeries. Main VTE preventable measures include mechanical prophylaxis and chemo-prophylactic agents such as ASA, warfarin, low-molecular-weight heparin (LMWH), low dose unfractionated heparin (UFH), fondaparinux and direct-oral anticoagulants (DOAC), (e.g., rivaroxaban, apixaban and dabigatran).

With substantial increase in the volume of major orthopaedic procedures, the increasing cost of thromboprophylaxis and limitation in health care resources, there is an indispensable need to create a balance between the effectiveness of different prophylactic measures and their cost[1257]. Most cost-effectiveness analyses in the literature evaluated the cost utility of VTE prophylactic measures following total hip arthroplasty (THA), total knee arthroplasty (TKA) and hip fracture surgeries with scarce evidence regarding other orthopaedic procedures.

In an audience response poll during the 2018 Annual meeting of American Association of Hip and Knee Surgeons (AAHKS), ASA was the most popular agent used for VTE prophylaxis after THA and TKA (86% of respondents)[1258]. It is effective, inexpensive, well tolerated by patients, and is an oral agent that requires no blood tests or other methods of monitoring[1259]. When studied against warfarin, the use of ASA was associated with a higher quality-adjusted life-year (QALY) measure and lower cost than warfarin for both TKA and THA in all ages[1260]. When compared to LMWH, 160 mg ASA had higher cost-effectiveness for VTE prophylaxis following THA for patients with no history of VTE[1261]. Following TKA, the evidence was less certain, but ASA was still superior to warfarin in TKA cases with no additional risk factor of thrombosis[1261]. Also, comparing with LMWH, ASA was associated with a cost-effectiveness benefit in TKA patients more than 80-years of age[1261]. It was demonstrated that in older patients with less life expectancy, less QALYs are lost secondary to mortality from PE and post-phlebitic syndrome[1260]. The cost per QALY gained is thus much higher following potent anticoagulants administration (e.g., LMWH) compared to ASA. Therefore, the older a patient is, the more cost-effective ASA might be[1262].

In 2018, Dawoud et. al.[1263], performed a systematic review and cost-effectiveness study of different VTE prophylactic strategies comparing no prophylaxis, LMWH (short term use [7 - 10 days]), LMWH (long term duration [28 - 30 days]), LMWH (short term use) followed by extended ASA use (28 days), LMWH + anti-embolic stocking (AES), AES, intermittent pneumatic compression devices, (IPCD) foot pump, foot pump + AES, fondaparinux + AES, ASA (short term use), apixaban and rivaroxaban. They considered a lifetime horizon and tried to include different drug

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complications including major bleeding, clinically related non major bleeding and heparin induced thrombocytopenia. They concluded that after THA, 14 days LMWH followed by 28 days ASA administration has the best cost-effectiveness. Regarding TKA, foot pump and ASA were the most cost-effective measures against VTE.

Previous studies demonstrated superior cost-efficacy of LMWH after major orthopaedic surgeries compared to low dose UFH, warfarin and no prophylaxis[1257,1264,1265]. Lazo-Langner et. al., compared the cost-effectiveness of warfarin, UFH, LMWH, fondaparinux and ximelgatran[1266]. They found that compared to placebo, ximelagatran has the best cost-effectiveness profile among other agents especially with TKA. Their findings showed that the highest rate of VTE occurred with prophylaxis with UFH, while the lowest VTE rate was seen with fondaparinux. Warfarin has the least bleeding complication, while fondaparinux has the highest rate of bleeding. They estimated 2.55 fatality ratio of major bleeding compared to VTE episode emphasizing the threatening potential of bleeding complications.

The cost-effectiveness of rivaroxaban 10 mg/day compared to LMWH (enoxaparin 40 mg/day) following TKA and THA was demonstrated by several studies from the United Kingdom (UK)[1267] , the United States (US)[1268], Canada[1269], Sweden[1270], the Republic of Ireland[1271], France, Italy, and Spain[1272]. These papers either compared extended rivaroxaban use (35 days) to extended LMWH administration (31 - 39 days) (RECORD 1)[1273], extended rivaroxaban use (31 - 39 days) to short term LMWH administration (10 - 14 days) (RECORD 2)[1274], or short term rivaroxaban to short term LMWH administration (RECORD 3 trial)[1275]. Most of them considered the benefit of VTE reduction against the cost of drug acquisition, as well as the major bleeding and its consequences. However, these studies did not take into account the cost of "non-major but clinically related" bleeding episodes. A few studies evaluating both major and non-major bleeding complication demonstrated a better profile of LMWH compared to rivaroxaban[1263].

Further, studies performed in Canada[1276] and the UK[1274] concluded the cost-effectiveness of apixaban over LMWH after THA and TKA and reports from Russia[1277], Ireland[1271] and UK[1267,1278] favoring dabigatran (compared to LMWH) following TKA and THA. Two studies found apixaban more cost-effective than dabigatran[1278]. Four studies demonstrated the superiority of rivaroxaban over dabigatran performed in the UK[1267], France, Italy, Spain[1272], Ireland[1271], and Norway[1279]. One study concluded the superiority of rivaroxaban compared to apixaban[1267].

Rafael et. al., compared the cost-effectiveness of apixaban, dabigatran, rivaroxaban, LMWH, IPCD, IPCD + LMWH and simultaneous IPCD and apixaban administration. They demonstrated IPCD with/without apixaban to be appropriate according to their cost-effectiveness profile. They recommended to use prophylactic measures in accordance with the bleeding/thrombosis risk of each patient[1280].

Interestingly, the cost-effectiveness of different methods depended mostly on the cost of acquisition of the drug or mechanical prophylactic device and their complications[1280]. For instance, studies comparing rivaroxaban vs. LMWH in countries with more expensive rivaroxaban acquisition including Germany (from hospital perspective) and China, favored LMWH following either THA or TKA despite the higher efficacy of rivaroxaban in preventing VTE[1256]. In addition, complications other than bleeding such as hematoma formation and infection which may lead to subsequent readmission or reoperation have not been considered in most of these studies[1256,1260]. Further, most of these studies on antithrombotic agents have compared LMWH and DOAC, or various DOAC. However, the most commonly used orally administered antithrombotic agents (ASA, rivaroxaban, and apixaban) have not been compared. Large scale studies are required to explore the difference in cost utility of these oral agents.

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49 - Are there differences between various venous thromboembolism (VTE) prophylaxis in terms of patient compliance/adherence?

Response/Recommendation: Although there is some variation in adherence to the various venous thromboembolism (VTE) prophylactic agents, most of the differences are explained by sociodemographic, socioeconomic, illness-related, patient-related, and medication-specific to health system-related factors. As a predictor of adherence, individual patient preferences present an opportunity to create value in person-centered care.

Strength of Recommendation: Limited.

Delegates vote: Agree 93.30% Disagree 2.39% Abstain 4.31% (Strong Consensus).

Rationale: Adherence is the extent to which a person's behavior coincides with medical or health advice. The greatest challenge in current therapeutics following the exponential development of the capacity of modern pharmacology is compliance[1281]. Interestingly, patients who adhere to treatment, even when that treatment is a placebo, have better health outcomes than poorly adherent patients[1282].

The rigorous measurement of variation in adherence to VTE prophylaxis poses a challenging question that would require a comparison among mechanical, pharmacological, or combined protocols. With compression device and molecule representative of each kind, evaluated according to the route of administration, dosing frequency, and tolerance to the device or medication. Furthermore, the lack of a unified definition of adherence adds variation to the outcomes literature[1283]. In the absence of such study, an approximation to the answer may be constructed from studies that report on some of the variables or with similar agents in different therapeutic situations.

The adherence to prophylaxis with outpatient portable compression devices in a rural population after total hip arthroplasty (THA) or total knee arthroplasty (TKA) was evaluated by Dietz et al.[1284]. Compliance defined as 20 hours of use per day. In 115 joint arthroplasties, day one had the highest adherence post-discharge with an average usage of 13.2 hours/day. However, by day 14, usage fell to an average of 4.8 hours per day. Poor compliance was related to inconvenience due to heat or difficulty using the device.

Wilke et al.[1283], studied adherence rates in outpatient thrombosis prophylaxis with low-molecular-weight heparins (LMWH) after major orthopaedic surgery using a telephone survey and logistic regression models. They interviewed 1,495 patients who had major orthopaedic surgery at 22 different clinics in Germany. Adherence rates ranged between 79% and 87%, depending on the indicator used for measurement. Non-adherent patients missed between 38% and 53% of their outpatient LMWH injections. If patients attended an outpatient rehabilitation program, the probability of their non-adherence increased substantially. Moreover, the non-adherent probability increased with each additional day between acute hospitalization and the start of rehabilitation (linking days). Non-adherence was lower for patients who feared thrombosis or who believed antithrombotic drugs to be the most critical measure in thromboprophylaxis.

Concerning contemporary regimes of oral prophylaxis, Carrothers et al.[1285], reported adherence rates to rivaroxaban of 83%, and Lebel et al.[1286], reported a rate of 98% to dabigatran, both requiring a single oral administration per day. The difference in compliance between full-strength vs. low-dose aspirin (ASA) for VTE prophylaxis following THA and TKA was measured by Hood et al.[1287], in 404 patients. They were able to reject the null hypothesis of decreased patient compliance utilizing full-strength 325 mg ASA twice daily following total joint arthroplasty (TJA) when compared to low-dose 81 mg twice daily. The VTE prophylactic regime was completed by 74% of the patients. The most cited reason for stopping ASA in both treatment groups was gastrointestinal issues (10.5% and 7%, respectively).

To address the question of the influence of administration route and dosage on adherence to extended thromboprophylaxis for THA or TKA, Moreno et al.[1288], undertook a cohort study of TJA patients who received pharmacological extended thromboprophylaxis. A telephonic questionnaire was applied 35 days after the day of the surgery with patients who omitted one or more doses of medication during the follow-up period classified as "non-adherent." Five hundred and twenty patients were included: 153 received apixaban (oral 2.5 mg, twice a day), 155 enoxaparin (injectable 40 mg/sq, once a day), and 212 rivaroxaban (oral 10 mg, once a day). Patients receiving oral medication once a day were more compliant than

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those who received oral medication twice a day. Non-adherence rates were 3.2 and 9.2%, respectively ($p = 0.033$). No significant differences ($p = 0.360$) were found between oral once a day and injectable once a day medication. The number of daily doses prescribed was related to adherence to extended chemical prophylaxis, while the route of administration did not seem to have a significant impact.

Single or double daily dose anticoagulants that do not require monitoring have reduced the question of pharmacological adherence to the dichotomy of receiving the dose as prescribed or not. However, with vitamin K antagonists, monitoring of the therapeutic window is required. Ahmed et al.[1289], recently pointed out the additional challenge with warfarin in a study focusing on patient's knowledge and adherence to anticoagulants and their effect on outcomes. The overall adherence to warfarin was 76.2%. However, only 20.45% were in the therapeutic range.

Patient preference may play a relevant role in adherence to VTE prophylaxis. Wong et al.[1290], analyzed patient preferences regarding pharmacologic VTE prophylaxis. Of the 227 patients, a majority (60.4%) preferred an oral medication, if equally effective to subcutaneous options. Dislike of needles (30.0%), and pain from injection (27.7%) were identified as rationales for their preference. Patients favoring subcutaneous administration (27.5%) identified a presumed faster onset of action (40.3%) as the primary reason for their preference. Patients with a preference for subcutaneous injections were less likely to refuse prophylaxis than patients who preferred an oral route of administration (37.5% vs. 51.3%, $p < 0.0001$).

Adherence to VTE prophylaxis; mechanical, pharmacological, or combined, requires management of the underlying factors that determine the output, which are diverse, and span sociodemographic, socioeconomic, illness-related, patient-related, and medication-specific to health system-related factors[1283]. Adherence to VTE prophylaxis is not independently attributable to the prescription.

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50 - Is there a role for sequential combination VTE prophylaxis in patients undergoing orthopaedic procedures?

Response/Recommendation: Based on the available evidence, sequential combination venous thromboembolism (VTE) prophylaxis has not been shown to be superior to other established treatment regimens.

Strength of Recommendation: Limited.

Delegates vote: Agree 95.73% Disagree 1.42% Abstain 2.84% (Strong Consensus).

Rationale: Consensus has grown[1291] for chemoprophylaxis of VTE disease. National guidelines such as the National Institute for Health and Care Excellence (NICE) guidelines in the UK suggest patients who had total hip arthroplasty (THA) should have 28 days of chemoprophylaxis and those who had total knee arthroplasty (TKA) should have 14 days of chemoprophylaxis[1292]. Evidence based guidelines such as the American College of Chest Physicians (ACCP) have suggested a minimum 10-14 days of prophylaxis for those who have undergone hip or knee arthroplasty[1293].

Many different drugs have been reported to be effective[1294] with varying degrees of side effects, and there continues to be discussions about the agent of choice for prevention of VTE after orthopaedic procedures. Some have advocated for a combination of pharmacological agents to attempt to increase compliance, decrease side effects, and maintain efficacy of prevention of disease.

A randomized control trial (RCT) published in 2018 by Tang et al., aimed to compare Rivaroxaban alone, enoxaparin alone, and enoxaparin followed by rivaroxaban. There was a small sample size of 287 patients with less than 100 in each group. There was no statistically significant difference in the rate of VTE between all groups. They found the group that received sequential therapy had increased compliance compared to enoxaparin alone. The rate of wound complications was higher in the rivaroxaban group. Their conclusion was "it is speculated that the clinical application of the sequential therapy is safe, convenient, cost-effective, and efficient". They did not however, demonstrate a significant benefit in their primary endpoint of VTE, but instead found the effectiveness of the sequential therapy was due in part to the increased compliance and cheaper cost of therapy. There was no multivariate analysis done regarding the compliance rates, and causes for non-compliance were multifactorial, and in some parts specific to the Chinese population[1295].

A double blinded, RCT sought to determine whether there was any benefit to following 5 days of rivaroxaban with aspirin (ASA) or continuing with rivaroxaban. A total of 3,427

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patients undergoing THA or TKA were randomized. There was no statistically significant difference in bleeding complications. The combination of ASA and rivaroxaban was not inferior to rivaroxaban alone, but neither was it superior[1296].

A retrospective analysis comparing ASA alone to ASA with additional unfractionated heparin (UFH) was published in 2018. Patients either received ASA alone, ASA with a single dose of UFH, and ASA with multiple doses of UFH. There were 5,350 patients who met inclusion criteria. The cohorts were not matched. They found an increase in perioperative blood loss and an increase in blood transfusion rates for those patients that received 1 or more doses of UFH. There was no statistically significant difference in VTE rates between groups[1297].

Gonzalez Della Valle et al., published a retrospective review of 257 high-risk patients over a 14-year period from 2004 - 2018. These were patients who had either a deep venous thrombosis (DVT), a pulmonary embolism (PE) or both in the past. Their chemoprophylaxis was grouped into ASA, anticoagulation other than ASA, or combined. They were unable to draw conclusions on the efficacy of different chemoprophylaxis regimens based on the small numbers involved and the selection biases of choosing medications[1298].

Based on the literature available, a recommendation cannot be made for or against sequential combination VTE prophylaxis in those patients undergoing orthopaedic procedures where there is an established requirement for VTE prophylaxis. Sequential therapy may have some advantages in improving compliance for extended VTE prophylaxis, reducing cost, and reducing the risk of wound complications.

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51 - Are there specific contraindications for the administration of each VTE prophylactic agent?

Response/Recommendation: Each venous thromboembolism (VTE) prophylactic agent has evidence-based relative and absolute contraindications, which should be considered and balanced with the patient's VTE risk.

Strength of Recommendation: Strong.

Delegates vote: Agree 100.00% Disagree 0.00% Abstain 0.00% (Unanimous Strong Consensus).

Rationale: Unfractionated heparin (UFH), low-molecular-weight heparin (LMHW), and vitamin K antagonists (VKA) have been used in the prevention of VTE after orthopaedic surgery for more than 30 years[1299]. More recently, VTE prophylaxis after elective hip and knee arthroplasty has evolved with the introduction of direct-oral anticoagulants (DOAC) including direct thrombin inhibitors (dabigatran) and Factor Xa inhibitors (rivaroxaban, apixaban). Recent literature also discloses aspirin (ASA) as safe and effective in the prevention of VTE in selected patients[1300-1303].

Prevention of VTE in clinical practice requires an assessment of (i) a patient's cumulative VTE risk; and (ii) patient characteristics that would contraindicate pharmacological prophylaxis. An important patient characteristic contraindicating the initiation of concurrent post-operative VTE pharmacological thromboprophylaxis is a pre-operative indication for therapeutic dosing of anticoagulation (e.g., atrial fibrillation, prior VTE or mechanical heart valves). If a patient is on anticoagulant therapy prior to surgery, the same anticoagulant regimen should be safely resumed post-operatively, if appropriate. For the other patients not on anticoagulation prior to surgery, the patient's cumulative VTE risk is the intrinsic VTE risk resulting from any medical conditions and the added risk resulting from surgery or trauma. Selection of the appropriate VTE prophylactic agent or combination of prophylactic measures for these patients, necessitates consideration of both absolute and relative contraindications to pharmacological prophylactic treatment[1304].

Vitamin K Antagonists (VKA): VKA were the mainstay of oral anticoagulation prior to DOAC development. This class of medications has the advantage of being administered orally, however VKA are challenging in clinical practice as they exhibit considerable variability in dose response, have a narrow therapeutic window, and are subject to interactions with many drugs and diet. Additionally, maintenance of a therapeutic level of anticoagulation requires consistent laboratory monitoring and patient compliance[1305]. A patient's inability or unwillingness to cooperate in frequent laboratory monitoring is a contraindication to use.

Contraindications to VKA for VTE prophylaxis include deficiency of antithrombin III, protein C, or protein S, pregnancy, or severe hepatic failure[1305]. Caution should be used in patients with chronic kidney disease. VKAs are almost entire

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metabolized before urinary excretion, however the current recommendations for VKA use in patients with chronic kidney disease (CKD) are mostly extrapolated from trials designed for the general population or based on observational studies, thus international normalized ratio (INR) levels but be watched closely. In patients with liver disease, the metabolism of VKA can be difficult to predict. Liver disease can also independently affect the INR, and thus routine INR monitoring may not be an accurate representation of therapeutic VKA dosing[1306].

Direct-Oral Anticoagulants (DOAC): DOAC overcome some of the practical limitations associated with VKA therapy due to their more predictable pharmacological properties. These medications have rapid onset and termination of action, fewer drug interactions, lack of dietary vitamin K interactions, an no need for routine drug monitoring[1307,1308]. This has led to rapid clinical adoption.

Prior to initiating VTE prophylaxis with any DOAC, renal and liver function testing should be performed. Limited data is available on the use of these agents in patients with severe renal or hepatic impairment, as these patients were excluded from the phase III trials for DOAC. All DOAC have a degree of renal excretion as active metabolites (dabigatran, 80%; rivaroxaban, 33%; apixaban, 27%) thus medication accumulation can occur in patients with impaired renal function[1306,1309,1310]. Caution should be used when prescribing these medications to patients with CKD[1311]. A recent meta-analysis of DOAC and warfarin use in patients with CKD and dialysis patients showed that DOAC had significantly better efficacy in patients with early stage CKD[1312]. However, the efficacy and safety profiles were similar in patients with CKD stages 4 - 5 or dialysis patients[1312]. Because renal function can decline over time, particularly in elderly patients, regular assessment of renal function during the use of anticoagulant therapy is necessary.

Rivaroxaban and apixaban are contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk[1313-1315]. Dabigatran is contraindicated in patients with hepatic impairment or liver disease expected to have an impact on survival[1311]. While no dose adjustment is required in cases of mild or moderate hepatic impairment, DOAC should be used with caution in these patients.

Many medications interfere with the efficacy and safety of DOAC. Nonsteroid anti-inflammatories (NSAID) and ASA are known to affect bleeding risk, but do not directly interact with DOAC[1306,1313]. The possibility may exist that patient are at increased risk of bleeding in case of concomitant use with selective serotonin or norepinephrine reuptake inhibitors (SSRI/SNRI) due to their reported effect on platelets. Patients taking these medications in addition to anticoagulants should be observed closely for bleeding. DOAC are a substrate of the P-glycoprotein transporter, and thus concomitant administration of P-glycoprotein inhibitors results in increased DOAC plasma concentration and increased risk of bleeding[1316]. P-glycoprotein inducers may decrease anti-thrombotic efficacy. Concomitant use of mild to moderate P-glycoprotein inhibitors (amiodarone, quinidine, verapamil) should be done with caution, and often requires dose reduction. DOAC are contraindicated in patients taking strong P-glycoprotein inhibitors (ketoconazole, cyclosporine, itraconazole, dronedarone, glecaprevir/pibrentasvir)[1313,1314]. Apixaban is contraindicated in patients taking human immunodeficiency virus (HIV) protease inhibitors (e.g., ritonavir).

Low-Molecular-Weight Heparin (LMWH) and Unfractionated Heparin (UFH): In addition to patient characteristics that are an absolute contraindication for any type of pharmacological thromboprophylaxis, such as active major bleeding and severe traumatic brain injury, also in the following hematological conditions the use of LMWH or UFH should be done carefully: coagulopathy; disseminated intravascular coagulation; hemophilia or other coagulation factor disorders; platelet function disorders; and thrombocytopenia[1304,1317,1318]. In a study with thrombocytopenic non-surgical patients, administration of thromboprophylactic dosing of enoxaparin appeared safe provided that the platelet count exceeded 25,000/μl[1319].

The use of ASA, NSAID, antiplatelets or anticoagulants concomitant with LMWH treatment increases the risk of bleeding and is not recommended[1304,1317]. A prospective observational study, including 339 patients, showed that the strongest correlation with a raise in adverse reactions occurred with coadministration of ASA. For concomitant NSAID treatment, the correlation was very low[1320].

Clearance of LMWH occurs primarily via renal excretion. This can increase the risk of bleeding in patients with renal impairment[1321]. Smaller LMWH are more dependent on renal excretion than larger ones. Data from three prospective trials confirms that patients with a low creatinine clearance (CrCl) are at risk of accumulation of anti-Xa heparin activity when treated with nadroparin or enoxaparin[1322-1324]. The exception appeared to be tinzaparin. A multidose prospective pharmacokinetic trial[1325] showed that the anti-Xa heparin effect of tinzaparin does not appear to accumulate as CrCl declines. UFH is sometimes preferred in patients with renal impairment[1326]. UFH clearance is dose-dependent, in contrast to LMWH, and can be monitored relatively easy[1321,1327].

The New South Wales Clinical Excellence Commission stated in 2015 that end-stage liver failure in combination with INR > 1.5 is an absolute contraindication for VTE chemoprophylaxis[1317] reflecting the main perception that thrombocytopenia and elevated INR predict bleeding risk in cirrhotic patients. However, previous studies have shown that elevated INR does not predict the risk of bleeding in patients with cirrhosis[1328,1329]. Also, elevated INR and thrombocytopenia do not mean that patients with cirrhosis have a low risk of VTE; these laboratory findings are insufficient to detect the balance between procoagulant and anticoagulant factors in liver cirrhosis[1330-1332]. Absolute contraindications for LMWH and UFH in cirrhotic patients are concomitant anticoagulation therapy; and active bleeding, including variceal bleeding[1333]. To

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conclude, administration of UFH or LMWH can be safe in patients with liver cirrhosis, and the decision to start anticoagulation therapy should not solely depend on INR and platelet count[1328,1334].

Both LMWH and UFH can elicit heparin-induced thrombocytopenia, an immune-mediated complication caused by the formation of antibodies to complexes of heparin and platelet Factor 4. These antibodies develop in 2 - 8% of patients treated with LMWH and 8 - 17% of patients using UFH. Eventually, only 0.2 - 3% of sensitized patients will develop thrombocytopenia[1335]. Heparin-induced thrombocytopenia, within the past 100 days or in the presence of circulating antibodies, is an absolute contraindication for the administration of UFH, enoxaparin, nadroparin, dalteparin and tinzaparin[1334,1336-1338]. The use in patients with a history > 100 days without circulating antibodies is allowed if caution is taken into account[1334].

In a retrospective review of enoxaparin and UFH administration on twenty-nine hospital wards (accounting for 10,516 patient visits) 11.9% of ordered doses were not administered, primarily due to patient refusal[1334]. In this respect, failure to adhere can be considered as a contraindication for LMWH-administration. Considering using oral VTE prophylaxis for non-adherent patients reporting dislike of needles and pain from injections can improve efficacy[1339].

As neither UFH, nor LMWH cross the placenta, heparins are the preferred anticoagulants in pregnancy[1334,1340]. There is no evidence for fetotoxicity or teratogenicity of enoxaparin, tinzaparin or dalteparin[1334,1337,1338]. For pregnant women using enoxaparin, there is no evidence for an increased risk of hemorrhage, thrombocytopenia or osteoporosis when compared to non-pregnant women[1334]. Furthermore, enoxaparin treatment can be continued during breastfeeding because expected passage in human milk is very low and oral absorption of enoxaparin is unlikely[1334].

Fondaparinux: Elimination of fondaparinux occurs primarily by urinary excretion of its non-metabolized form and is therefore prolonged in patients with renal insufficiency. The use of fondaparinux is contraindicated in patients with severe renal insufficiency (CrCl < 30 mL/min) and in patients with body weight less than 50 Kg. As fondaparinux clearance is decreased by 30% in the latter patient population, the incidence of major bleeding is doubled compared with patients weighing > 50 Kg[1341,1342].

No evidence exists of fetotoxicity due to fondaparinux administration. However, this might be due to a lack of adequate research in pregnant patients[1342].

Acetylsalicylic Acid (Aspirin [ASA]): ASA is a nonselective NSAID as it irreversibly binds to both cyclooxygenase-1 and cyclooxygenase-2, leading to enzyme inactivation through acetylation[1343]. Low doses of ASA mainly inhibit cyclooxygenase-1, thereby opposing thromboxane synthesis in platelets and preventing platelet aggregation[1344,1345].

The use of ASA is contraindicated in patients with hemophilia or congenital coagulopathies; in patients with thrombocytopenia; and in the presence of an acquired bleeding diathesis, e.g., dengue or yellow hemorrhagic fever[1346-1348].

The risk of gastro-intestinal bleeding is increased by ASA in patients with active peptic ulcer disease or gastritis; in patients with a history of recurrent peptic ulcer or a history of gastro-intestinal hemorrhage[1348]; in patients on warfarin; or if there is concomitant alcohol consumption[1346,1347]. Susceptibility for gastro-intestinal bleeding due to administration of ASA is particularly high in elderly patients[1348].

Administration of ASA is not recommended in children under 16 years unless the predicted benefits outweigh potential risks[1348]. ASA can elicit Reye's syndrome in children suffering from a viral infection. Reye's syndrome causes coagulopathy, and in its most severe form cerebral edema and liver failure[1349].

ASA is renally cleared. If administered in a low-dose regimen, it does not accumulate in patients with renal insufficiency and can be used if the benefits outweigh the risks[1348].

The antiplatelet effect of ASA can be attenuated through competitive binding of other NSAID to cyclooxygenase-1. However, this interaction is highly variable amongst different types of NSAID and depends on timing of administration, dose of ASA and dose of the concomitantly administered NSAID[1350,1351]. This competitive effect is reported for ibuprofen and naproxen[1352-1356], but not for diclofenac[1352,1353]. Findings for celecoxib are conflicting: in vivo studies by Renda et al., and Wilner et al., showed no attenuating effect of platelet inhibition by ASA[1357,1358], whereas an in vitro study by Saxena et al., and a study on dog models by Rimon et al., demonstrated interference with ASA[1345,1356]. Another study found that administration of ASA 2 hours before single-dose ibuprofen could prevent the interaction with ASA, although this strategy did not prevent interference when multiple doses of ibuprofen were given[1352]. In conclusion, the choice to administer ASA concomitantly with other NSAID should be guided by clinical decision making at patient level[1351].

Low doses of ASA (up to 100 mg/day) appear safe in the first six months of pregnancy[1359]. Clinical data concerning the administration of doses above 100 mg/day are lacking. During the third trimester of pregnancy, prescription of ASA at doses higher than 100 mg/day is contraindicated[1348,1359], because of the risk of premature closure of the ductus arteriosus and fetal renal dysfunction. Furthermore, all prostaglandin synthesis inhibitors may cause inhibition of uterine contractions and, consequently, delayed, or prolonged labor[1348]. Suspending lactation is not required for short-term use of ASA in its recommended dose. However, discontinuation of breastfeeding is necessary in patients using ASA for longer periods of time[1348].

Recommendations for Future Research: As the number of elective arthroplasties performed annually continues to rise, optimization of the perioperative care continues to be a priority. Selection of an effective thromboprophylaxis protocol is critical, and should take into account patient characteristics, medication safety profile, and drug metabolism. Solid evidence

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is still lacking to formulate clear guidelines, in particular for drug interaction patterns and for patients with renal or hepatic disease. Prospective study designs in an orthopaedic setting will be necessary to draw firm conclusions for VTE prophylaxis in these populations.

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52 - Does VTE prophylaxis in patients with chronic kidney disease need to be altered when undergoing orthopaedic procedures?

Response/Recommendation: In patients with chronic renal disease, pharmacological agents used in venous thromboembolism (VTE) prophylaxis may need a dose adjustment to prevent major bleeding or other complications based on their biochemical properties. In unstable advanced renal disease, unfractionated heparin (UFH) or mechanical prophylaxis alone may be preferred as VTE prophylaxis.

Strength of Recommendation: Limited.

Delegates vote: Agree 94.58% Disagree 0.99% Abstain 4.43% (Strong Consensus).

Rationale: Chronic kidney disease (CKD) increases the risk for both VTE and bleeding due to specific changes in the hemostatic system (platelet alteration, endothelial injury, loss of natural coagulation and anticoagulation factors), uremic toxins, and proinflammatory shifts[1360]. Compared to CKD patients with a 10 - 50 percentile of renal function, there is a 2.6-fold increase in the odds ratio of VTE in cases with less than one percentile of renal function[1361]. Decreased levels of Factor VIII, von Willebrand factor and albuminuria, are the most predicting factors of thrombotic events in CKD cases[1361,1362]. Central venous catheters and arteriovenous fistula predispose end-stage renal disease (ESRD) patients to thrombosis secondary to disturbance and activation of the platelets. CKD significantly alters VTE outcomes in the population by increasing the risk of all-cause mortality, recurrent VTE, and major bleeding by approximately 1.4 times[1363]. In patients undergoing major orthopaedic procedures, the prevalence of CKD varies from 3.9% - 17%, and it increases with age[1364-1368]. Analysis of a large cohort of patients undergoing total knee arthroplasty (TKA) (n = 41,852) and total hip arthroplasty (THA) (n = 20,720) by Miric et al., considering the International Classification of Diseases version 9 (ICD-9) codes and the Diagnosis Related Groups (DRG) to identify patients with CKD, did not reveal a significant increase in the risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) after both procedures[1366,1367]. However, numerically higher incidence of DVT was reported in CKD patients. In contrast, another analysis of a big dataset of more than one million patients demonstrated an increased risk of DVT by 1.38 times (95% confidence interval [CI], 1.04 - 1.84) in patients with CKD according to the disease codes[1368]. However, this tendency was not confirmed for patients with ESRD on dialysis. In an analysis of a prospective registry by Warth et al., with the estimation of glomerular filtration rate (GFR) by pre-operative serum creatinine level, there was a significantly greater rate of overall complications in patients with moderate to severe renal impairment, as compared to patients with no or mild disease but without a significant difference for DVT and PE[1364]. Another retrospective study with the calculation of GFR showed a 2.68-fold (95% CI, 1.28 - 5.59) increase in the risk of DVT after total joint arthroplasty in those with GFR < 60 mL/min[1365]. A meta-analysis by Zhang et al., suggested that CKD can increase VTE risk by 8.31 times (95% CI, 1.98 - 34.93) after spine surgeries[1369].

Besides a higher rate of VTE events, patients with CKD have an increased risk of receiving blood transfusion after major orthopaedic procedures, especially if they have

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preoperative anemia[1370-1372]. CKD with albuminuria is associated with 1.4- to 2.7-fold increase in bleeding risk, including intracranial hemorrhages, regardless of the GFR[1361,1362,1373,1374]. As a double-edged sword, dialysis can decrease the chance of bleeding by eliminating uremic toxins but lead to bleeding episodes by continuous activation and consumption of the coagulation factors[1361]. Decreased renal function (GFR < 30 mL/min) is one of the accepted bleeding risk factors in several risk assessment models, including the Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile international normalized ratio [INR], Elderly, Drugs/Alcohol Concomitantly (HAS-BLED)[1375], the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA)[1376], and the Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-bleeding [Previous Bleed], Hypertension [Uncontrolled], Anemia, Genetic Risk Factors [CYP 2C9 snp], Excessive fall risk, Stroke ($HEMORR_2HAGES$)[1377].

There is no strong evidence comparing the efficacy and safety of chemoprophylaxis (with/without mechanical prophylaxis) vs. mechanical prophylaxis alone after major orthopaedic procedures in CKD patients. The 2011 American College of Chest Physicians (ACCP) guidelines, however, recommended mechanical prophylaxis only after orthopaedic surgery in those with increased risk of bleeding, including CKD patients (Grade 2C)[1378,1379]. The American Academy of Orthopaedic Surgeons (AAOS) guidelines also recommended aspirin, warfarin, or no chemoprophylaxis after orthopaedic surgery in those having both risks of bleeding and thrombosis[1380]. In 2018 the European guidelines for perioperative chemoprophylaxis recommended using weight-adjusted low-molecular-weight heparin (LMWH) or low-dose UFH for VTE prophylaxis in elderly patients with CKD (Grade 2C) and low-dose UFH (Grade 2C), or reduced doses of enoxaparin (Grade 2C), or dalteparin (Grade 2B) for critically ill CKD patients[1381]. The United Kingdom National Institute for Health and Care Excellence (NICE) 2018 guidelines also preferred low-dose LMWH or UFH[1382].

Pharmacological agents require following the specific instructions and related restrictions for kidney function while choosing an appropriate drug and dosage for chemoprophylaxis[1360,1383]. Thus, warfarin and UFH could be used without limitation. Low-dose UFH may be appropriate in unstable renal disease as it has a short half-life and non-renal metabolism, and its anticoagulant effect can easily be reversed. LMWH may be preferred to UFH as it can be administered once daily and has decreased risk of heparin-induced thrombocytopenia. Also, evidence suggests no bioaccumulation of LMWH in patients with GFR > 30 mL/min. Enoxaparin should be used according to the official restrictions by GFR with the possible dose correction and may require control of anti-Factor Xa activity. Dalteparin was not associated with bioaccumulation in CKD patients[1384] and was equivalent in terms of safety and superior in terms of PE risk reduction compared with UFH in critically ill patients, of whom 2.1% had CKD[1385]. Tinzaparin also showed no bioaccumulation in patients with GFR > 20 mL/min[1386].The dose of fondaparinux should be adjusted if GFR < 50 mL/min, and it is restricted if GFR is lower than 30 mL/min[1383,1387,1388].

Direct-oral anticoagulants (DOAC) such as dabigatran should be used appropriately depending on GFR with required dose correction. There is emerging evidence from the non-surgical population that although DOAC are non-inferior regarding their efficacy for prevention of recurrent VTE in CKD patients, they are superior in terms of safety compared to warfarin[1389-1391]. A subgroup analysis of CKD patients from DOAC phase III orthopaedic trials is available for rivaroxaban, apixaban and dabigatran, and it shows no interaction of efficacy and safety with the kidney function[1392-1394]. In retrospective studies on patients with CKD stage of 4 - 5, no significant difference was observed between apixaban and warfarin in terms of major bleeding or VTE, if usage was less than 3 months[1395,1396]. A similar analysis is not available for edoxaban[1397,1398].

A direct thrombin inhibitor, e.g., desirudin, may be suggested for thromboprophylaxis in CKD patients. Compared to enoxaparin after THA, it was non-inferior in terms of bleeding regardless of the CKD stage but superior in terms of VTE risk reduction in the CKD stage 3b (GFR of 30 - 45 mL/min)[1399]. This effect may be related to the lower levels of antithrombin in advanced renal disease. Antithrombin is required for the action of LMWH but not necessary for direct thrombin inhibitors which function through inactivation of circulating and clot-bound thrombin.

In patients with GFR < 30 mL/min, the evidence regarding the efficacy and safety of DOAC agents is insufficient[1392].

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53 - Does VTE prophylaxis in patients with chronic liver disease need to be altered when undergoing orthopaedic procedures?

Response/Recommendation: Chronic liver disease (CLD) alone should not be considered a reason to withhold or alter venous thromboembolism (VTE) prophylaxis. The decision to possibly modify VTE prophylaxis should be multidisciplinary and individualized based on risk factors for both VTE and bleeding.

Strength of Recommendation: Consensus.

Delegates vote: Agree 95.12% Disagree 0.49% Abstain 4.39% (Strong Consensus).

Rationale: CLD encompass a broad spectrum of etiologies and ranging from viral diseases and alcohol abuse to hereditary and autoimmune disorders, altogether representing the fifth cause of mortality worldwide[1400].

CLD patients often present an associated coagulopathy with an increase international normalized ratio (INR). In the past, this acquired coagulopathy led the physicians to the false perception that such patients could be considered "self-anticoagulated". The known reduction of anticoagulant factors is often balanced by an analogue reduction of procoagulant ones.

In a prospective case control study on hospitalized patients, Gulley et al., found that the rates VTE events were doubled in cirrhotic patients, 1.8% vs. 0.9%[1401]. Smith et al., retrospectively

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reviewed 410 patients hospitalized with a diagnosis of cirrhosis, founding an overall incidence of VTE events of 0.7%[1402]. In a nation-wide cohort study conducted on the Danish population, Jepsen et al., found that the risk for VTE events in the cirrhotic outpatient population was almost doubled with respect to their healthy, matched controls. Moreover, it was also observed that cirrhotic patients, after a VTE, had an increased 90-days mortality[1403]. An increased risk of deep venous thrombosis (DVT) in liver cirrhosis with respect to the general population was also described by Zhang et al., in a systematic review on the prevalence of venous thromboembolism in the Asian population[1404].

It has been widely recognized that CLD patients have poorer outcome in orthopaedic surgery with an increased risk of disseminated intravascular coagulation, infections, intraoperative bleeding, post-operative anemia requiring blood transfusions, 90-days readmission and hardware failure[1405-1407].

Few studies analyzed VTE in CLD patients undergoing orthopaedic surgery. In several studies, DVT and pulmonary embolism (PE) are included in a broader category of "medical complications" and, even if these resulted as increased in CLD orthopaedic patient, it is not possible to assume a clear increased risk without extrapolated data[1406,1408-1413].

Nevertheless, the association between CLD and an increase in VTE in the orthopaedic population is not so straightforward, as some studies in literature report conflicting results[1411,1414-1416].

On the other hand, a robust body of works exists analyzing the question of VTE prophylaxis in the patients hospitalized with CLD. One major concern is its safety against bleeding. Literature does not support this concern[1417-1420]. The main independent risk factors for bleeding in CLD population were INR and platelets levels[1420].

There is low-quality evidence on safety profile of direct-oral anticoagulants (DOAC) in CLD patients[1421-1423]. Recent guidelines[1424] recommend the preferential use of DOAC over low-molecular-weight heparin (LMWH) in the setting of VTE prophylaxis in orthopaedic surgery, but questions must be raised about such a recommendation in patients with liver disease who undergo orthopaedic surgery. Phase III studies with DOAC did not include subjects with severe liver disease/liver damage[1425].

Data regarding the efficacy of VTE prophylaxis in reducing VTE rates remain quite conflicting in this specific population. Barclay et al., reported a decreased incidence of VTE events in their cohorts treated with anticoagulants[1418,1423], while other studies failed in retrieving the same results. In a systematic review on VTE prophylaxis in hospitalized patients with CLD, Wonjarupong et al., could not find any difference in thromboembolic events and bleeding events in patients with and without VTE prophylaxis[1426]. In a retrospective analysis, also Moorehead et al., could not demonstrated an association between prophylaxis and a decrease in VTE risk[1427]. Similar, not univocal results have also been reported by many other studies[1402,1418,1419].

Even tough not widely investigated throughout literature, CLD patients undergoing orthopaedic procedures not only are not protected by liver coagulopathy, but also show a possibly increased tendency toward VTE events. In this regard, given the acceptable safety of anticoagulants in this group of patients, CLD alone should not be considered a reason to withhold VTE prophylaxis, despite the conflicting results about its efficacy in the literature. The orthopaedic surgeon should anyway seek the advice of a multidisciplinary team of experts in an effort to maximize a thorough pre-operative evaluation and post-operative care. The use of risk scores like the Caprini Risk Assessment model[1428-1432], can help in this population.

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54 - What are the indications for seeking a thrombosis specialist or a hematology consult for VTE prevention, in patients undergoing elective orthopaedic procedures?

Response/Recommendation: In the absence of reliable evidence, it is the opinion of this work group that patients with known or suspected bleeding or coagulation disorder, creatinine clearance < 30 mL/min, active hepatobiliary disease, with significant anemia or thrombocytopenia or patients requiring continuous use of antiplatelet and/or anticoagulant might benefit from a thrombosis specialist or a hematology consult.

Strength of Recommendation: Consensus.

Delegates vote: Agree 95.31% Disagree 2.82% Abstain 1.88% (Strong Consensus).

Rationale: Randomized controlled trials (RCT) have been performed to establish the efficacy and safety of thrombophylatic strategies in patients undergoing orthopaedic procedures and the main strategies are currently well studied[1433]. However, RCT exclude some patients for whom the thrombophylatic strategies might not be well established and individualization is required. Currently there are not any robust data about the indications for a thrombosis specialist or a hematology consult and its impact in thrombosis and/or hemorrhage after surgery. Therefore, it is the opinion of this guideline work group that patients excluded from most of the contemporary trial, namely, those with known or suspected bleeding or coagulation disorder, creatinine clearance < 30 mL/min, active hepatobiliary disease, with significant anemia or thrombocytopenia or patients requiring continuous use of antiplatelet and/or anticoagulant might benefit from seek a thrombosis specialist or a hematology consult in the absence of antithrombotic strategy established by the surgeon and/or the specialist usually follows the patient.

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55 - If a patient is in an "increased risk" group for the development of VTE, are there certain agents which have increased efficacy over other anticoagulants?

Response/Recommendation: There is limited evidence to support that certain anticoagulants have increased efficacy over other anticoagulants. The specific factor that increases a patient's risk for venous thromboembolism (VTE) must be considered and treatment tailored to that specific cause, after considering drug class, and dosing regimen.

Strength of Recommendation: Limited.

Delegates vote: Agree 97.07% Disagree 1.95% Abstain 0.98% (Strong Consensus).

Rationale: The presence of certain conditions are known to increase a patient's risk for venous thromboembolism (VTE), such as cancer[1434,1435], older age[1436], cystic fibrosis[1437], chronic kidney disease (CKD)[1438], and obesity[1439]. Surgery can also increase a patient's risk for VTE, especially many types of orthopaedic surgeries which tend to limit a patient's ability to be physically active for a period of time following a procedure[1440]. While there are many drug regimens to combat the increased risk from surgery and the above comorbidities, there lacks a consensus as to which drugs, if any, have increased efficacy in the setting of orthopaedic surgery performed on patients with increased risk for VTE[1441,1442].

Two studies examined VTE prophylaxis in the setting of cancer. Key et al., compared direct-oral anticoagulants (DOAC) and low-molecular-weight heparin (LMWH) for VTE prophylaxis in patients with cancer[1435]. Their results showed that both categories of drugs were effective VTE prophylaxis, but the DOAC had a higher risk of bleeding compared to LMWH. The authors recommended apixaban, rivaroxaban, or LMWH

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in high-risk cancer patients and advised for the start of pharmacotherapy prior to surgery and to continue 7 - 10 days after surgery. A systematic review by Lex et al., was performed regarding VTE prophylaxis in orthopaedic oncology patients[1443]. The authors concluded that there is limited evidence to guide clinicians in VTE prophylaxis in this population. They suggest that both mechanical and pharmacologic techniques can be utilized. They also report that no specific pharmacological agent has been shown to be superior to others as VTE prophylaxis.

A study by Krantz et al., compared incidence of VTE in high-risk elderly trauma patients receiving either unfractionated heparin (UFH) or the LMWH (enoxaparin)[1444]. They found similar incidence of VTE between the two groups but concluded that further research is required to determine noninferiority of UFH compared to enoxaparin in this population of older individuals.

CKD has been shown to increase the risk of VTE[1445]. Shorr et al., performed a study of VTE and bleeding incidence in patients undergoing total hip arthroplasty (THA) with stage 3B CKD receiving either desirudin or enoxaparin[1438]. The results showed similar rates of bleeding events, but a markedly increased incidence of VTE in the enoxaparin group compared to the desirudin group.

The use of aspirin (ASA) as a form of VTE prophylaxis in an obese population was examined by Tang et al.[1446]. This study compared VTE incidence in obese patients vs. non-obese patients receiving ASA following revision THA or total knee arthroplasty. The study revealed similar rates of VTE between the two groups and the authors concluded that ASA was safe and effective for VTE prophylaxis in obese patients as compared to non-obese patients, although this study does not include another drug for comparison. Other studies of VTE prophylaxis in obese populations have revealed better outcomes with high dose regimens of LMWH compared to standard dosing regimens, but these too did not compare the efficacy against a different drug[1447,1448].

At this time when outpatient surgery especially in surgical centers remote from main hospitals is increasing and accelerated with the 2020 pandemic, it is important to consider that this venue may create a potential differential risk group. Venclauskas et al., published guidelines for perioperative VTE prophylaxis in the setting of outpatient surgery[1449]. They recommend that patients with additional risk factors for VTE undergoing a lower risk surgery receive general measures of thromboprophylaxis and offer a suggestion of LMWH. In patients with additional risk factors for VTE undergoing a higher risk surgery, they suggest preferential administration of LMWH over other drugs.

Further work needs to be done to conclude if certain anticoagulants are more effective than others for VTE prophylaxis in patients at increased risk of VTE. Attention must be given to the specific cause of increased risk along with dosing regimen of the chosen mechanical and chemoprophylaxis.

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56 - Should the perioperative VTE prophylaxis of a patient undergoing orthopaedic procedure who is diagnosed with acute atrial fibrillation be altered?

Response/Recommendation: There is no evidence to indicate that the perioperative venous thromboembolism (VTE) prophylaxis of patients undergoing orthopaedic procedure and diagnosed with acute atrial fibrillation (AF) should be altered. However, according to the latest recommendations of the American Heart Association (AHA), the American College of Cardiology (ACC), the Heart Rhythm Society (HRS), and the European Society of Cardiology (ESC), the patients with AF, and high risk of embolic events should receive anticoagulation therapy.

Strength of Recommendation: Moderate.

Delegates vote: Agree 97.04% Disagree 0.49% Abstain 2.46% (Strong Consensus).

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Rationale: Based on published data, the risk of stroke in patients with AF increases[1450] in the presence of common stroke risk factors. The common risk factors for stroke have been evaluated and a clinical risk tool based on 7 variables: congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, and female sex (CHA_2DS_2 VAS_C) score[1450-1452]. In all AF patients except with moderate- to severe-mitral stenosis or a mechanical heart valve, the CHA_2DS_2-VASc score is used to determine the risk of thromboembolic events for selecting an anticoagulant regimen regardless of the AF pattern (paroxysmal, persistent, permanent)[1452-1454]. For patients at high-risk for VTE events (defined as CHA_2DS_2 VAS_C score ≥ 2 in men and ≥ 3 in women), an anticoagulant therapy is recommended (Class I recommendation)[1450,1452]. In male patients with AF and CHA_2DS_2 VAS_C score = 2 and in females with CHA_2DS_2 VAS_C score = 1, individualized evaluations should be considered for anticoagulation therapy.

Some studies have recommended that in the absence of other AF risk factors, female patients carry a low risk of stroke and have proposed to consider ≥ 2 non-sex-related risk factors for female individuals to mark them as high risk for thromboembolic events[1452,1455].

Based on the ACC/AHA guidelines for the management of patients with AF[1452], "valvular AF (defined as AF in the setting of moderate-to severe-mitral stenosis which potentially requires surgical intervention, or in the presence of a mechanical heart valve) is considered an indication for long-term anticoagulation with warfarin" while in patients with non-valvular AF, the CHA_2DS_2-VASc score is recommended for assessment of stroke risk. In score ≥ 2 in men or ≥ 3 or in women, oral anticoagulants including warfarin, dabigatran, rivaroxaban, apixaban or edoxaban are recommended. On the other hand, "bridging therapy with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) is recommended for patients with AF, and a mechanical heart valve undergoing procedures that require interruption of warfarin".

Also, as mentioned above, according to the 2020 ESC guidelines for the diagnosis and management of AF[1450], stroke risk assessment has been discussed in the setting of "AF in the absence of severe-mitral stenosis, or prosthetic heart valves because AF increases the risk of stroke five-fold". Furthermore, it is mentioned that non-paroxysmal AF is associated with an increase in thromboembolism compared with paroxysmal AF (multivariable adjusted hazard ratio [HR] 1.38; 95% confidence interval [CI] 1.19 - 1.61; $p < 0.001$). Compared to AF patients without valvular heart disease (VHD), "the risk of thromboembolism and stroke is increased among AF patients with VHD other than mitral stenosis, and mechanical heart prostheses, mostly owing to older age and more frequent comorbidities". The similar CHA_2DS_2-VASc score risk stratification tool is recommended for stroke risk assessment to identify patients at stroke risk.

In conclusion there is no specific difference in VTE prophylaxis of a patient diagnosed with acute AF in the perioperative period however these patients should be precisely evaluated with respect to common stroke risk factors via the CHA_2DS_2 VAS_C score and be treated with appropriate anticoagulant regimen in high-risk conditions. Otherwise, they should be evaluated individually to assess the perioperative risk of VTE.

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57 - What is the most optimal management of a patient with elevated coagulation parameters, such as high INR, undergoing emergency orthopaedic surgery?

Response/Recommendation: In patients on vitamin K antagonist (VKA) with an elevated international normalized ratio (INR) requiring emergency orthopaedic surgery, we suggest correction to an INR ≤ 1.5.

Strength of Recommendation: Limited.

Delegates vote: Agree 93.50% Disagree 3.00% Abstain 3.50% (Strong Consensus).

Rationale: The prothrombin time (PT) test measures the extrinsic and common coagulation pathways. The PT correlates to the degree of inhibition of Factors II, V, VII, X and fibrinogen which are synthesized by the liver. The INR is an expression of the results of a PT in a standardized testing environment allowing for universal standardization of anticoagulant therapy[1456-1458]. The most common reason for an isolated elevated INR is VKA anticoagulation therapy (e.g., warfarin). However, a prolonged PT and elevated INR can also occur in vitamin K deficiency, lupus anticoagulants, extrinsic pathway coagulation factor deficiencies, disseminated intravascular coagulation, bile duct obstruction, malabsorption, malnutrition, and other conditions[1456]. Furthermore, other anticoagulants,

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including the direct oral anticoagulants (e.g., rivaroxaban), hirudin, argatroban, and heparin, may also prolong the PT.

VKA are widely used for variety of different clinical indications including primary prevention of stroke for patients with atrial fibrillation and for the acute treatment or secondary prevention of venous thromboembolism (VTE). VKA inhibit hepatic production of the vitamin K dependent coagulation Factors (II, VII, IX, X), protein C and S. The clinical effect is measured by the INR. Previous studies have reported that the use of VKA was associated with a delay in time-to-surgery and higher mortality for patients requiring emergency orthopaedic procedures[1459-1462]. Furthermore, these patients experience increased surgical blood loss and higher risk of red blood cell transfusions[1463], highlighting the importance reversing the anticoagulation effect prior to emergency surgery.

Current VTE guidelines presented by the American Society of Hematology and the American College of Chest Physicians do not provide direction on the correction of INR for patients on VKA undergoing emergency surgery[1457,1464]. Although current literature still lacks consensus regarding the most appropriate management strategy for VKA reversal in patients undergoing emergency orthopaedic surgery, recommendations for the management of major bleeding episodes related to VKA have been published. In patients on VKA with elevated INR and major bleeding complications, the clinical practice guidelines *suggest* using 4-Factor prothrombin complex concentrates (PCC) rather than fresh-frozen plasma (FFP) in addition to cessation of VKA and administration of intravenous vitamin K[1457].

Vitamin K (phytonadione) may be given orally, intravenously, or subcutaneously depending on the value of the INR and the desired time frame for anticoagulant reversal. In stable, semi-urgent cases (within 24 - 36 hours), low-dose oral administration (1 - 2.5 mg) is preferred[1465-1468]. Although intravenous administration of vitamin K is associated with a risk of anaphylactoid reaction, it has a more rapid effect and may be more effective in the truly emergent case. For urgent surgical procedures that can be delayed for 6 - 12 hours, the anticoagulant effect of warfarin can be effectively reversed with 10 mg of intravenous vitamin K[1469-1471]. For patients requiring emergent surgical procedures (within less than 6 hours), 4-Factor PCC containing Factors II, VII, IX, and X or FFP is required to rapidly reverse the anticoagulant effect of VKA[1472,1473]. The concentration of coagulation factors in PCC is approximately 25 times greater than that available in FFP, allowing for it to be administered in small volumes of fluid[1469]. The reversal of anticoagulation with PCC or FFP is temporary and decreases after six hours due to the short half-life of Factor VII. Therefore, it is recommended that vitamin K be administered concurrently to ensure sustained reversal effect. Previous observational studies have shown that reversing the effect of VKA to an INR ≤ 1.5 using vitamin K and/or PCC or FFP is safe and effective in patients requiring emergency orthopaedic surgery[1472,1474-1478].

Although it is widely recognized that the use of VKA is associated with a delay in time to surgery as well as morbidity and mortality in patients requiring emergency orthopaedic surgery, existing studies have not defined the optimal management strategy to reverse the anticoagulant effect of VKA. Notwithstanding, based on the proven efficacy and safety of vitamin K, 4-Factor PCC and FFP in the management major bleeding episodes and the reassuring observational data in patients requiring emergency orthopaedic surgery, there is some evidence to support the recommendation to correct the INR to ≤ 1.5 in patients on VKA who requires emergency surgery.

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58 - What is the optimal VTE prophylaxis modality for patients with bleeding disorders such as hemophilia or Von Willebrand disease?

Response/Recommendation: Mechanical venous thromboembolism (VTE) prophylaxis is most appropriate for patients with bleeding disorders undergoing orthopaedic surgery. However, the addition of mild pharmacologic VTE prophylaxis should be considered for select patient groups that may express a higher prothrombotic phenotype, and in those using clotting factor concentrates bypassing agents or monoclonal antibodies that may increase the risk of thrombosis.

Strength of Recommendation: Limited.

Delegates vote: Agree 96.50% Disagree 0.00% Abstain 3.50% (Strong Consensus).

Rationale: The normal clotting mechanism of blood is altered in patients with bleeding disorders. These patients most frequently exhibit musculoskeletal bleeding including hemarthrosis as a symptom of their condition, thereby resulting in progressive joint damage, especially when they are not administered a clotting factor replacement regimen for early prophylaxis[1479]. Ultimately, the presence of resulting arthropathy usually necessitates major orthopaedic surgery such as total knee arthroplasty (TKA) and total hip arthroplasty (THA) in patients with bleeding disorders[1480-1482]. In theory, perioperative administration of coagulation factor concentrates in order to correct a hemostatic defect leads to a normalized risk of VTE, and therefore such patients would then have a similar risk of VTE as the general population[1483]. Various practices for VTE prophylaxis have emerged as a result of the bleeding complications encountered in this patient population[1484]. However, evidence-based results cannot be obtained due to the lack of controlled studies.

Hemophilia is an inherited bleeding disorder and has two main types, i.e., hemophilia A that stems from Factor VIII deficiency and hemophilia B that stems from Factor IX deficiency. Many (90%) of the patients with hemophilia develop hemophilic arthropathy before the age of 30 due to recurrent hemarthroses[1485,1486]. Despite the high rate of surgical complications including infection, the number of patients undergoing total joint arthroplasty (TJA) has been rising with increased availability of factor replacement therapy[1481,1487,1488]. The risk of VTE complications is decreased in patients with hemophilia due to the deficiency of coagulation factors[1489]. On the other hand, these patients are perioperatively administered clotting factor replacement therapy in order to correct the hemostatic defect, leading potentially, to an increased risk of postoperative VTE[1490]. In this patient group, prolonged use of central venous catheters, which are frequently utilized in treatment[1491], as well as the use of intensive replacement therapy and bypassing agents, immobilization and malignancies are known to cause an increased risk of VTE[1480,1492-1496]. According to the literature, while the risk of VTE ranges between 1 - 2% in the general population[1497,1498], the incidence of symptomatic VTE after major orthopaedic surgery (THA or TKA) has been reported to be 0.5 - 1% in patients with hemophilia[1480,1483,1487]. Studies conducted with hemophilic patient groups have shown that short-term therapy (two weeks) with low-molecular-weight heparin (LMWH) can be administered to the patients who develop thrombosis[1495,1499]. In an extensive survey study including centers that provide treatment for patients with hemophilia in Europe, it was found that pharmacologic VTE was preferred in more than half of these centers[1500]. According to another USA-based survey study, 67% of the participants thought that some type of VTE prophylaxis could be required in patients with hemophilia undergoing TJA, whereas only 37% of the participants actually used VTE prophylaxis as part of routine practice[1484].

Considering the risk of VTE in patients with rarer bleeding disorders, it was reported that patients with Von Willebrand Disease (VWD) had increased risk of thrombosis compared to those with hemophilia[1501,1502], and thrombotic events were frequently associated with surgery[1496]. Thrombotic events have also been reported in patients with congenital Factor VII deficiency, afibrinogenemia and Factor XI deficiency[1503,1504]. In such patients, coagulation factor replacement therapy for surgery, immobilization and advanced age were reported to be risk factors for VTE[1480]. Therefore, VTE prophylaxis is also recommended for these patient group as in patients with hemophilia A and B.

Recent studies have shown that compression stockings and intermittent sequential compression device can be recommended as part of routine practice and are beneficial for the mechanical prophylaxis for VTE prevention in patients with hemophilia. On the other hand, the use of pharmacologic agents for VTE prophylaxis, i.e., LMWH, warfarin, unfractionated heparin, fondaparinux and aspirin, should be based on the individualized risk according to the choice and level factor replacement or bypassing agents like prothrombin complex concentrates in combination with monoclonal antibodies (emicizumab), and prothrombotic risk factors[1483,1485,1505]. Antifibrinolytics can be used with standard doses of clotting factor concentrates, including bypassing agents. However, they should not be used with prothrombin complex concentrates due to the increased risk of thromboembolism[1505].

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59 - What is the optimal VTE prophylaxis modality for patients with clotting disorders such as thrombophilia?

Response/Recommendation: Patients with thrombophilia should receive venous thromboembolism (VTE) prophylaxis for major orthopaedic surgery. We recommend a combination of mechanical and pharmacological interventions for up to 35 days after the procedure to address the variability of VTE risk, which is difficult to estimate in frequency and magnitude. For less invasive musculoskeletal procedures, the VTE prophylaxis should be tailored according to the prothrombotic risk of each procedure, with emphasis on those of lower extremities.

Strength of Recommendation: Limited.

Delegates vote: Agree 95.02% Disagree 1.49% Abstain 3.48% (Strong Consensus).

Rationale: The prevalence of thrombophilic abnormalities ranges from 0.02% up to 14.5%[1506-1509] and is known to be an independent risk factor for spontaneous VTE events providing a 2-fold up to a 50-fold increased risk[1510], depending on the underlying disease and its severity. However, thrombotic events attributed to thrombophilia, in the absence of additional risk factors, do not surpass half of the VTE events[1511]. This reflects the requirement for several thrombotic risk factors or high-risk situations to be present, for a clinical event to occur in patients with inherited thrombophilia[1512], such as surgery. Performing surgery in a patient with inherited thrombophilia supposes a 13-fold increased risk of VTE within 1 year (odds ratio [OR], 13.3 95% confidence interval [CI]; 7.2 - 24.7)[1513]. Furthermore, VTE risk was highest within the first 30-days following surgery (OR adj 17.5; 95% CI, 9.2 - 33.4) and remained high up to 90-days postoperatively in this population[1513-1518].

In terms of VTE risk, thromboprophylaxis guidelines stratify orthopaedic procedures in low-, intermediate-, and high-risks groups. All patients with thrombophilia should be classified in the high-risk VTE groups independently from the underlying procedure[1513].

The safety and effectiveness of anticoagulants or mechanical interventions on specific subtypes of thrombophilia evaluating the frequency of VTE events after surgery as a primary outcome has not been established. According to the

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2016 guidelines on antithrombotic therapy by the American College of Chest Physicians (ACCP) recommend that the choice of anticoagulant should be individualized considering patient factors such as renal/liver/coronary artery diseases, adherence, and preference, however no specific mechanical and/or pharmacological protocol for patients with thrombophilia has been specified[1519]. The low prevalence of thrombophilia, as well as the high economic burden on screening for its subtypes, would require extensive resources to answer this complex clinical question. Intuitively, one might consider a higher dose of antithrombotic medication will result in a higher protection against VTE events, however, this would affect the safety window of anticoagulants increasing the bleeding rate.

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60 - What are the indications for use of an IVC filter in patients undergoing orthopaedic procedures?

Response/Recommendation: Inferior vena cava (IVC) filters may be considered for patients who have a high risk of venous thromboembolism (VTE) and in whom chemical anticoagulation is contraindicated. IVC filters should not be used on a routine basis for deep venous thrombosis (DVT) prophylaxis, particularly when chemical prophylaxis can be administered.

Strength of Recommendation: Limited.

Delegates vote: Agree 94.23% Disagree 3.85% Abstain 1.92% (Strong Consensus).

Rationale: VTE is a significant concern in patients undergoing orthopaedic procedures. VTE may result in morbidity and mortality through pulmonary embolism (PE), post-thrombotic syndrome, and symptomatic DVT[1520-1525]. Without anticoagulation, risk of VTE after orthopaedic surgery has been estimated from 40% - 80%[1526,1527]. Anticoagulation protocols are designed to balance the benefits of reducing these complications with the risks of bleeding. In patients with contraindication to pharmacologic anticoagulation or particularly high risk of VTE, orthopaedic surgeons may consider the prophylactic use of IVC filter.

For most patients, the rate of PE after orthopaedic surgery is low, estimated at approximately 0.5%[1528-1532]. Many comorbidities are known to increase the risk of VTE, including advanced age, cancer, obesity, Glasgow coma scale (GCS) < 8, and multiple long bone fractures[1529,1533-1541]. The risk of VTE is higher still in patients with prior history of VTE or familial clotting disorders[1542,1543]. In these high-risk groups, VTE risk may approach 10 - 15%, with 5% developing PE after orthopaedic procedures[1543].

In nonrandomized trials, IVC filters have proven effective in reducing the risk of PE in high-risk patients. In patients with prior VTE undergoing elective arthroplasty, IVC filter reduced the risk of PE from 5.5% - 0.8%[1543]. Similarly, in a group of high-risk spine surgery patients, defined as fusions > 5 levels, anesthesia time > 8 hours, and prolonged immobilization, 3.6% developed PE in the IVC group vs. 13.1% in a group of matched controls[1544-1546]. These reports were retrospective and were not controlled for modern chemical anticoagulation. More recently, in trauma patients with contraindication to anticoagulation, the placement of IVC filters significantly reduced the risk of symptomatic PE after injury from 14.7% - 0%[1547].

In deciding whether to employ a filter, surgeons must also consider the risks associated with the placement of IVC filters. Filter migration, puncture site, hematoma, have been reported[1548-1551]. In addition, IVC filters are associated with increased risk of long-term complications such as post-thrombotic syndrome. Historically the rate of complication associated with IVC filter placement has been estimated at 12%, with up to 20% of IVC filters unable to be removed[1521]. These risks, however, are decreasing as technology and technique are improving, with recent cohorts demonstrating much lower complication rates with filter retrieval[1543,1552,1553]. Technological advances and systematic improvements in monitoring and an increased rate of planned removal have lowered, but not eliminated the risks of filter placement. Filters may be unable to be removed for various reasons including a clot load distal to the filter as well as technical difficulties.

Data is less supportive regarding the utility of IVC filters in patients also receiving pharmacologic anticoagulation. Most

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studies demonstrating reduced PE risk have included patients also receiving medical anticoagulation, but these standards have also changed over time. Most recently, the Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption (PREPIC) - 2 trial was unable to demonstrate decreased PE risk after IVC filter placement in patients admitted with VTE who received chemical anticoagulation[1549,1550].

In summary, IVC filters have been shown to decrease rate of PE in patients at high risk of VTE undergoing orthopaedic surgery who cannot tolerate anticoagulation. Placement and retrieval of IVC filter is associated with some risks bordering on 10% with inability to remove the filter being the highest risk. IVC filter placement should not be used routinely for VTE prophylaxis, particularly in patients who can receive VTE prophylaxis within 24 - 48 hours. The use of IVC filters should be limited to patients who either have a known VTE or are high risk for clot formation and cannot receive prophylaxis. The use of IVC should also be considered in patients who developed VTE despite being on chemical anticoagulation.

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61 - Does the availability of reversal agents influence the choice of a selected chemical VTE prophylaxis agent?

Response/Recommendation: Yes. Commonly used venous thromboembolism (VTE) prophylaxis agents have acceptable safety profiles as well as established guidelines for reversal. Some agents

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may be safely continued during surgery (e.g., aspirin [ASA], clopidogrel), while others can be promptly reversed by discontinuation (e.g., low-molecular-weight heparin [LMWH]). Other agents such as vitamin K antagonists (e.g., warfarin) and direct-oral anticoagulants (DOAC) require a longer discontinuation interval before surgery. The reversal agents such as such as Prothrombin Complex Concentrates as well as specific antidotes such as idarucizumab and endexine alfa, with limited availability may need to be administered for emergency cases. As such, the availability and cost of reversal agents are important factors that influence the choice of VTE prophylactic agent.

Strength of Recommendation: Limited.

Delegates vote: Agree 89.15% Disagree 4.25% Abstain 6.60% (Strong Consensus).

Rationale: In general, orthopaedic surgeons are likely to face one of two scenarios that may require reversal of anticoagulation: (1) a patient who is on long-term anticoagulation (e.g., cardiac conditions) presenting with a fracture that requires urgent surgical intervention (e.g., proximal femur fracture); (2) a patient who is on short-term chemical thromboprophylaxis following an elective orthopaedic procedure (e.g., total joint arthroplasty) and develops a complication (e.g., wound breakdown or infection) or sustains a fracture that requires urgent surgical intervention. An increasing number of elderly patients on long-term anticoagulants and newer guidelines on rapid recovery surgical protocols have led to extensive research on this topic[1554-1563]. Deciding whether anticoagulation reversal is absolutely necessary or defining its specific indications are beyond the scope of this review.

Although there are several platelet inhibitors alternatives, ASA, dipyridamole and clopidogrel are most commonly used for VTE prophylaxis after orthopaedic procedures. In contrast, newer, more potent platelet inhibitors are usually prescribed for severe cardiovascular disease. No specific reversal agent exists for platelet inhibitors, hence discontinuing antiplatelet therapy is the only method of reversal. Notwithstanding, ASA and dipyridamole are considered safe for surgery and no discontinuation is required before neuraxial anesthesia[1564]. It has been shown that patients receiving ASA, dipyridamole, or both, who undergo proximal femur fracture surgery have no increased intraoperative blood loss[1565]. Clopidogrel is a more potent antiplatelet and has a washout period of 5 – 7 days. Similarly, recent evidence has questioned the discontinuation of clopidogrel in the context of urgent surgery, as no clear negative outcomes have been reported despite a possible increase in the rate of blood transfusion especially when surgery is performed under dual ASA-clopidogrel treatment[1566-1570]. If unexpected or serious bleeding occurs, supportive treatment with platelet transfusions may be necessary[1571] (Table V).

When platelet transfusions are indicated, the half-lives of platelet inhibitors and their metabolites should be considered. If the patient is on dual ASA-clopidogrel treatment, surgery should be delayed for at least 12 - 24 hours after the last intake of both drugs to allow clearance of free active metabolites from circulation before platelet transfusions are administered[1571-1573].

Desmopressin: Is another alternative to minimize perioperative blood loss in patients receiving antiplatelet therapy, although the evidence for its use in orthopaedic surgery is scarce[1574].

Low-molecular-weight heparin (LMWH): Were developed for surgical VTE prophylaxis and are widely used in this context. There are several different drug types, and although all of them are derived from unfractionated heparin (UFH), each has its own specific pharmacokinetics.

Protamine: Is a classic antidote to use for UFH reversal. Both molecules combine to form a salt, making protamine a highly effective reversal agent if dosed appropriately[1575]. However, it incompletely reverses Factor Xa inhibition of LMWH despite complete neutralization of the antithrombin

TABLE V Costs and availability of reversal agents

	Reversal Target	Availability	Cost*
Platelet transfusions	Platelet Inhibitors	Widespread	$5,258 – $13,117
Desmopressin	Platelet Inhibitors	Widespread	$26 – $50 (10mL IV)
Protamine	UFH (LMWH less effective)	Widespread	$34 – $40 (25mL IV)
Phytonadione (vitamin K)	Vitamin K antagonists	Widespread	Around $200 (1mg IV) or $30 (5mg PO)
Prothrombin Complex Concentrates	Vitamin K antagonists (DOAC less effective)	Widespread	$4,050 – $8,100
Idarucizumab	Dabigatran	Limited	$4,500 (2.5g/50mL)
Andexanet alfa	Factor Xa inhibitors	Limited	$24,750 – $49,500 (200mg)
Ciraparantag	LMWH, Dabigatran, Factor Xa inhibitors	Not commercially available	

*Approximate cost per unit (recommended dosages/associated costs may vary according to different protocols) available @ https://www.drugs.com/price-guide/. IV=Intravenous; UFH=Unfractionated heparin; LMWH=Low-molecular-weight heparin; PO=By mouth; DOAC=Direct-oral anticoagulants.

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effect. This results in only 60% reversal of LMWH effects. Consequently, drug discontinuation is the mainstay of reversal. Surgery is usually delayed for 12 hours after the last injection if prophylactic doses are administered and delayed for 24 hours in patients receiving higher (therapeutic) doses[1564].

Vitamin K antagonist: Such as warfarin or acenocoumarol are also frequently used as chemical VTE prophylaxis. The most commonly used reversal strategy is drug discontinuation and intravenous (IV) or oral administration of phytonadione (i.e., vitamin K) to overcome the antagonistic effect while allowing the liver to increase production of clotting factors. Although the IV route offers faster reversal of the international normalized ratio (INR) and hence less preoperative delay, this process may be lengthy and patients with very high prothrombin (PT)-INR or the need for urgent surgery may require accelerated reversal[1576-1579].

Fresh-frozen plasma (FFP): Is a commonly used alternative, although its efficacy in this context has never been definitively proven, and it has several well-known drawbacks related to blood-typing and transfusion-related complications owing to the large volume of infusion necessary.

Prothrombin Complex Concentrates (PCC): Have been shown to be superior to plasma, offering significant reduction in all-cause mortality, more rapid INR reduction, and less volume overload without a significantly increased risk of thromboembolic events[1580,1581]. Three different PCC products (a 3-Factor PCC, a 4-Factor PCC, and an activated PCC) and one recombinant-activated Factor VII are commercially available. The 4-Factor PCC is the most commonly used and has been proven to be superior to plasma both in INR reduction and clinical efficacy in patients requiring urgent surgery including major orthopaedic procedures[1582,1583], and proximal femur fractures in particular[1584].

Regarding non-vitamin K anticoagulants or DOAC, evidence for reversal in patients in need for urgent surgery is scarce. Before the advent of specific antidotes, several trials have examined the use of off-label PCC in major bleeding with somewhat conflicting results[1585-1588]. A study focusing on patients undergoing urgent surgery (only 8 orthopaedic procedures) showed favorable results. More recently, specific reversal agents have been approved both for direct thrombin inhibitors (i.e., dabigatran) and Factor Xa inhibitors (e.g., rivaroxaban, apixaban, edoxaban).

Idarucizumab: A monoclonal antibody fragment antigen binding, has 350 times more affinity for dabigatran than thrombin, and hence effectively neutralizes its activity[1589]. In a subgroup analysis of patients undergoing surgery, it was shown to offer normal periprocedural hemostasis in over 90% of 45 orthopaedic procedures[1590], and no intraprocedural bleeds were reported among 31 orthopaedic procedures in a real-world setting[1591].

Andexanet alfa: Is a modified recombinant Factor Xa protein that rapidly binds to Factor Xa inhibitors so that native Factor Xa can function normally[1592]. Although its use has been approved both in North-America (Food and Drug administration [FDA]) and Europe (EMA) for patients with major bleeding, no specific data on patients requiring urgent surgery exists to date[1593]. The safety profile of idarucizumab and andexanet alfa use has been addressed in a recent systematic review and meta-analysis, which showed that the incidence of thrombotic events was 3.3% for idarucizumab, and 10.6% for andexanet alfa[1594]. This result should be interpreted with caution, as the incidence of thrombotic events was only 0.7% when examining patients who required urgent or emergent surgery (although no andexanet alfa data available in this context)[1594].

Ciraparantag: Is the newest agent in this category. It is a synthetic molecule that binds to UFH and LMWH, as well as fondaparinux, dabigatran, and Factor Xa inhibitors[1595]. At present, there is no data from phase III trials and this drug has not been approved for clinical use.

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62 - Does post-operative rehabilitation protocol such as early ambulation influence the incidence of VTE after orthopaedic procedures?

Response/Recommendation: It is the opinion of this group that early ambulation reduces the incidence of venous thromboembolism (VTE) after orthopaedic procedures.

Strength of Recommendation: Moderate.

Delegates vote: Agree 99.07% Disagree 0.93% Abstain 0.00% (Strong Consensus).

Rationale: The evidence to date has been mixed on the impact of post-operative rehabilitation protocols that include early ambulation on the incidence of VTE after orthopaedic procedures. Immobilization, frequently seen with orthopaedic procedures, or from orthopaedic injuries to the extremities is a risk factor for VTE[1596,1597], especially in the elderly population (> 70 years old)[1598]. The quantity and duration of immobilization as it relates to the degree of risk for VTE are unknown and there is wide variability in the literature regarding the risk for VTE from reduced mobility. Early research has shown that a loss of mobility for > 3 days has been correlated with the presence of deep venous thrombosis (DVT) on ultrasound[1599,1600]. In addition, an epidemiologic case-control study of DVT risk factors in 1,272 patients found that patients who were ambulatory had an increased risk of VTE development with a standing time of > 6 hours (odds ratio [OR] = 1.9) or resting in a chair or bed (OR = 5.6)[1601].

Guidelines written for hip and knee arthroplasty from the American Academy of Orthopaedic Surgeons (AAOS) and the American College of Chest Physicians (ACCP) on current VTE prophylaxis do not provide specifics on the type of VTE prophylaxis to be used. However, they do include recommendations on early ambulation[1602,1603]. Early post-operative mobilization is also recommended by the European Society of Anesthesiology and Intensive Care (ESAIC) as a general

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thromboprophylaxis measure for most low and high-risk procedures[1604]. Older guidelines recommended bed rest for patients who were diagnosed with a lower extremity DVT as there was concern that ambulation would cause clot dislodgement leading to further complications such as a pulmonary embolism (PE). However, recent findings of a meta-analysis that compiled 5 randomized control trials (RCT) with 3,048 patients showed that when compared to bed rest, early ambulation was not associated with a higher incidence of a new PE. In fact, early ambulation was shown to be associated with a lower incidence of new DVT/PE compared to bed rest[1605]. A further systematic review assessing the impact of physical activity in patients with an acute or previous DVT of the leg found that early ambulation was safe in patients with acute DVT and helped prevent further complications[1606]. The physiological foundation for early ambulation is well understood following the principles of Virchow's triad. Nakao et al., reported that early postoperative ambulation was associated with lower levels of D-dimers in patients with osteoarthritis and rheumatoid arthritis following total knee arthroplasty (TKA)[1607]. However, the definition and duration of early ambulation varies across studies[1608].

Furthermore, several factors have a negative impact on early ambulation following surgery, such as low patient compliance due to postoperative pain, lack of intrinsic motivation, inadequate staffing, use of indwelling urinary catheter, acute complications, and specific hospital policies[1609].

There is some evidence to support the recommendation for early ambulation in postoperative orthopaedic patients. Pearse et al.[1610], assessed the influence of a rapid rehabilitation protocol on TKA patients and the rate of DVT, as determined by Doppler ultrasound scanning on the fifth postoperative day. The early mobilization group (beginning to walk < 24 h after knee replacement) was compared to a historical cohort. In the early mobilization group, the incidence of DVT was considerably low 1.0% compared to 27.6% in the control group ($p < 0.001$). Husted et al.[1611], reported their results with short-duration pharmacological prophylaxis combined with early mobilization and reduced hospitalization protocol in 1,977 consecutive, unselected patients who were operated on for primary total hip arthroplasty (THA), TKA or bilateral simultaneous TKA (BSTKA) in a fast-track setting between 2004 - 2008. Patients mobilized within four hours postoperatively and short duration of VTE prophylaxis (1 - 4 days), had a mortality rate of 0% (95% confidence interval [CI] 0 - 0.5). The incidence of DVT in the latter study was 0.60%, 0.51%, and 0.0% for patients undergoing TKA, THA, and BSTKA, respectively. Based on these results, the authors indirectly concluded that early mobilization and short hospitalization are associated with lower VTE risks following arthroplasty and the principles of routine prolonged chemical thromboprophylaxis should be reconsidered.

In another small prospective study of TKA patients, 50 patients who underwent mobilization on the first postoperative day were compared with 50 patients who had strict bed rest on the first postoperative day. The incidence of VTE in the mobilization group (seven in total) compared with the control group (16 in total) was significantly lower ($p = 0.03$). Additionally, the odds of developing a thromboembolic complication was significantly reduced with greater walking distance[1612]. A multicenter retrospective cohort study in China found that early ambulation within 24 hours after TKA was associated with reduced length of hospital stay, improved knee function and range of motion, and lower incidence of DVT. Interestingly, the incidence of pulmonary embolism did not differ between the early ambulation group and control group[1613]. Additionally, a VTE prevention team at Boston Medical Center designed a protocol that mandated early postoperative mobilization along with VTE risk stratification for patients and found an 84% reduction in the incidence of DVT over a two-year time period compared to the two years prior[1614]. Some of the reduction was correlated to the emphasis on early ambulation. However, the patient demographics varied and were only based on general surgery and vascular surgery patients.

There are some studies demonstrating evidence to the contrary. A RCT evaluating early functional mobilization on the incidence of DVT during leg immobilization after achilles tendon rupture surgery found that early functional mobilization did not prevent the high incidence of DVT compared to expectant management[1615]. There is some thought that this is explained by postoperative pain and thus less weight bearing. In addition, another systematic review of five RCT examining the effect of early mobilization after THA or TKA found no differences in negative outcomes such as venous thrombosis in the control versus experimental groups[1616]. No studies reported negative outcomes associated with early postoperative mobilization.

In summary, there is some direct evidence to suggest that early mobilization following orthopaedic procedures may be protective against VTE, while some evidence suggests that early mobilization has no impact on VTE risk. Given the low risk and cost associated with early mobilization, early ambulation is recommended in all patients, if clinical circumstances permit. Additional RCT are needed to broaden the strength of recommendation, as well as to better quantify the duration of reduced mobility that leads to increased risk for VTE as well as the timing and duration of when to introduce early ambulation following orthopaedic procedures.

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63 - What is the most optimal VTE prophylaxis for patients who are on strict bed rest pre- or post-operatively?

Response/Recommendation: The most optimal thromboprophylaxis in patients on strict bed rest is not known. Any combination of chemical and/or mechanical (i.e., intermittent compression devices) prophylaxis may be considered in patients who will be on prolonged and strict bed rest.

Strength of Recommendation: Limited.

Delegates vote: Agree 96.60% Disagree 1.94% Abstain 1.46% (Strong Consensus).

Rationale: Prolonged bed rest is well-known to increase the risk of venous thromboembolism (VTE)[1617]. Strict bed rest for more than 7 days, especially after a fracture, is a significant risk factor in developing VTE[1618,1619]. Despite the recognized risk, there is a paucity of literature recommending the optimal prophylaxis for these patients[1620]. Chemical prophylaxis, including low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH), and mechanical measures (such as graduated compression stockings [GCS], and intermittent pneumatic compression devices [IPCD]) have been suggested by some authors[1621,1622].

Paucity in the literature regarding optimal prophylaxis often results in clinicians prescribing aggressive or long-term anticoagulation for patients on strict bed rest. The United Kingdom's National Institute of Clinical Excellence (NICE) guidelines[1623], and the American Society of Hematology (ASH) guidelines[1624] do not provide precise recommendations on how to prevent VTE in patients who are restricted to bed rest. LMWH is advised up to 12 hours from surgery in hip fractures if surgery is delayed beyond the day of admission[1624]. In patients where pharmacological prophylaxis is contraindicated, mechanical prophylaxis, including IPCD, or GCS is advised[1623,1625]. One of the common limitations of these guidelines is that they do not focus specifically on the issue of "strict bed rest" during the pre-or post-surgery period.

For patients who are bedbound/bedridden due to acute medical illness, LMWH is an effective prophylactic option[1622,1626] and reduces VTE-related events but does not reduce mortality[1627]. Studies have also shown the use of IPCD, and GCS to be efficacious in hospitalized patients with prolonged immobilization[1628-1630]. Ho et al., reviewed this in a meta-analysis and concluded that combining IPCD with pharmacological prophylaxis to be more effective than IPCD alone[1629]. It must be noted that their sub-analysis was not limited to patients on strict bed rest but involved hospitalized patients. A multicenter randomized clinical trial (RCT) analyzing dose-specific prophylaxis in bedridden patients due to acute illness found that a 20 mg daily dose of subcutaneous LMWH (enoxaparin) for 10 days to be effective in preventing VTE[1631].

Although it is widely recognized that bed rest increases the risk of deep venous thrombosis (DVT), and pulmonary embolism (PE), there is only limited evidence which addresses the most optimal VTE prophylactic agent in this group of patients, especially with regards to orthopaedic surgery. Nevertheless, despite the proven efficacy of LMWH in reducing VTE risk in patients with immobilization and evidence from a multicenter RCT, there is limited evidence to suggest that subcutaneous LMWH is effective in the prevention of VTE. The role of combined prophylaxis, including chemical and mechanical prophylaxis, including IPCD in this subset of patients, needs to be analyzed in well-designed prospective studies in the future.

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64 - Is there a role for the use of intermittent compression devices as VTE prophylaxis for patients undergoing orthopaedic procedures?

Response/Recommendation: Yes. Intermittent compression devices (ICD) provide protection against venous thromboembolism (VTE) development following orthopaedic surgery. Utilizing these devices has been shown to be an effective prophylactic measure.

Strength of Recommendation: Moderate.

Delegates vote: Agree 95.81% Disagree 3.26% Abstain 0.93% (Strong Consensus).

Rationale: ICD protect against the development of VTE following orthopaedic surgery primarily by decreasing venous stasis, a contributing factor to thrombus formation. Current guidelines support the use of mechanical prophylaxis for patients undergoing orthopaedic procedures[1632,1633]. Variability among devices and a lack of strong evidence to support individual modalities makes it difficult to agree upon specific recommendations. Below-knee portable ICD that synchronize cuff contraction to venous phasic flow signal may be superior to other mechanical modalities[1634,1635]. Avoidance of complications associated with anticoagulation is a major advantage of ICD use. However, similar to chemoprophylactic regimens, compliance remains a concern. Some modalities allow for providers to monitor device use during hospitalization and after discharge, which may foster improved patient adherence[1636].

A retrospective database review of revision arthroplasty patients compared the use of aspirin (ASA) and ICD to warfarin and ICD. The ASA group had symptomatic pulmonary embolism (PE) and deep venous thrombosis (DVT) rates of 0.2% and 0.4%, respectively, compared to 0.9% for both in the warfarin group. Additionally, the warfarin group showed a significantly higher rate of major bleeding compared to the ASA group[1637]. In a retrospective review of a prospectively designed VTE prophylaxis protocol, 856 consecutive primary and revision total knee arthroplasty (TKA) patients received ASA with circumferential knee-high compression devices. Each patient was evaluated for DVT via duplex ultrasonography prior to discharge and assessed for symptomatic VTE during 90-day follow-up. Sixty-six thrombi were seen, nine patients had symptomatic DVT, and three patients developed symptomatic non-fatal PE[1638]. The authors found that the incidence of both asymptomatic and symptomatic DVT in their study was comparable to that of using anticoagulative agents. Results from these studies support the concomitant use of mechanical compression and ASA for VTE prophylaxis, with a decreased risk of bleeding compared to anticoagulant chemoprophylaxis regimens.

The majority of studies evaluating mechanical compression device (MCD) use in orthopaedic patients focus on lower extremity arthroplasty. However, some studies have assessed their use in non-arthroplasty procedures[1639–1641]. A prospective study reported VTE rates of 1% and 7% in patients using ICD alone following cervical discectomy with fusion and cervical decompression, respectively. These rates are similar to rates seen using common anticoagulants as prophylaxis[1641]. A similar study of patients who underwent lumbar laminectomy with instrument fusion led the author to conclude that ICD use was sufficient for VTE prophylaxis while also lowering risks, such as hematoma, that are seen with chemoprophylaxis[1640]. In a prospective trial, 1,803 German patients undergoing various orthopaedic procedures were randomized to receive a chemoprophylactic regimen including low-molecular-weight heparin (LMWH) alone or the chemoprophylactic regimen with ICD. The procedures consisted of arthroplasty (24%), knee soft tissue repair (19%), open fracture fixation (21%), tumor resection (6%) and other (28%). The ICD augmented group had a DVT rate of 0.44% compared to 1.66% with chemoprophylaxis alone, which was a statistically significant difference. Furthermore, the ICD group demonstrated a significantly lower DVT rate in total hip arthroplasty (THA) and TKA than the chemoprophylaxis group[1639]. All three studies commented on the decreased bleeding risk associated with ICD use. Although there is a need for more studies evaluating their use in non-arthroplasty procedures, the previously mentioned

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studies suggest that compression devices may lower DVT and PE rates following various orthopaedic procedures.

Some orthopaedic surgeons feel that the adoption of contemporary surgical techniques and peri-operative management make it possible to use ICD as monoprophylaxis. A randomized trial comparing the use of a portable ICD to LMWH with respect to major bleeding and efficacy following THA evaluated 392 patients. The device allowed patient mobilization and continued utilization following discharge. The PE and symptomatic DVT rate were 5% in both the mobile ICD group and the LMWH group. However, a significant difference was detected between the portable compression device group (0%) and the LMWH group (6%) with regard to bleeding events[1642]. Limitations of the study are that it was powered to detect a difference in bleeding rates and not the incidence of symptomatic VTE. Additionally, 61% of the ICD group also used ASA as part of their prophylactic regimen. Colwell et al.[1636], conducted a large multicenter study evaluating the use of a mobile ICD, with or without ASA, in preventing VTE. In this non-inferiority designed study, 3,060 patients who underwent either primary TKA or THA used an ICD perioperatively for a minimum of 10 days. Symptomatic VTE occurred in 28 patients, with a rate of 0.5% and 1.3% in patients who had THA and TKA, respectively. The results demonstrated non-inferior efficacy in the prevention of VTE compared with the most commonly used pharmacological protocols, with the exception of rivaroxaban use in TKA. ICD use missed the pre-determined 1% non-inferiority margin by 0.06% in rivaroxaban in TKA. The authors recommend that surgeons consider the use of this mobile compression device, with or without ASA, as an alternative to pharmacological prophylaxis in patients treated with lower-extremity arthroplasty. Findings from these studies support the augmentation of ASA with mechanical compression, particularly in patients undergoing lower extremity arthroplasty. Additionally, patients using ICD experienced significantly less major bleeding, with similar rates of VTE events, compared to patients receiving chemoprophylaxis with LMWH.

A prospective trial of 440 Asian patients undergoing TKA randomized patients to receiving no prophylaxis (control group), ICD, graded compression stockings (GCS) or LMWH. The rate of DVT was significantly lower in the ICD group in comparison to the control group. The LMWH group also showed a statistically lower DVT rate. However, patients using GCS did not demonstrate a statistically significant lower DVT rates[1643]. This study suggests the use of ICD is superior to no thromboprophylaxis at protecting against DVT, while showing similar efficacy to LMWH in TKA patients.

In summary, ICD effectively reduce VTE following orthopaedic surgery to the corresponding levels of appropriate chemoprophylaxis. Additionally, ICD are shown to have increased safety with regard to bleeding complications compared to commonly used anticoagulant agents.

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65 – Is a foot pump as effective as a lower extremity intermittent compression device for VTE prophylaxis?

Response/Recommendation: The use of a foot pump is as effective as a lower extremity intermittent compression device, when used in combination with chemical prophylaxis.

Strength of Recommendation: Moderate.

Delegates vote: Agree 95.07% Disagree 1.97% Abstain 2.96% (Strong Consensus).

Rationale: Deep venous thrombosis (DVT) is a prevalent early complication after lower extremity surgery and extended periods of immobilization[1644-1646]. Accurate prevention of these events is therefore of substantial importance following orthopaedic surgery to the lower limb. The foot pump is a recognized method of venous thromboembolism (VTE) prophylaxis after orthopaedic surgery[1647]. The foot-sole pump works similarly to the lower extremity intermittent compression device (ICD), in that it simulates active weight-bearing in the bed-ridden patient through sudden and intermittent increases in venous flow. Overall, the foot pump has been shown to maintain venous circulation as well as normal ambulation[1647-1649].

Various randomized control trials (RCT) have evaluated the effectiveness of the foot pump against DVT and pulmonary embolism (PE) after orthopaedic procedures. Although a significant effect is often reported[1647,1650-1653], there were limitations in many of these studies, including small sample sizes[1647,1650-1652] and a

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lack of power analysis[1647,1650-1654]. In addition, DVT and PE were diagnosed by postoperative duplex ultrasonography, ascending venography, or perfusion scintigraphy regardless of symptoms, which likely overestimates the number of events[1647,1650,1651,1653-1655].

A number of studies have shown that the foot pump is not effective as monotherapy against VTE[1651,1654-1658]. For example, a single large retrospective review of 1,659 primary total hip arthroplasty (THA) surgeries found the foot-sole pump alone to be less effective at preventing DVT[1658]. Patients using only the foot pump had a significantly greater incidence of DVT (9.5%) compared to those who received combined mechanical and chemical prophylaxis (fondaparinux 0.7%, enoxaparin 0.0%).

However, combined prophylaxis consisting of both a foot pump and chemoprophylaxis is consistently reported to significantly lower the risk of DVT in comparison to the administration of chemoprophylaxis alone after orthopaedic procedures[1651,1654,1656,1658-1661]. A RCT by Sakai et al., evaluated the effectiveness of the foot pump in 120 patients given edoxaban after total knee arthroplasty (TKA)[1656]. The incidence of DVT was significantly reduced with combined prophylaxis of the foot pump with edoxaban (31.0%) compared to the control group with edoxaban alone (17.7%).

A small number of studies directly compared the foot pump to the lower extremity ICD. Although a single study did find the ICD to be preferred to the foot pump in combined mechanical and chemical VTE prophylaxis[1648], most studies report no significant differences between the two pump[1658,1660-1664]. A comparative study of 121 patients evaluated the efficacy of the lower extremity ICD and foot pump by comparing pre- and postoperative D-dimer values following THA[1663]. At seven days postoperative, the mean D-dimer value was significantly reduced for both pumps (< 10 μg/ml), whereas in patients using no pump it was significantly more elevated (16.5 μg/ml)[1663]. Although promising results, there's limited data on the correlation between actual clinical cases of DVT and the D-dimer value, undermining the strength of these findings[1665]. A non-randomized controlled trial by Spain et al., compared the incidence DVT in 184 high risk patients with lower extremity fractures using the foot pump or another lower extremity ICD[1664]. Incidence of DVT (7% ICD; 3% foot pump) and PE (2 foot pump; 1 ICD) were similar between groups.

Interestingly, the foot-sole pump may have greater compliance and patient satisfaction than other lower extremity ICD[1654,1655]. The popular reasons for inpatient non-compliance include heat/sweating, discomfort, and sleep disturbance[1648,1654,1655,1666-1668]. Since compliance to a lower extremity ICD is generally low and appliances are often placed incorrectly, a smaller, simpler device like the foot pump may be a user-friendlier and better-tolerated choice[1667,1669,1670].

To conclude, only few studies compared the foot-sole pump with other ICD and none of these mechanical means of VTE prophylaxis proved to be superior to one another.

However, patient compliance and user-friendliness are probably better with a foot-sole pump. A systematic review and meta-analysis of six RCT found that a lower extremity ICD combined with chemical prophylaxis decreases the risk of DVT after TKA and THA compared to chemical prophylaxis alone[1671]. Likewise, the current guidelines from the American College of Chest Physicians recommends combining chemical antithrombotic agents with ICD during a patient's hospital stay[1671]. Based on the current evidence, similar conclusions can be drawn in regard to the use of a foot pump. Therefore, the foot pump is as effective as other types of lower extremity ICD, when used in combination with chemical prophylaxis.

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66– Is there a role for the use of compression stockinette, as VTE prophylaxis, in patients undergoing orthopaedic procedures?

Response/Recommendation: Elastic compression stockinette may provide some protection against venous thromboembolism (VTE).

Strength of Recommendation: Moderate.

Delegates vote: Agree 87.79% Disagree 8.92% Abstain 3.29% (Strong Consensus).

Rationale: Mechanical agents can be used alone or in conjunction with other modalities, including anticoagulation agents, as prophylaxis against venous thromboembolism (VTE). Mechanical thromboprophylaxis include rapid postoperative mobilization and ambulation, intermittent pneumatic compression devices (IPCD), and the use of graduated compression stockings (GCS), which apply varying amounts of pressure to different parts of the leg.

There is controversy regarding the efficacy of GCS to prevent VTE following orthopaedic procedures, with studies reporting conflicting results. A prospective trial of 440 Asian patients undergoing total knee arthroplasty (TKA), randomized patients to receiving no prophylaxis, GCS, IPCD, or low-molecular-weight heparin (LMWH). A significantly lower rate of deep venous thrombosis (DVT) was observed for patients receiving IPCD (8%, p = 0.032) or enoxaparin (6%, p = 0.001). Patients using GCS had a lower rate of asymptomatic DVT (13%) in comparison to the control group (22%); however, the difference was not statistically significant[1672]. This observation suggested that the use of GCS may provide some protection against DVT in comparison to receiving no thromboprophylaxis, however, the effect is likely to be substantially lower than that provided by anticoagulants and IPCD.

Camporese et al., evaluated the combined incidence of asymptomatic proximal DVT, symptomatic VTE, and all-cause mortality in 1,761 adult patients undergoing knee arthroscopy. Patients were randomly assigned to wear GCS for 7 days (660 patients), or to receive a once-daily subcutaneous injection of LMWH for 7 days (657 patients) or 14 days (444 patients). The 3-month cumulative incidence of asymptomatic proximal DVT, symptomatic VTE, and all-cause mortality was 3.2% (21 of 660) in the GCS group, 0.9% (6 of 657 patients) in the 7-day LMWH group (p = 0.005), and 0.9% (4 of 444 patients) in the 14-day LMWH group[1673].

As chemoprophylaxis appears to be more protective against DVT than GCS, the use of GCS in patients who are concomitantly receiving anticoagulation prophylaxis may not be necessary. Cohen et al., conducted a prospective, randomized study in 795 patients undergoing elective and emergency hip arthroplasty, and hip fracture fixation; to determine whether the addition of GCS to fondaparinux conferred any additional benefit. Fondaparinux was given post-operatively for 5 to 9 days, either alone (400 patients) or combined with GCS (395 patients). GCS were worn for an average of 42 days. The prevalence of asymptomatic DVT was similar in the two groups (5.5 and 4.8% respectively, p = 0.69)[1674]. In another systematic review, Milinis et al., recently reported no additional reduction in the rate of DVT when comparing patients who underwent orthopaedic or abdominal surgery and received anticoagulation with and without GCS[1675].

Similarly, as IPCD has shown to provide efficacious prophylaxis, the concomitant use of GCS in patients using IPCD may not provide additional protection. In a comparative study of 846 consecutive patients undergoing total hip arthroplasty (THA) or TKA, Pitto et al., reported that those who used GCS and IPCD had a similar rate of DVT and pulmonary embolism (PE) to those who only used IPCD[1676].

There is a lack of large, randomized control trials (RCT) evaluating the efficacy of GCS for the prevention of DVT in patients undergoing orthopaedic surgery; with some studies being likely underpowered[1672] or using GCS in conjunction with other mechanical methods or different chemoprophylactic agents. These factors diminish the ability to determine if GCS should be prescribed postoperatively. In order to overcome these limitations, some investigators have recently conducted systematic reviews. Lin et al., compared the efficacy and safety of chemoprophylaxis with and without the use of GCS in patients undergoing hip surgery. Three studies published between 1989 - 2007 were included in the systematic review. Chemoprophylaxis included dextran, fondaparinux and LMWH. There were 478 patients using a combination of chemoprophylaxis and GCS, and 779 using only chemoprophylaxis. A significantly lower rate of distal DVT was observed in the combinational group (Odds ratio [OR] 0.46, p = 0.03). The combination group exhibited similar rates of proximal DVT and PE in relation to the group using chemoprophylaxis

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alone (OR 0.66, p = 0.13; and OR 0.91, p = 0.86, respectively)[1677]. However, it may be argued that this study included a limited number of patients, some of which received obsolete chemoprophylaxis.

More recently, Sachdeva et al., conducted a systematic review to evaluate the effectiveness of GCS for the prevention of DVT in hospitalized medical and surgical patients. Twenty RCT encompassing 1,681 individual patients and 1,172 individual legs were included. Six of the 20 RCT included patients undergoing orthopaedic surgery. GCS were applied on the day before surgery or on the day of surgery and were worn until discharge or until the participants were fully mobile. Duration of follow-up ranged from 7 - 14 days. When all specialties were considered, the GCS group had a significantly lower risk of distal DVT (9%) and proximal DVT (1%) in comparison to the control group (without GCS) (21% and 5%, respectively) ($p < 0.001$ and $p < 0.001$, respectively). The authors concluded that there is high-quality evidence that GCS are effective in reducing the risk of DVT in hospitalized patients who underwent general and orthopaedic surgery, with or without other methods of thromboprophylaxis. There was moderate quality evidence that GCS reduced the risk of proximal DVT, and low-quality evidence that GCS may reduce the risk of PE[1678]. These results confirmed what was proposed by the authors in a prior systematic review[1679].

In summary, GCS may be used alone or in combination with other forms of thromboprophylaxis. The protective effect is likely to be additive and may be lower when used concomitantly with chemoprophylaxis or IPCD.

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67 - Is there a difference between different types of intermittent pneumatic compression devices (IPCD)?

Response/Recommendation: The current evidence does not demonstrate notable differences in the clinical outcomes between different types of intermittent pneumatic compression devices (IPCD). However, devices with patient monitoring sensors and sequential compression may improve patient compliance.

Strength of Recommendation: Moderate.

Delegates vote: Agree 94.76% Disagree 1.90% Abstain 3.33% (Strong Consensus).

Rationale: There are numerous types of IPCD currently available[1680-1682]. These devices can be categorized into anatomical locations of application, such as thigh-calf compression, calf compression only, and foot compression. In addition, these devices can be subdivided into providing sequential or uniform pressure, gradual or rapid inflation, and portable (outpatient) or stationary (in-hospital) devices[1681,1682]. The assessment of efficacy for IPCD is complicated by the inclusion of various types and doses of anticoagulant and antithrombotic medications in the published studies. The outcomes evaluated included: venous thromboembolism (VTE), (deep venous thrombosis [DVT], and pulmonary embolism [PE]), adverse events, such as postoperative bleeding and swelling, ease of application and use, and patient compliance with the device[1681-1687].

Determining differences in the efficacy and other outcomes between the numerous IPCD on the market is not possible, because these devices have been evaluated in small number of randomized controlled trials (RCT) that were underpowered[1682,1688]. The influence of the amount of pressure, inflation rate, timing of initiation, and duration of prophylaxis for maximum benefit are still unclear[1689,1690]. There is little evidence for the comparison of efficacy of IPCD between different orthopaedic procedures, although the benefits have been generally accepted in total knee arthroplasty (TKA), total hip arthroplasty (THA), and hip fracture surgery[1681,1682,1688,1690].

In a systematic review, Zhang et al.[1682], noted one RCT comparing patients with thigh-calf-compression (n = 58) and foot compression (n = 63) in first 3 weeks after THA[1682]. There no cases of symptomatic DVT or PE in either group[1682,1691]. Postoperative swelling of the thigh, as measured by thigh circumference, was significantly milder in thigh-calf compression group (1.22%) than in foot compression group (3.19%)[1682,1691]. This study was underpowered, with a high risk of bias. One recent meta-analysis noted that venous foot pumps decreased the rate of VTE after THA and TKA compared to chemical prophylaxis[1692]. One comprehensive review of IPCD in orthopaedic surgery made recommendations based on the levels of evidence and adherence to established guidelines[1693]. Compression stockings alone were the lowest rated, and venous phasic flow-regulated below-knee sequential IPCD were the highest rated in each grading category[1693]. However, this review included studies with heterogeneous low level of evidence. The superiority of IPCD depending on anatomical location is

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uncertain, and high-quality studies with large numbers of patients would be required to determine this.

A sequential compression device (SCD) would seem more hemodynamically effective due to the increase in blood flow and prevention of venous stasis, one factor in the initiation of DVT[1683,1694]. One retrospective comparative study reported that a SCD had lower rate of VTE, better compliance, and shorter length of hospital day than a uniform IPCD in 1,577 cases after total joint arthroplasty (TJA)[1695]. Other clinical studies have not reported significant differences in the incidence of VTE, comparing sequential to uniform IPCD[1694,1696]. There are no high-quality, adequately powered comparative studies on the type of compression.

Pavon et al.[1681], performed comprehensive systematic review of 14 RCT with 2,633 cases and 3 observational studies with 1,724 cases to evaluate effectiveness of IPCD in patients after TJA. Only 3 RCT directly compared different types of IPCD for VTE events[1688,1697,1698]. One adequately powered RCT study (moderate risk of bias) of 423 patients having TKA compared a rapid-inflation calf SCD (VenaFlow [Aircast, Summit, NJ]) and a slow-inflation calf SCD (Kendall SCD [Kendall, Mansfield, MA]). The rate of DVT was significantly lower in rapid inflation group than the slow compression group[1688]. Another likely underpowered RCT (high risk of bias) compared Kendall SCD to a rapid-inflation IPCD (PlexiPulse [NuTech, San Antonio, TX]) in 107 patients having pelvic fracture surgery and reported no difference in the rate of VTE events between the two groups[1697]. A third likely underpowered RCT (moderate risk of bias) also compared Kendall SCD with PlexiPulse in 136 patients having spinal surgery and reported no significant differences[1698]. There were no major bleeding events in these three RCT[1688,1697,1698]. This systematic review concluded that current evidence-based to guide selection of a specific device or type of device is limited[1681]. With one more caveat, some of the evaluated devices in these studies are no longer available today.

Despite the benefits of IPCD, research has shown considerable variability in adherence to IPCD use ranging from 40% - 89%[1699] and a systematic review identified several factors affecting the adherence such as patient discomfort and mobilisation[1700]. In evaluating the adherence to different IPCD, a systematic review included three RCT[1697,1698,1701] including 308 patients, and 3 observational studies[1696,1702,1703] including 1,724 patients[1681]. Two studies compared PlexiPulse foot device and Kendall SCD calf-thigh device regarding ease of use. One moderate-sized RCT[1698] reported no difference in comfort ratings. One larger observational study noted that PlexiPulse device was more comfortable[1703]. Another small RCT[1701], comparing the ease of use between Kendall intermittent slow calf device and Flowtron (Huntleigh, Manalapan, NJ) uniform slow compression calf device, reported that Flowtron device was more comfortable for patients and more convenient for hospital staff[1701]. An observational study compared five different devices, with multiple different sleeve types, and noted no significant difference in ease of use[1696]. Comparing in-hospital patient compliance, there were no consistent associations between specific manufacture's devices or location of sleeve and patient compliance[1681]. The addition of patient sensing technology, such as the one seen in Kendell SCD, is believed to improve patient compliance and ability of health staff to track patient therapy.

Portable devices for IPCD after surgery and for use at home have been developed recently and potentially allow better compliance, patient satisfaction, and continuation of mechanical VTE prophylaxis after discharge[1704-1706]. Although portable IPCD has shown effective mechanical prophylaxis for VTE after THA and TKA[1695], the evidence is limited due to confounding variables. One observational study reported that a portable (mobile) IPCD had significantly better compliance, lower rate of DVT, reduction in symptomatic PE, and shorter length of hospital stay than a stationary IPCD[1695]. However, all patients were also given pharmacologic prophylaxis with low-molecular-weight heparin[1695].

Although there are important differences between various IPCD in anatomical sleeve location, inflation pattern, and device portability, the available evidence is limited to recommend a certain IPCD type for patients having a specific surgical procedure.

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68 - In patients with confirmed acute distal DVT, should a mechanical compression device be discontinued in the affected limb?

Response/Recommendation: The practitioner might continue the mechanical compression device (MCD) in patients with an acute distal deep venous thrombosis (DVT), in combination with the DVT treatment protocol (anticoagulation) as recommended in current guidelines.

Strength of Recommendation: Limited.

Delegates vote: Agree 85.00% Disagree 9.00% Abstain 6.00% (Strong Consensus).

Rationale: Venous thromboembolism (VTE) constitutes a major interdisciplinary challenge in health care[1707]. It represents a common complication for hospitalized patients that could prolong hospital stay and significantly cause increased morbidity and mortality[1707-1710]. Critically ill patients and those that underwent major surgical interventions are at a particularly increased risk of VTE, i.e., DVT and pulmonary embolism (PE)[1708,1711]. These events result from the dynamic influence of 3 factors: hypercoagulability, venous stasis, and endovascular injury, commonly recognized as the Virchow's triad[1709,1711].

The oldest and simplest VTE prophylactic approach is early mobilization[1707]. However, this method is not always feasible in some individuals, such as critically ill or traumatic patients. For this reason, significant effort has been placed over the years on studying prophylactic alternatives for VTE, such as chemoprophylaxis and mechanical prophylaxis[1711]. Pharmacological methods presented in current guidelines considerably reduce the risk of VTE, as has been evidenced in most clinical situations through all the available studies[1707,1708]. MCD are an alternative prophylactic measure that has been recommended in recent guidelines, mainly as a combined approach with chemoprophylaxis in high-risk patients[1712-1714].

The use of MCD has ranged from intermittent pneumatic compression devices (IPCD), and sequential compression of the calves and thighs to plantar compression pumps and even compression sleeves applied to the upper extremities[1715]. These devices exert their prophylactic effect by decreasing peripheral venous stasis and promoting endogenous fibrinolysis, both contributing to a continuous blood flow and potential clot dissolution[1707,1710]. The various types of MCD could vary by the speed of cuff inflation, duration of compression, duration of deflation, as well as fixed cycle vs. physiologically triggered cycling. No mechanical device has been demonstrated to be superior to the other[1716-1720]. These methods have been used in DVT prophylaxis involving a spectrum of patients, including the medically ill, trauma patients, and those undergoing elective total hip and total knee arthroplasty. Studies have demonstrated their effectiveness in the prophylaxis against DVT combined with a pharmacologic agent and singly as a standalone strategy[1721-1725].

While recognized as an effective thrombophylactic strategy, the role of mechanical compression in the setting of an acute distal DVT remains a debatable issue that has not been well-established in current literature. Most of the conflict around the use of compression strategies in established DVT appears to be based on theoretical grounds, as compression might promote clot dislodgment and cause a PE even when no data supports this idea[1726]. Such is the case by Siddiqui et al., they presented a patient who sustained a PE in an apparent temporal association with the activation of a lower extremity pneumatic compression pump for intraoperative prophylaxis against DVT during surgery for small bowel obstruction. Yet, no causality has been established[1727]. Additionally, Parvizi et al., demonstrated through a cross-sectional retrospective study that there is no statistically significant relationship between lower extremity DVT and PE[1728].

Similarly, a prospective cohort study by Hou et al., assessed the safety of postoperative application of IPCD in patients with pre-existing DVT who were undergoing joint surgery. Their study suggests that IPCD reduces the risk of symptomatic PE in general patients after surgery without an increased rate of postoperative PE in those patients with distal DVT[1729]. In addition, a systematic

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review by Rabe et al., evaluated the risks and contraindications of medical compression treatments, including their use in acute DVT[1726]. In this review, they presented a cohort by Partsch et al., that found no significant increase in the percent of PE compared with patients with DVT treated with chemoprophylaxis (low-molecular-weight heparin [LMWH]) and bedrest against chemoprophylaxis, compression, and walking[1730]. In addition, three randomized control trials (RCT) demonstrated that early mobilization does not increase the frequency of PE compared with bed rest in patients with DVT treated with anticoagulation[1731-1733]. Another study consisted of an RCT of patients with isolated superficial venous thrombosis treated with LMWH plus compression stockings that demonstrated faster thrombus regression and no increased risk of PE compared with LMWH alone[1734]. Based on these studies, the review by Rabe et al., provides recommendations in favor of compression therapy (including IPCD) in acute thrombotic events, with favorable outcomes when applied with caution[1726]. Compression therapy in the acute phase of DVT has reduced the occurrence of pain on calf compression and the incidence of hyperpigmentation, venectasia, and skin induration, which are irreversible skin signs associated with post-thrombotic syndrome (PTS)[1735-1737]. However, these articles and their foundations consist of diverse populations, inconsistent study designs, and endpoints, providing poor data significance and generalizability.

These findings challenge the common impression and some of the statements that consider the use of MCD in the presence of an acute distal DVT as an unsafe practice or even a contraindication. Currently, there is no data report or comprehensive study that confirmed that the compression of veins with an established clot would lead to an increased risk of PE or PTS[1726,1732,1738]. The presented conclusions suggest that continuing this prophylactic measure during an acute distal DVT events may possess some benefits. However, the studies available provide limited evidence with heterogeneous features and modest significance. Therefore, further studies are necessary to provide robust evidence about the role of MCD in the setting of an acute distal DVT. Future research should contemplate a randomized homogenous population, evaluate specific types of MCD, in addition to specific endpoints that demonstrate the benefit of continuous compression therapy in the setting of a distal DVT. Based on the results presented by the aforementioned studies, there is a limited set of evidence supporting the use of mechanical compression in the setting of an acute distal DVT in combination with the DVT treatment approach (anticoagulation) designated in current guidelines. Practitioners might continue the MCD in patients with an acute distal DVT. Their decision should be based on their clinical judgment as this therapy does not substitute the management of acute DVT as per existing guidelines. Physicians should be alerted to emerging evidence that might counter the current findings.

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69 - What is the optimal management of patients who are on antiplatelet medications prior to an elective orthopaedic procedure?

Response/Recommendation: There is insufficient evidence to recommend continuing or discontinuing antiplatelet medications prior to an elective orthopaedic procedure. Literature pertaining to this subject is of low quality and most studies pertain only to aspirin (ASA) and do not investigate other antiplatelet medications such as clopidogrel, ticagrelor, prasugrel, etc. Higher quality studies are needed before more definitive recommendations can be made.

Strength of Recommendation: Low.

Delegates vote: Agree 92.02% Disagree 5.16% Abstain 2.82% (Strong Consensus).

Rationale: Antiplatelet drug therapy has become increasingly more common in the treatment of cardiovascular disease. Continuation of these medications may reduce cardiovascular events in the perioperative period, but due to their inhibitory effect on platelets, there is concern that they may also lead to an increase in blood loss, transfusion requirements, or post-operative hematoma formation if they are not discontinued prior to surgery. The American Academy of Orthopaedic Surgeons (AAOS) recommends in its 2011 guidelines that antiplatelet medications be discontinued before total hip arthroplasty (THA), or total knee arthroplasty (TKA) based on three cardiac studies which did not contain any arthroplasty cases[1739]. Similarly, the American College of Chest Physicians (ACCP) also recommends stopping ASA in low-risk patients for 7 - 10 days prior to surgery[1740].

Several studies have concluded that continuation of antiplatelet medications through the perioperative period may be associated with higher risk of bleeding and need for post-operative blood transfusion; however all are either case-control studies or case series and are of low or moderate quality[1741–1743]. Chen et al., reported on their series of 1,655 patients who underwent unilateral or simultaneous bilateral TKA and found higher calculated blood loss (969.1 ± 324.9 vs. 904.0 ± 315.5 ml), transfusion amounts (1.3 ± 1.5 vs. 1.0 ± 1.3 IU), and percentage of transfused patients (53.0% vs. 40.2%) in unilateral TKA patients on continued ASA monotherapy versus those in whom ASA was withheld perioperatively. However, they found no difference in overall complication rate[1741].

Cossetto et al., prospectively studied 63 patients who were continued on ASA in the perioperative period and underwent TKA or THA and compared them to 76 controls who were not taking ASA[1744]. They found no difference in mean postoperative blood drainage, drop in hemoglobin level, intraoperative blood loss, or operative time. Similarly, a retrospective review comparing 175 patients undergoing TKA or THA which either discontinued or continued their ASA through the perioperative period showed no difference in blood loss, post-operative change in hemoglobin, or transfusion rate[1745]. Discontinuation of ASA prior to surgery trended towards an increase in cardiac complications, but this was not significant ($p = 0.107$). Schwab et al., reported similar findings in their retrospective review of 198 unicondylar knee arthroplasty (UKA) and TKA patients who continued ASA through the perioperative period compared to 403 UKA and TKA patients not on ASA[1746]. They found no difference in estimated blood loss, postoperative hemoglobin change, or transfusion rates. Findings of no difference in complications or blood loss while taking antiplatelets through the perioperative period have also been duplicated in several other lower quality studies[1747–1753].

The vast majority of studies on this topic pertain to ASA only and do not investigate clopidogrel, ticagrelor, prasugrel, or other novel antiplatelet medications. These drugs differ in terms of mechanism of action, peak onset, duration of effect, and method of excretion and therefore warrant specific evaluation in elective orthopaedic procedures before recommendations regarding their continuation or discontinuation in the perioperative period can be made. Clopidogrel has received the most study. Jacob et al., published their retrospective review of 142 patients taking clopidogrel prior to TKA/THA and found that 24 (16.9%) patients had continued clopidogrel during the perioperative period[1743]. Patients who remained on clopidogrel through the perioperative period had a higher rate of blood transfusion within 24 hours of surgery, as well as during the length of their hospitalization (31.8% vs. 7.7%; $p = 0.004$ and 37.5% vs. 15.3%; $p = 0.02$, respectively). There was no difference in cardiac events postoperatively between the two groups. Nandi et al., reported their experiences with 114 patients who

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were continued on clopidogrel during elective THA/TKA vs. withholding clopidogrel for 1 - 4 days or 5+ days prior to surgery[1754]. They found higher rates of reoperation for infection, cellulitis, and wound drainage in patients who had clopidogrel continued through the perioperative period, however there was substantial risk of Type I error, as there were only 8 patients in this group. Another underpowered yet persuasive article by Tescione et al., reviewed platelet function with thrombolelastogram (TEG) in patients who were on clopidogrel and reported that 4/9 patients still had normal platelet function[1755]. They proposed an algorithm whereby a TEG could be done prior to surgery to assist in the decision of whether to delay surgery in these patients who did have abnormal platelet function.

Studies pertaining to elective spine surgery also warrant discussion. Zhang et al., in their meta-analysis on the safety of continuing ASA therapy during spinal surgery[1756] identified four studies which met inclusion criteria[1757–1760]. They concluded that patients undergoing spinal surgery with continuation of ASA during the perioperative period did not have an increased risk of bleeding, post-operative blood transfusion, or longer operative times. They also noted no difference in post-operative cardiac events between the two groups, but this was thought to be underpowered, and all 4 studies included in the meta-analysis were retrospective cohort studies with some methodological flaws. Prather et al., performed a retrospective review of 37 patients undergoing one to two-level cervical and lumbar fusions who took clopidogrel through the perioperative period and matched them to 99 patients who had not been on antiplatelet therapy[1761]. They found no difference in operative time, blood loss, post-operative complications, readmission, or 90-day mortality between the two groups. They did note, a higher drain output in patients taking clopidogrel while undergoing cervical procedures (97.4 mL vs. 43.1 mL; p = 0.010) which did not translate to any difference in postoperative complications, but nonetheless an increase in drain output is concerning due the risks of nerve, esophageal, and airway compromise associated with hematoma formation and swelling in this area. As such, the authors recommended drain use and careful monitoring for these complications in patients undergoing cervical procedures while on antiplatelet therapy.

In summary, the data surrounding continuing or withholding antiplatelet therapy through the perioperative period remains conflicting and of low quality. The majority of studies are retrospective, small in sample size, and lack randomization. Most studies pertain only to ASA and do not investigate other antiplatelet medications such as clopidogrel, ticagrelor, or prasugrel. There is insufficient evidence to recommend continuing or discontinuing antiplatelet medications prior to an elective orthopaedic procedure. Higher quality studies are needed before more definitive recommendations can be made.

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70- What is the optimal management of patients who are on antiplatelet medications prior to an emergency orthopaedic procedure?

Response/Recommendation: There is no evidence to support delaying emergent orthopaedic procedure in patients on antiplatelet medications. However, literature pertaining to this topic is of low quality with no randomized controlled trials (RCT) to date and most studies focus on hip fracture surgery. These studies primarily concentrate on aspirin (ASA), and/or clopidogrel with few investigations about other antiplatelet medications like ticagrelor, prasugrel, etc. Higher quality research is needed before a more definitive recommendation can be made.

Strength of Recommendation: Low.

Delegates vote: Agree 94.84% Disagree 2.82% Abstain 2.35% (Strong Consensus).

Rationale: Antiplatelet medications are used in patients for the management and prevention of cardiovascular or cerebrovascular events. Due to the irreversible inhibitory action on platelets, there is a question as to surgical timing and continuation of antiplatelet medication in order to minimize blood loss and postoperative complications, such as hematoma or wound complications. The American Academy of Orthopaedic Surgery (AAOS) makes a limited recommendation against delaying hip fracture surgery in their 2014 clinical practice guideline citing six low-strength studies which suggested no difference in outcome or improved outcome in not delaying surgery for patients on ASA and/or clopidogrel[1762].

There are few moderate quality studies that address this question. Yang et al.'s 2020 systematic review and meta-analysis investigated a delay in surgery (> 5 days) compared to early surgery in hip fracture patients on ASA and/or clopidogrel therapy[1763]. They noted a significant decrease in mortality (odds ratio [OR] = 0.43; 95% confidence interval [CI], 0.23-0.79; p = 0.006) between patients treated early compared to late surgery. They did find that early surgery was associated with a statistically significant difference in blood loss (weighted mean difference [WMD] = 0.75; 95% CI, 0.50-1.00; p < 0.001) yet this yielded no significant difference in transfusion rate. There was a significant decrease in length of hospital stay in the early surgery group (WMD = − 6.05; 95% CI, −7.06 - 5.04; p < 0.001) with no identified differences in acute coronary syndrome, cerebrovascular events, or venous thromboembolism amongst these groups. Of note, their analysis did demonstrate an increase in the mean number of units transfused for patients on ASA and clopidogrel dual antiplatelet therapy (WMD = 0.69; 95% CI, 0.10 - 1.28; p = 0.02) compared to no therapy or ASA alone groups.

Doleman and Moppett's 2015 meta-analysis and review investigated patients taking clopidogrel vs. no therapy with a subgroup analysis of early and late surgery for hip fractures[1764]. They found that while there was a significant increase in patients on clopidogrel receiving a transfusion, there was no significant difference in transfusion between early and late surgery groups (OR 0.44; 95% CI: 0.15 – 1.30). They did identify a significantly reduced length of stay between the early and delayed surgery groups favoring a shorter stay for the early surgery cohorts (WMD= 7.09 days; 95% CI -10.14 - 4.04).

Ohmori et al.'s 2020 retrospective cohort of 206 patients evaluated perioperative hidden blood loss and transfusion requirements between propensity score matched hip fracture patients on ASA vs. no antiplatelet medication[1765]. They found no significant difference in perioperative blood loss of 598 mL for patients on ASA versus the control group blood loss of 556 mL (p = 0.14). In addition, they found no significant difference in blood transfusion requirements between the two groups (48% vs. 38%, p = 0.21) with a higher transfusion requirement in the ASA group.

Continuing antiplatelet medication throughout the perioperative period was investigated in several studies. Abdulhamidet, in 2020 published a retrospective study of 325 patients with hip fractures comparing patients on long term ASA or clopidogrel therapy that was continued throughout the hospitalization with a control group[1766]. They found no significant increase in intraoperative blood loss or duration of surgery. A prospective cohort study of 44 patients with hip fractures in 2011 by Chechik et al., evaluated clopidogrel and/or ASA use compared with a control group[1767]. Postoperative hemoglobin drops were significantly greater among patients treated with clopidogrel (1,091 ± 654 ml, range 178 – 3,487, p = 0.005) and higher still in patients treated with ASA and clopidogrel (1,312 ± 686 ml, range 392 – 2,877, p = 0.0003) compared to those without antiplatelet therapy. Despite this, there was no increase in early (30-day) mortality although the study was underpowered. Jang et al., in 2019 published a cohort study of 162 patients undergoing cephalon-medullary nail placement for proximal femur fractures with continued antiplatelet medication and no operative delay[1768]. Patients on ASA and/or clopidogrel were continued on their antiplatelet therapy throughout the surgical period. There was no significant difference in estimated blood loss or postoperative hemoglobin. Despite this, there was a significant increase in total transfusion (695.3 ± 487.5 vs. 956.6 ± 519.5 p = 0.003).

Literature on this topic in non-hip fracture studies is limited. Bogunovic et al., in 2013 published a prospective cohort trial of 186 patients comparing bleeding related complications in surgery of the hand and wrist between patients who were continued on their antiplatelet medication and those who were not on antiplatelet medication[1769]. They found no surgical complications in either group; however, one patient in the continued medication group required a return to the operating room for surgical site bleeding. There was no difference in hematoma formation, two-point discrimination, and

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postoperative pain and swelling by 4 weeks. There was a finding of increased bleeding complications with high-dose antiplatelet medication, but this did not reach statistical significance.

In conclusion, patients taking antiplatelet medication may proceed with emergent orthopaedic surgery with minimal complications. The most common associated complication appears to be a tendency to increased blood loss and blood transfusion. However, the bulk of these studies focus on hip fracture patients and are of low quality[1770–1776]. High quality RCT would best address this question.

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71 - Should aspirin be stopped pre-operatively in patients undergoing orthopaedic procedures?

Response/Recommendation: Aspirin (ASA), administered for cardiovascular reasons, should not routinely be stopped in patients undergoing orthopaedic procedures. Continuation of ASA is likely to be cardioprotective and unlikely to be associated with increased blood loss.

Strength of Recommendation: Limited.

Delegates vote: Agree 97.67% Disagree 2.33% Abstain 0.00% (Strong Consensus).

Rationale: ASA has been shown to be effective for secondary prevention of cardiovascular diseases (CVD) and hence is used by a large proportion of the population for primary prevention of CVD[1777]. ASA exerts its beneficial effects by inhibiting the aggregation of platelets. It reduces the risk of vascular death by about one sixth and the risk of non-fatal myocardial infarction and stroke by about one third in patients with unstable angina or a past history of myocardial disease[1778].

Contrary to studies such as the pulmonary embolism prevention (PEP)[1779] and the Perioperative Ischemia Evaluation-2 (POISE-2)[1780] trials that evaluated the effect of ASA on the prevention of venous thromboembolism (VTE) after surgery, the question of whether to stop ongoing treatment with ASA for patients using it as prophylaxis against thrombotic vascular events is still unclear.

Currently, we are in an epidemiological transition with cardiovascular disease being rife in the society. Thus, many individuals are placed on cardioprotective antiplatelet drugs, including ASA[1781]. For those patients with a well-known CVD history, taking ASA may be critical. Thus, stopping ASA preoperatively can cause a platelet rebound phenomenon and prothrombotic state leading to major adverse CVD events[1782–1784]. Unless contraindicated, ASA should not be stopped preoperatively in group of patients at high risk of CVD or at least this issue should be discussed with the patient's cardiologist. For patients with CVD, the risk of thrombotic events after acute ASA withdrawal is mostly felt to outweigh the risk of bleeding complications following surgery[1781].

The evidence for ASA having a clinically significant effect on perioperative blood loss is conflicting, with some studies supporting and others refuting such association[1781,1785]. One study reports that transfusion rate and intensive care unit (ICU) admissions were higher in a group on ASA with no cessation of therapy compared to a control group after proximal femoral fracture, although there were no other significant findings[1786]. A more recent study in patients with hip fracture compared 114 patients taking ASA at the time of their fracture surgery to 103 propensity score matched controls not taking ASA[1787], and found that taking ASA did not affect peri-operative blood loss or blood transfusion requirements.

The case for elective hip and knee replacement is more unclear and evidence is largely based on specialties other than orthopaedics. One study investigated the cessation or continuation of ASA prior to elective abdominal surgery and concluded that continuing ASA was not associated with excessive bleeding[1788]. Mantz et al., performed a randomized controlled trial, the Strategy for Managing Antiplatelet Therapy in the Perioperative Period of Non-Coronary Surgery (STRATAGEM) trial where 52% of patients were undergoing orthopaedic procedures and compared continuation vs. cessation of ASA 10 days prior to surgery. They reported no significant differences in outcomes of major thrombotic or bleeding events between the groups. However, the trial was stopped early

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due to recruitment issues, including the publication of recommendations to avoid stopping ASA[1783,1784].

Similarly, Oscarsson et al.[1789], also attempted to study this subject matter and had to end the recruitment of patients early (220 of planned 540 patients recruited), again largely due to the publication of new recommendations endorsing continuation of ASA in the perioperative period[1790–1792]. In the latter underpowered study, no significant difference in myocardial damage (defined as elevated Troponin T) was seen. The study was also not powered to identify a difference in bleeding complications, and no differences between groups was observed.

Shaw et al.[1785], found a conflicting result when they performed a retrospective cohort study on 2,853 total hip and knee arthroplasty patients in order to identify whether preoperative dose or time of discontinuation affected surgical outcomes. They determined that patients receiving ASA prior to surgery had an increased risk for readmission and 90-day post-operative events compared to those not receiving ASA, mostly related to lower rate of postoperative complications (such as hematoma formation). Interestingly, the study found that the risk for postoperative complications was also higher in patients who stopped ASA closer to the time of surgery.

In conclusion, the decision to stop ASA or continue it perioperatively depends on many variables including the risk profile of the patients for cardiovascular disease, the nature of surgery, risk, and significance of bleeding (intracranial bleed for example) and so on. Based on the available evidence, continuation of ASA in patients undergoing elective procedures does not seem to increase the risk of bleeding or transfusion requirements significantly. Orthopaedic surgeons intending to stop ASA prior to elective procedures may wish to communicate this decision with the cariology team caring for the patient.

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72 - When should chronic anticoagulation be stopped in patients undergoing elective orthopaedic procedures?

Response/Recommendation: Acenocoumarol should be stopped 3 days, warfarin and fluindione should be stopped 5 days, and phenprocoumon should be stopped 7 days prior to elective orthopedic surgery. Direct-acting oral anticoagulants (DOAC) (apixaban, edoxaban, dabigatran, and rivaroxaban) should be stopped at least two days prior to elective orthopedic surgery with an additional day added for dabigatran in patients with a creatinine clearance (CrCl) < 80 mL/min and two to three additional days for patients with a CrCl > 30 mL/min but < 50 mL/min.

Strength of Recommendation: Limited.

Delegates vote: Agree 94.86% Disagree 2.80% Abstain 2.34% (Strong Consensus).

Rationale: Orthopedic surgery, and specifically total joint arthroplasty, is considered to be associated with a high risk of bleeding[1793,1794]. The quality of evidence supporting a specific timeframe to stop chronic anticoagulation prior to undergoing elective orthopaedic surgery is limited. For this specific question, we: 1) searched the literature for relevant articles in respect to lower extremity surgery and 2) retrieved relevant society guidelines. We did not address upper extremity surgery, spine surgery, or trauma surgery as these topics are

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addressed elsewhere. Further, we did not include anti-platelet agents in our searches because these are addressed elsewhere in this document. However, a number of studies conducted in the setting of other surgery types, while limited by their design, provided some relevant data and were considered. Croci et al., retrospectively studied consecutive spine surgery patients and found that among those taking DOAC, there was no difference between the mean discontinuation time among those who had a bleeding event[1795]. In contrast, Young et al., compared patients undergoing spinal fusion who were chronically taking warfarin to those who were not and found that despite stopping warfarin 7 days prior to surgery and achieving normal international normalized ratio (INR) levels, warfarin patients had greater blood loss and had greater odds of receiving a postoperative blood transfusion[1796].

A retrospective study among total knee arthroplasty (TKA) patients found no difference in 30-day complication rates between patients who did and did not stop antithrombotic agents prior to surgery[1797]. Their institutional protocol included cessation of warfarin 5 days prior to surgery. However, DOAC were not included in the study. An additional study by Radovanovic et al., found that TKA patients who routinely stopped warfarin 3 - 5 days prior to surgery and achieved an INR of less than 1.4 had a greater blood transfusion rate (40% vs. 13%, $p = 0.03$) and longer operative times than controls[1798]. Conversely, a retrospective study of 48 patients compared a cohort who continued warfarin uninterrupted perioperatively in the setting of TKA to a cohort who was not taking warfarin. The authors found that there were no differences in blood transfusion rates (24% vs. 38%, $p = 0.178$). Another retrospective analysis of TKA patients compared 38 patients taking warfarin who continued perioperatively to 39 patients who had warfarin stopped 1 week prior to surgery and found no difference in the adjusted risk ratio of receiving a blood transfusion or experiencing a wound complication[1799].

The Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) trial was a multicenter observational cohort study of over 3,000 patients with atrial fibrillation who were taking a DOAC (apixaban, dabigatran, or rivaroxaban) and separated patients into low- and high-bleeding-risk surgeries, the latter of which included hip and knee arthroplasty. Patients who underwent high-bleeding-risk surgery stopped DOAC two days before their procedure unless they were taking dabigatran and had a CrCl < 50 mL/min, in which case this time was extended. They found that within the high-bleeding-risk group, major bleeding events occurred in less than 3% of patients with this regimen[1794]. It was not known how many orthopedic patients experienced a bleeding complication.

A sub-analysis of patients in the PAUSE trial found that separating patients into residual levels of > 50 ng/mL or ≤ 50 ng/mL did not result in significant association with major and nonmajor bleeding events, suggesting that checking residual drug levels prior to surgery does not help to predict bleeding events when drugs are stopped at the times used in the study[1800].

Guidelines from relevant societies, such as the American Society of Regional Anesthesia and Pain Medicine (ASRA), the American Academy of Orthopedic Surgeons (AAOS), and the American College of Cardiologists (ACC), should be taken into consideration when advising patients on when to stop an anticoagulant. In particular, if neuraxial (spinal or epidural) anesthesia is preferred for the procedure, the risk of epidural hematoma should be factored into patient recommendations. The 2018 Evidence-Based guidelines for regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy from the (ASRA) recommend a preoperative cessation time of 72 hours for apixaban and rivaroxaban and a range of times from 72 - 120 hours for dabigatran depending on the CrCl[1801]. These guidelines are followed by many anesthesiologists but are more stringent than those published by others. In contrast, the AAOS currently recommends a cessation time of two days for all DOAC (assuming a CrCl > 50 mL/min), even if neuraxial anesthesia is planned[1802]. Finally, the guidelines from the ACC recommend cessation at least 48 hours prior to high-bleeding-risk procedures if the CrCl > 50 mL/min for apixaban, edoxaban, and rivaroxaban and a graded approach of 48 - 120 hours prior to a high-bleeding-risk procedure for dabigatran, depending on the CrCl[1803].

The more restrictive recommendation for cessation time made by ASRA likely reflects the potentially devastating nature of an epidural hematoma. We do not recommend routine assessment of DOAC plasma levels because of the difficulty in interpretation, lack of widespread availability, and unknown level beyond which clinically significant bleeding events, including epidural hematomas, occur. We agree with the ASRA and the AAOS that the INR should be checked within 24 hours of surgery for patients taking warfarin or another vitamin K antagonist to ensure appropriate response[1802,1804].

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73 - Should bridging by an injectable anticoagulation be considered in patients who are on chronic anticoagulation prior to undergoing elective orthopaedic procedures?

Response/Recommendation: Patients on chronic oral anticoagulation for venous thromboembolism (VTE) prevention or non-valvular atrial fibrillation should not be bridged with low-molecular-weight heparin (LMWH) or intravenous unfractionated heparin prior to orthopaedic procedures. Several high-quality studies demonstrate an increased risk of perioperative bleeding complications with no difference in thromboembolic events in patients undergoing bridging anticoagulation therapy. For patients on oral anticoagulation for prosthetic heart valve, bridging should be considered weighing the patient's risk of thromboembolic events versus the risk of bleeding. However, a recent randomized controlled clinical trial which included 305 patients with mechanical heart valves demonstrated no benefit to bridging therapy.

Strength of Recommendation: Strong.

Delegates vote: Agree 94.88% Disagree 1.40% Abstain 3.72% (Strong).

Rationale: Many patients are on chronic anticoagulation for prevention of VTE or stroke from atrial fibrillation and approximately 250,000 require interruption of treatment for surgical procedures[1805]. Bridging with intravenous unfractionated heparin or low-molecular weight heparin (LMWH) prior to surgery has been described to minimize VTE, but it is not without risks.

The American College of Cardiology issued consensus guidelines in 2017 for periprocedural anticoagulation. Patients on direct oral anticoagulation (apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban) rarely need bridging preoperatively due to the short half-life of these medications[1805]. They suggest patients on vitamin K agonists (such as warfarin) may benefit from bridging therapy as these medications have longer half-lives and take longer to become therapeutic after surgery but recognize the risk of bleeding[1805]. One study on patients being treated with warfarin to prevent VTE demonstrated an increased risk of bleeding in patients undergoing bridging therapy versus those who did not[1806].

In a randomized double-blinded placebo control trial, 1,884 patients on warfarin therapy for treatment of atrial fibrillation received bridging therapy with LMWH or a placebo. The placebo group demonstrated non-inferiority for arterial thromboembolism (0.4% placebo vs. 0.3%) and a statistically significant decreased incidence of bleeding events (1.3% placebo vs. 3.2%)[1807]. The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) (7,372 patients) also demonstrated higher risk for bleeding and adverse events in patients using bridging anticoagulants as did several other institutional-level studies[1808–1810]. Another study utilizing the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) database demonstrate increased bleeding events in patients on chronic dabigatran (6.5% in bridged patients versus 1.8%) and warfarin treatment (6.8% in bridged patients versus 1.6%) without differences in VTE rates[1811].

Data is limited regarding perioperative anticoagulation management of patients with a prosthetic heart valve. Since these patients are at a much higher risk for an embolic event, bridging should be considered weighing the patient's risk of thromboembolic events versus the risk of bleeding after consultation with the patient's cardiologist. While there is no validated perioperative assessment tool, congestive heart failure, hypertension, age > 75 years, diabetes, history of stroke or vascular disease, and female gender are all risk factors for stroke risk in these patients[1805,1812].

A recent randomized controlled trial performed over 9 years in 1,471 patients demonstrated no significant benefit for postoperative dalteparin bridging to prevent VTE. The rate of major thromboembolism was 1.2% (eight events in 650 patients) for placebo and 1.0% (eight events in 820 patients) for dalteparin. The study comprised of 1,166 patients with atrial fibrillation alone and 305 patients with mechanical heart valves and atrial fibrillation[1813].

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74 - Is there a difference between low dose and regular dose aspirin for the prevention of VTE following orthopaedic procedures?

Response/Recommendation: There seems to be no difference in the efficacy of low dose and regular dose aspirin (ASA) for the prevention of venous thromboembolism (VTE) following orthopaedic procedures. However, tolerability and gastrointestinal side effect profile of low dose ASA is more favorable.

Strength of Recommendation: Limited.

Delegates vote: Agree 93.87% Disagree 3.30% Abstain 2.83% (Strong Consensus).

Rationale: Despite the relative abundance of literature comparing ASA thromboprophylaxis at different doses with other regimens, most investigations comparing low-dose (e.g., 81 mg by mouth [*per os* (PO)] – twice a day [*bis in* die (bid)]) to regular-dose (e.g., 325 mg PO-bid) ASA have been conducted in a retrospective manner. Only two prospective studies comparing the efficacy and safety of low-dose to regular-dose ASA have been performed to date. Both studies used ASA for approximately one month and included primary hip and knee arthroplasty patients. In their prospective open-label crossover study (n = 4,651), Parvizi et al., reported similar rates of 90-day VTE between both groups (0.1% low-dose and 0.3% regular-dose, p = 0.345), and there were no differences either in gastrointestinal (GI), bleeding/ulceration, acute periprosthetic joint infection, or mortality[1814]. Similarly, Feldstein et al., (n = 643) reported no difference in the incidence of GI bleeding between both regimens, although the authors did note an increased risk of nausea and GI distress with regular-dose (3.2%) compared to low-dose ASA (0.8%) (p = 0.04). Only one patient (0.3%) developed deep venous thrombosis (DVT) in the 81 mg group, which was not statistically different from the regular-dose group (0.3% vs. 0%). However, due to the small sample size as well as the low incidence of VTE post-arthroplasty, the study was likely underpowered to compare both regimens[1814,1815].

Seven retrospective studies have directly compared the two dosing regimens in orthopedic surgery. In these studies, ASA was provided for 4 - 6 weeks, and all data (VTE, bleeding, mortality etc.) was reported at 90 days postoperatively. The following data presented in parentheses compares the outcome low-dose to regular-dose ASA, respectively. In the first retrospective study, Faour et al., (n = 5,666) reported an initial reduction in VTE incidence (0.7% vs. 1.5%, p = 0.02) following elective primary total knee arthroplasty (TKA). However, regression modeling showed no difference after adjusting for age, gender, body mass index (BMI), Charlson comorbidity index (CCI), and surgeon. Bleeding and mortality rates were also similar between the groups (0.2% and 0.1%, respectively)[1816]. Faour et al. later reported the results of a similar study (n = 3,936) in total hip arthroplasty (THA) patients, with no difference in VTE (0.6% vs. 1.0%, p = 0.35), bleeding (0.5% vs 0.8%, p = 0.75), or death (0.1% both), even after adjusting for confounders in adjusted regression analyses[1817].

Retrospective studies by Tang et al., in revision THA (n = 1,361) and TKA (n = 1,438) patients also reported similar VTE rates between the groups (0.77% vs. 1.34%, p = 0.38, and 0.23% vs. 0.9%, p = 0.16, respectively), which were also noted in regression analyses after adjusting for differences in age and race[1818,1819]. The authors also reported no significant difference in bleeding, infection, and mortality rates between the dosing regimens.

Merkow et al., conducted a substantially larger (n = 12,866) study in patients with standard VTE risk undergoing primary TKA[1820]. While they reported a significant reduction in VTE incidence in patients receiving low-dose ASA (0.23% vs. 1.41%, p < 0.001), analyses were limited to univariate analyses and no cohort comparisons were included. Shohat et al., also compared dosing regimens in primary TKA patients (n = 9,208) and reported no significant difference in VTE rates (0.9% vs. 1.0%, p = 0.669)[1821]. Although both groups were demographically and medically similar, there were statistically significant differences in surgical variables that were not accounted for[1821]. Uvodich et al., also conducted a retrospective review, but unlike other studies in this review, it included data as far back as 2000[1822]. All other papers limited the data collection period to at least 2010 onwards. In their study of primary TKA and THA patients (n = 3,512), Uvodich et al., reported no difference in VTE or mortality (0% vs. 0.1%, p = 0.79, and 0.3% vs. 0.1%, p = 0.24, respectively). While cohorts showed significant baseline differences, these differences were small and likely clinically irrelevant. Multivariate analyses were not performed due to the small event rate.

In contrast to the studies discussed hitherto, Halbur et al., retrospectively compared the efficacy and safety of two ASA protocols in 2,284 standard-risk primary elective total joint arthroplasty patients[1823]. The first cohort received 81 mg bid, and the second cohort received ASA regimen bases on their weight, either 81 mg bid (if < 120 kg) or 325 mg bid (if ≥ 120 kg). Outcomes were compared at 6 weeks and 6 months postoperatively. The adjusted relative risk (RR) of VTE was found to be significantly lower in the weight-based ASA dosing group: RR 0.31 (95% confidence interval [CI] 0.12 - 0.82, p = 0.03) at 42 days and 0.38 (95% CI 0.18 - 0.80, p = 0.03) at 6 months, with an overall RR reduction of 62%. There was no difference in the relative risk of GI bleeding events between cohorts at 6 weeks or 6 months. In a subgroup analysis of patients

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weighing ≥ 120 kg, the incidence of VTE was significantly higher in the cohort receiving 81 mg (n = 111) compared to the cohort receiving 325 mg (n = 180) (3.48% vs. 0%, p = 0.02). There was no difference in VTE incidence between both cohorts in patients weighing < 120 kg. Subgroup analyses using only patients weighing ≥ 120 kg revealed no increased risk of bleeding in those who received 325 mg vs. 81 mg.

In addition to the aforementioned studies, there are two additional retrospective studies comparing ASA to an *anticoagulant*, in which some patients in the ASA cohort received either 81 mg bid or 325 mg bid. These studies included subanalyses comparing outcomes for both ASA cohorts. Goel et al., compared the safety and efficacy of a one-month course of ASA against warfarin for VTE prevention following either unilateral or bilateral TKA[1824]. In their sub-analysis (n = 1,527 bilateral TKA), they reported a similar 90-day incidence of VTE and pulmonary embolism (PE) between the cohorts (1.22% vs. 2.20%, p = 0.14, and 0.82% vs. 1.47%, p = 0.23, respectively). Azboy et al., (n = 683) compared three hip preservation surgery cohorts receiving: (1) low-dose ASA, (2) regular-dose ASA, or (3) warfarin[1825]. The authors similarly reported no difference in VTE rates among the three cohorts.

Hood et al., specifically explored patient compliance in patients prescribed one month of either low-dose or regular-dose ASA after TKA and THA (n = 404)[1826]. There was no significant difference in the proportion of patients who completed their course of therapy, nor the proportion who attributed new GI symptoms to the initiation of ASA (7% vs. 10.5%, p > 0.30).

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75 - What VTE prophylaxis should be administered to a patient who is allergic to aspirin?

Response/Recommendation: In light of the advantageous safety profile and cost-effectiveness of aspirin (ASA) for prevention of venous thromboembolism (VTE), a detailed workup to confirm true hypersensitivity to ASA should be strongly considered unless systemic allergic reactions have been reported. Patients determined to have true aspirin-exacerbated respiratory disease (AERD) or mucocutaneous reactions may then undergo a desensitization protocol. On the rare occasion that a patient has a systemic allergic reaction to ASA, desensitization should be avoided, and alternative agents for VTE prophylaxis should be used.

Strength of Recommendation: Limited.

Delegates vote: Agree 90.82% Disagree 5.31% Abstain 3.86% (Strong Consensus).

Rationale: ASA is a safe and cost-effective agent for VTE prevention in orthopaedic surgery[1827–1833]. This chemoprophylactic agent has been endorsed in the most recent guidelines of the American Academy of Orthopaedic Surgeons (AAOS)[1834] and the American College of Chest Physicians (ACCP)[1835]. Despite the increased utilization of ASA in recent years[1829,1830], there is still a paucity of evidence to guide the selection of an alternative prophylactic agent in patients with a true or self-reported ASA allergy[1828]. As the number of orthopaedic procedures requiring VTE prophylaxis grows annually[1836–1839], it is imperative that surgeons understand how to manage this patient population.

ASA intolerance has been estimated to occur in 6 - 20% of the population, with 0.6 - 2.4% being a 'true' ASA allergy[1840,1841]. Patients with asthma, chronic rhinosinusitis, chronic urticaria, and nasal polyps have a higher prevalence of up to 20 - 30%[1842–1844]. Notwithstanding, the prevalence of ASA allergies is thought to be under-reported since no reliable skin or blood test for hypersensitivity currently exists[1841,1845]. While provocative challenge testing can be used to confirm an ASA allergy, potential risks for life-threatening systemic reactions limit its diagnostic practicality[1840,1845].

The underlying pathophysiology of ASA allergies can be pharmacologic and/or immunologic[1840,1846]. A variety of classification systems utilize patient symptoms to determine the underlying mechanism and proper treatment[1844,1845,1847,1848]. Most commonly, ASA allergy has been classified into the following hypersensitivity reactions: (1) asthma and rhinitis, or AERD, (2) worsened urticaria and angioedema in the setting of chronic urticaria, (3) urticaria and angioedema induced by

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multiple non-steroidal anti-inflammatory drug (NSAID), and (4) isolated single NSAID-induced reactions[1845,1848]. For treatment purposes, reactions to ASA can be further classified into mucocutaneous, and systemic AERD[1844].

Literature on the assessment and treatment of patients with an ASA allergy has been largely restricted to cardiac patients[1840,1841,1845,1847]. A variety of protocols suggest that nearly all patients with a history of ASA allergy can be successfully treated with a graded dose challenge or desensitization[1840,1845,1849–1853]. However, these reports were limited by the fact that ASA allergies were not confirmed in the respective cohorts[1852,1853]. Current evidence suggests that the reliability of self-reported allergies is extremely low[1854]. It is possible that patient-reported allergies to ASA or NSAID may preclude certain patients from receiving ASA for VTE prophylaxis following an orthopaedic procedure. However, it remains uncertain whether the use of non-ASA agents due to these allergies is associated with a higher incidence of VTE.

To adequately protect against VTE, a physician must first ensure an allergy exists, yet the rate of true allergic reactions in patients who self-report an allergy remains unknown. It is not uncommon for patients to mistake side effects including tinnitus, easy bruising, or gastrointestinal symptoms for an allergy; or believe that an allergy to another NSAID suggests a coexisting allergy to ASA[1845]. Therefore, hypersensitivity must be confirmed using a provocative challenge test. Secondly, the allergy must be identified as mucocutaneous, or systemic AERD. For patients with AERD, it is recommended that premedication be utilized for their AERD, followed by a desensitization protocol[1845,1855]. Patients with mucocutaneous reactions do not require pretreatment prior to the desensitization protocol. However, ensuing a mucocutaneous reaction, antihistamines and/or leukotriene receptor agonists are suggested[1845]. On the rare occasion that patients experience systemic reactions to ASA, many authors suggest to avoid desensitization and consider alternative agents for VTE prophylaxis[1840,1845].

In conclusion, it is important to confirm a true allergy in patients with a suspected allergy to ASA or NSAID due to the low reliability of self-reporting. Although, the mechanism underlying ASA allergy has been well described, there are no studies that directly investigate the efficacy of alternative VTE prophylactic agents in orthopaedic patients with a true ASA or NSAID allergy. As such, surgeons may opt to prescribe an alternative VTE prophylactic agent for these patients. However, in light of the advantageous safety profile and cost-effectiveness of ASA, desensitization protocols should be strongly considered in this population unless systemic allergic reactions have been reported. Nevertheless, further research is required to validate the safety and efficacy of provocative challenge testing and desensitization in orthopaedic patients.

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76 - Can non-steroidal anti-inflammatory drugs (NSAIDs) be used as prophylactic agents against VTE in patients undergoing orthopaedic procedures?

Response/Recommendation: There is inadequate evidence to support the use of non-steroidal anti-inflammatory drugs (NSAIDs) as sole pharmacological agents to prevent venous thromboembolism (VTE) in patients undergoing orthopaedic surgery.

Strength of Recommendation: Limited.

Delegates vote: Agree 97.66% Disagree 0.93% Abstain 1.40% (Strong Consensus).

Rationale: There is a risk of developing VTE in patients who undergo any major surgery. Since VTE can be a potentially life-threatening complication, thromboprophylaxis is commonly administered to patients at high-risk[1856,1857]. There is very limited literature examining the use of NSAID as prophylaxis against VTE post-orthopaedic surgery.

A systematic review of the literature was conducted. The published studies report conflicting results related to this specific question. A few studies reported that the use of NSAID, in patients undergoing orthopaedic surgeries, is associated with a decrease in the risk of post-operative VTE. One prospective clinical study showed that the use of indomethacin, significantly decreased the prevalence of symptomatic and asymptomatic deep venous thrombosis (DVT) in patients undergoing total knee arthroplasty (TKA) compared to patients not receiving indomethacin. It was postulated that the effect is related to the role of NSAID in inhibiting platelet aggregation, and in decreasing the serum levels of thromboxane A2, and thus its metabolite thromboxane B2[1858].

In two other studies, the incidence of VTE after TKA was compared between patients with rheumatoid arthritis (RA) and osteoarthritis. The studies showed that the incidence of DVT was lower in patients treated for RA. However, when patients treated with NSAID for RA were excluded, the incidence of VTE was no different between the 2 groups. The authors postulated that the administration of NSAID in patients with RA is providing some protection from developing VTE[1857,1859].

On the contrary, a study that enrolled patients who underwent a major orthopaedic surgery, showed that the occurrence of venous and arterial thromboembolic events was similar in those who took NSAID and those who did not. It compared a group of patients who received rivaroxaban along with NSAID, to a group who received rivaroxaban only. The study also divided patients into a group that was administered any one of the following: low-molecular-weight heparin, unfractionated heparin, fondaparinux, dabigatran etexilate, acetylsalicylic acid or vitamin K antagonists, along with NSAID, and compared it to a group who took the listed medications but was not on NSAID. It was found that whether NSAID were given or not, the incidence of VTE was the same; therefore, the study concluded that NSAID did not have an influence on the incidence of VTE after orthopaedic surgery[1860].

Finally, and as shown in different studies, a case report re-emphasized the interaction of NSAID, as pain medications, with aspirin, as VTE prophylactic agents, in patients who underwent orthopaedic surgery. It was suggested that the concomitant use of those two medications resulted in an increase in post-operative VTE incidences. This was presumed because NSAID competitively inhibits aspirin (ASA) at its site of action. Therefore, the authors recommended that NSAID should be taken two hours prior to ASA[1861].

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77 - Can NSAIDs be co-administered with aspirin, when used as a VTE prophylaxis, in patients undergoing orthopaedic procedures?

Response/Recommendation: Non-steroidal anti-inflammatory drugs (NSAID) ingested together with aspirin (ASA) may reduce the antithrombotic activity of ASA. This effect is greater with the use of non-selective NSAID. Therefore, ASA should be taken at least 2 hours before taking NSAID.

Strength of Recommendation: Moderate.

Delegates vote: Agree 89.52% Disagree 3.81% Abstain 6.67% (Strong Consensus).

Rationale: NSAID are often used for postoperative pain control. These drugs are effective in reducing postoperative pain and opioid use. In addition, NSAID for postoperative analgesia may facilitate for early mobilization and rehabilitation[1862,1863]. In recent years, the use of ASA for venous thromboembolism (VTE) prophylaxis has increased after orthopaedic surgeries, and ASA may be prescribed in conjunction with NSAID for postoperative pain control[1864,1865].

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Nociceptive pain and platelet aggregation are mediated by cyclo-oxygenase (COX) enzymes in the form of COX-1 and COX-2. Platelet aggregation is mediated by COX-1, whereas COX-2 mediates the inflammatory response and pain when tissue damage occurs[1866]. COX inhibiting drugs can be selective or non-selective. Nonselective NSAID inhibit both COX-1 and COX-2. Ibuprofen, naproxen, diclofenac, indomethacin, and ASA are in this group. However, Coxibs specifically inhibit COX-2, and examples of coxibs include celecoxib, rofecoxib, etoricoxib. NSAID reversibly inhibit COX enzymes and have a longer half-life compared to ASA. In contrast, ASA irreversibly inhibits COX-1, but circulates only transiently. Consequently, the administration of non-selective NSAID several hours before ASA inhibits the antiplatelet effect of ASA, which is mediated almost entirely by COX-I inhibition[1867–1871].

There are many studies in the literature demonstrating the pharmacodynamic interaction when ASA and NSAID are given together, although the extent of this interaction may differ between agents[1865,1867,1872–1883]. A total of 20 studies evaluating the relationship between ASA and other NSAID since 2001 were reviewed[1862,1865,1872–1879,1882–1891]. However, almost all of these studies evaluated the relationship between ASA and other NSAID in vitro as opposed to in the clinical setting. In addition, most of these studies were conducted in healthy volunteers. To the best of our knowledge, no clinical studies with a high level of evidence has been performed to investigate the effect of concomitant use of ASA and other NSAID on VTE. Since drug interactions and clinical conditions of patients (age, weight, gender, comorbidity, etc.) are multifactorial, it may be difficult to conduct such studies.

Many studies have claimed that ibuprofen interacts with ASA and interferes with the antiplatelet effects of ASA[1865,1874–1883,1886]. However, Cryer et al., did not find any interaction between ASA and ibuprofen in their study[1886]. Although there is conflicting information about naproxen in the literature, it has been cited as an alternative to ibuprofen in patients with cardiovascular risk[1892]. In addition, several studies have found that naproxen does not interact with ASA[1876,1881,1893], low-dose ASA[1883] or ASA at ≥ 300 mg[1877,1880], and others have reported no interaction when these two drugs were not used simultaneously[1873,1882]. In other studies, no interaction was reported for diclofenac[1880,1889], celecoxib[1875,1877,1883] and meloxicam[1865,1874].

Catella–Lawson et al., first demonstrated the interaction between ASA and NSAID in vivo[1872]. In the study, it was reported that ibuprofen inhibited the platelet inhibitory effect of ASA clinically, but diclofenac or rofecoxib did not demonstrate this effect. In some subsequent in vivo and in vitro studies, it was found that naproxen and indomethacin were also ASA-blocking agents, but celecoxib and sulindac did not interact with ASA[1877]. MacDonald and Wei evaluated the use of ibuprofen, diclofenac and other NSAID in patients on low-dose (< 325 mg) ASA in a study with 7,107 patients, observing that the mortality risk in ASA and ibuprofen users was statistically and clinically significantly higher than that of patients using ASA alone. No such increase in risk was observed in those using diclofenac, rofecoxib or acetaminophen together with ASA[1894], although rofecoxib was subsequently withdrawn from the market.

Several studies have investigated the interaction between naproxen and ASA in the literature. Capone et al., investigated the interaction between the two drugs in vitro and ex vivo in 9 healthy subjects who took 100 mg ASA and 500 mg naproxen twice a day, and found that a single dose of naproxen taken less than 2 hours before ASA interfered with the antiplatelet effect of the latter[1873]. Similarly, the effect of ibuprofen, naproxen, meloxicam, and etoricoxib taken 2 hours before ASA was evaluated in a separate placebo-controlled, ex vivo, serial crossover study by Meek et al., on 30 healthy subjects[1865]. Accordingly, it was stated that although ibuprofen and naproxen inhibited the antiplatelet effect of ASA, meloxicam and etoricoxib did not show this effect. On the other hand, Gurbel et al., noted in their randomized controlled trial (RCT) that there was no interaction within the first 10 days. This study was initiated with 117 healthy subjects, and the pharmacodynamic interaction between ASA 81 mg and naproxen 220 mg was investigated with the data of 80 subjects. After 10 days of treatment, varying degrees of pharmacodynamic interaction were reported[1891].

There is inconsistency regarding the interaction between celecoxib and ASA in the literature. Li et al., evaluated the interactions of ibuprofen, naproxen, and celecoxib with ASA 325 mg in a study of 61 healthy subjects. In that study, there was a strong interaction between ibuprofen and ASA, and between naproxen and ASA, but no such interaction between celecoxib and ASA was reported[1883]. Renda et al., similarly, evaluated the interaction between celecoxib and ASA in patients with osteoarthritis and stable ischemic heart disease. They found that unlike ibuprofen, celecoxib did not interfere with the inhibition of platelet COX-1 by ASA[1875]. Other studies reported contrasting results[1889,1890]. Ruzov et al., found that when ASA was added to the treatment of those who received 200 mg of celecoxib daily, the effects of ASA were reduced by 15% in the first few days, and this interaction did not change with the timing of drug intake. No interaction was observed in the chronic concomitant use of these drugs, and the authors concluded that the combination of the two drugs did not increase the risk of cardiovascular and cerebrovascular events[1890].

The timing of drug administration has been shown to affect the degree of interaction[1867]. In the study by Catella-lawson et al., 400 mg of ibuprofen given 2 hours before 81 mg of ASA negated the effect of ASA, but this interaction was not observed when ASA was taken 2 hours before ibuprofen[1872]. A similar effect was seen with naproxen use. In the study by Anzelotti et al., sequential dosing of 220 mg of naproxen and low-dose ASA twice a day interfered with the irreversible inhibition of platelet COX-1 by ASA, although the interaction was minimal when naproxen was given 2 hours after low-dose ASA[1882]. Capone et al., concluded that ASA should be administered before naproxen to minimize drug interactions[1873]. Gurbel et al., evaluated the co-administrating of

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81 mg of ASA and 220 mg of naproxen and reported that when naproxen was used for more than a certain period of time, it could interact with ASA, and this interaction could be reduced by taking ASA at least 30 minutes before naproxen[1891].

Although more acute myocardial infarctions were observed in patients using ASA and NSAID concurrently in clinical studies, other studies found that there was not enough evidence to prove this relationship[1894,1895]. In a clinical study conducted by Krauss et al., patients were routinely given meloxicam or celecoxib in addition to 81 mg ASA twice a day for VTE prophylaxis in a high-volume joint replacement center. A total of 2 cases of VTE were observed within 1 month, after which ASA was administered 2 hours before the NSAID. Following this change in protocol, only 2 cases of VTE were observed within 1 year. Notwithstanding, it was difficult to attribute this reduction to the change in timing of drug administration[1896].

In light of the available literature, it is likely that NSAID and ASA demonstrate pharmacodynamic interactions when taken together. This interaction differs among different NSAID and is highly dependent on many factors such as the time of administration, the dose of ASA or the NSAID, and its pharmacokinetic properties[1873,1882,1896]. However, the clinical significance of this pharmacodynamic interaction has not been established in large, RCT studies. Taking ASA 2 hours before an NSAID may minimize the interaction between the two drugs. Nonetheless, further clinical research is needed to confirm this recommendation.

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78 - Are there differences between various Factor Xa inhibitors in prevention of VTE with regard to efficacy and safety profile?

Response/Recommendation: There is insufficient data to demonstrate superiority for one Factor Xa inhibitor over another as venous thromboembolism (VTE) prophylaxis.

Strength of Recommendation: Limited.

Delegates vote: Agree 92.52% Disagree 4.21% Abstain 3.27% (Strong Consensus).

Rationale: With the advent of factor Xa inhibitors, also known as direct-oral anticoagulants (DOAC), multiple investigations comparing DOAC to more traditional VTE chemoprophylactic agents in orthopaedic surgery have been undertaken[1897–1901]. However, while there is ample research on DOAC for VTE prophylaxis, controversy exists regarding the superiority of one specific DOAC over other members of this drug class.

No randomized control trials (RCT) directly comparing various DOAC exists, although several indirect comparisons are currently available[1900,1902,1903]. A meta-analysis evaluating DOAC and dabigatran for VTE prophylaxis in 20 orthopaedic trials found that rivaroxaban 20 mg/day and apixaban 5 mg/day were comparable in terms of clinical efficacy, but these two regimens more effective than dabigatran 110 or 150 mg/twice daily[1902]. A second meta-analysis conducted by Cohen et.[1900], consisting of 40 RCT found a similar efficacy between rivaroxaban 10 mg/daily and apixaban 2.5 mg/ twice daily in the prevention of VTE and all-cause mortality following total hip arthroplasty (THA) (odds ratio [OR] 0.686; 95% confidence interval [CI] 0.375 - 1.253) and total knee arthroplasty (TKA) (OR 0.827; 95% CI 0.573 - 1.192). Similarly, there was no difference in major VTE rates for both TKA (OR 0.757; 95% CI 0.272 - 2.105) and THA (OR 0.301; 95% CI 0.081 - 1.135) after excluding the RECORD 2 trial. Hur et al.[1903], performed a meta-analysis of 19 studies of THA and TKA patients, and found no difference in VTE rates between the cohorts receiving rivaroxaban 10 mg/day and apixaban 2.5 mg/ twice daily (OR 0.75; 95% CI 0.52 - 1.07). Additionally, there was no significant difference when comparing edoxaban 30 mg/day, apixaban 2.5 mg/twice daily (OR 0.75; 95% CI 0.36 - 1.55) and rivaroxaban 10 mg/day (OR 1.08; 95% CI 0.53 - 2.21).

Multiple studies have used enoxaparin as a base reference for comparing the effectiveness DOAC. Yoshida et al.[1904], performed a meta-analysis of 15 studies comparing multiples DOAC to enoxaparin in major orthopaedic surgery. They found that rivaroxaban (relative risk [RR] 0.50; 95% CI 0.34 - 0.73) was superior to mixed-dose enoxaparin for any deep venous thrombosis (DVT), nonfatal pulmonary embolism (PE), and all-cause mortality, whereas no difference was observed with apixaban (RR 0.63, 95% CI 0.65 - 1.01). A similar meta-analysis of 10 RCT in THA and TKA patients by Nieto et al., found identical results[1905]. A network meta-analysis of 42 RCT ranked rivaroxaban as the most effective at preventing DVT (RR 0.06; 95% CI 0.01 -0.29), while apixaban ranked lower (RR 0.16; 95% CI 0.03 - 0.76) compared to no chemoprophylaxis or mechanical prophylaxis[1906]. The same group reported similar results in a network meta-analysis of 25 RCT[1907]. Conversely, a meta-analysis of 9 RCT in elderly TKA and THA patients found that VTE or VTE-related death (OR 0.10; 95% CI 0.01 - 0.81) was reduce with apixaban compared to enoxaparin, although the rates were similar for rivaroxaban compared to enoxaparin (OR 0.75; 95% CI 0.35 - 1.59)[1908].

Cohen et al.[1900], found no difference in major bleeding when comparing rivaroxaban 10 mg/daily and apixaban 2.5 mg/twice daily for TKA (OR 1.859; 95% CI 0.473 - 7.304) and THA (OR 2.475; 95% CI 0.444 - 13.81) after excluding the RECORD 2 trial. Similar findings were observed for any bleeding and clinically relevant non-major bleeding. Conversely, Hur et al.[1903], found an increased risk of major and clinically relevant non-major bleeding when comparing rivaroxaban 10 mg/day and apixaban 2.5 mg/twice daily (OR 1.53; 95% CI 1.16 - 2.01). However, there was no difference between edoxaban 30 mg/day and apixaban 2.5 mg/twice daily (OR 1.54; 95% CI 0.86 - 2.77), and rivaroxaban 10 mg/day (OR 0.99; 95% CI 0.55 - 1.80). Nieto et al.[1905], found that there was the highest risk of major bleeding with rivaroxaban compared to enoxaparin (RR 1.88; 95% CI 0.92 - 3.82), while apixaban (RR 0.76; 95% CI 0.43 - 1.33) trended toward less events compared to enoxaparin. Pathak et al.[1908], found that apixaban (OR 0.71; 95% CI 0.47 - 1.08) and rivaroxaban (OR 0.78; 95% CI 0.48 - 1.27) had similar risk of major or clinically relevant bleeding compared to enoxaparin. Lewis et al.[1906], reported similar risk of major bleeding for apixaban (RR 3.16; 95% CI 0.47 - 21.15) and rivaroxaban (RR 2.74; 95% CI 0.42 - 16.16). The same group went on to report similar results in a smaller network meta-analysis[1907].

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79 - Are there any blood tests that can be used to monitor the activity/efficacy of factor Xa inhibitors used as VTE prophylaxis?

Response/Recommendation: Activated partial thromboplastin time (aPTT) and prothrombin time (PT) can be used to monitor the activity of unfractionated heparin and vitamin K antagonists respectively. Neither the aPTT nor the international normalized ratio (INR) can be reliably used to monitor the activity of factor Xa inhibitors. The application of chromogenic anti-Xa assays is reliable for assessing the activity of factor Xa inhibitors in serum or plasma. No therapeutic ranges of anti-Xa assays are available, either for prevention or for therapy.

Strength of Recommendation: Limited.

Delegates vote: Agree 93.84% Disagree 1.42% Abstain 4.74% (Strong Consensus).

Rationale: Rivaroxaban, apixaban, edoxaban, and fondaparinux are direct inhibitors of Factor Xa and are recommended for patients after total hip arthroplasty (THA) or total knee arthroplasty (TKA) for the prevention of venous thromboembolism (VTE)[1909,1910]. According to International Council for Standardization in Hematology (ICSH) recommendations, the range of peak concentration in blood of each drug is established to achieve a therapeutic effect in the case of VTE prophylaxis[1911]. However, it is necessary to take into account the peculiarities of the dosage in the case of VTE prophylaxis after THA or TKA[1911]. Monitoring of the effectiveness of Factor Xa inhibitors is usually not required after administration. However, situations that require an assessment of the blood levels of these drugs may arise. In particular, rivaroxaban and apixaban may cause clinically significant bleeding when given after THA or TKA[1912,1913]. The search for the most optimal test for monitoring the effect of Factor Xa inhibitors continues.

There is a qualitative and quantitative assessment of Factor Xa inhibitors in the blood. However, a qualitative assessment PT; aPPT; thromboelastography, and rotational thromboelastography) are not reliable for monitoring rivaroxaban, apixaban, edoxaban due to the complexity of standardization related to the large number of reagent variants used and the variability of results among patients[1911]. This is also demonstrated by studies involving patients after orthopedic interventions[1914,1915].

Several studies have identified a relationship between the concentration of Factor Xa inhibitors in the blood and coagulometric measurements. The concentrations of rivaroxaban[1916,1917] and apixaban[1916] in the blood of patients after THA or TKA directly depend on the results of the thrombin generation test. At the same time, according to research by Samama et al., thrombin generation test results can vary greatly in each patient (n = 106) after THA or TKA and rivaroxaban administration[1918]. Mani et al., found that in 47 patients after major orthopedic surgery 12 hours after administration of rivaroxaban the PT and aPTT values did not differ from those before the administration of the drug, and also they did not reveal the effect of rivaroxaban on thrombin time[1919]. Mueck et al., found a relationship between blood concentration of rivaroxaban and PT (in seconds) in 1,181 patients after THA during treatment[1920]. Rivaroxaban and apixaban have different effects on the coagulometric measurements of patients after THA and TKA. Freyburger et al., found that rivaroxaban resulted in a higher increase of antithrombin levels, aPTT, PT and D-dimer compared to apixaban[1914]. Also, rivaroxaban more pronouncedly reduced the concentration of thrombin (thrombin generation test) than apixaban[1914,1916]. Fuji et al., showed the dependence of the blood concentration of edoxaban in 264 patients after THA on PT, INR, and aPTT[1921]. Hasegawa et al., also found the effect of edoxaban on increasing the peak time of aPTT waveform in 99 patients after orthopedic surgery[1922]. Kodato et al., found that in the case of the development of deep venous thrombosis (DVT) in patients with edoxaban administration after TKA (n = 286), the INR is lower on the third postoperative day than in patients without DVT[1923].

Quantification of the activity of rivaroxaban, apixaban, and edoxaban in the serum or plasma is preferred[1924,1925]. This includes liquid chromatography-mass spectrometry/mass spectrometry, drug-calibrated clot-based, and chromogenic anti-Xa assays[1911]. Mass spectrometry is the standard for determining the concentration (ng/ml) of factor Xa inhibitors in the blood, while chromogenic anti-Xa assays are clinically more accessible, although they require calibration for a specific drug[1911]. In the case of low drug levels (< 30 ng/ml), the sensitivity of the specifically calibrated chromogenic anti-Xa assays is reduced[1911,1914]. At the same time, the ex vivo concentration of rivaroxaban is more accurately determined as compared to apixaban[1926]. Also, the exaggerated result of the chromogenic anti-Xa assay can be influenced by body weight less than 50 kg and renal failure, as shown by Delavenne et al., in 809 patients with VTE prophylaxis with fondaparinux after major orthopedic surgeries[1927].

The use of different types of anti-Xa assay can give different results. Ikejiri et al., measured anti-Xa activities using 3 different chromogenic anti-Xa assays in 200 patients who underwent THA or TKA and were treated with edoxaban for the prophylaxis of DVT. The anti-Xa activities were

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significantly higher in the patients without DVT than in those with DVT on Day 4. There were no significant differences in the anti-Xa activities between patients with and without massive bleeding on Days 1, 4, 8, and 15[1928]. Ikejiri et al., also found differences in anti-Xa activity when comparing three anti-Xa assays in 99 patients after THA or TKA after taking fondaparinux, but there was a similar increase in anti-Xa activity over 15 days[1929]. No differences were found in anti-Xa activity in patients with and without DVT[1929]. Ninety-eight orthopedic patients including those receiving THA or TKA were treated with fondaparinux for prophylaxis of DVT. Anti-Xa activity using chromogenic anti-Xa assay gradually increased from days 1 - 8 and showed no significant differences between patients with and without DVT[1930]. Yukizawa et al., also showed no differences in anti-Xa activity (after 1, 3, 7, and 14 days) in 85 patients with and without DVT taking fondaparinux after THA[1931]. Reinecke et al., found no relationship between blood rivaroxaban levels and the occurrence of VTE in a model for predicting VTE in patients after THA or TKA, based on data from 12,729 patients from phase 3 RECORD1-4 studies[1932].

Different Factor Xa inhibitors have different effects on coagulometric measurements and different types of anti-Xa assays. As a result, in selected cases in which assessment of their activity is deemed helpful, it is necessary to select a blood test method specific for the Xa inhibitor that the patient is taking. Further research may help standardize the methodology for evaluating the efficacy of Factor Xa inhibitors in patients requiring VTE prophylaxis.

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80 - Does warfarin cause hypercoagulable state during initial administration?

Response/Recommendation: The available literature suggests that the administration of warfarin leads to a temporary hypercoagulable state.

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Strength of Recommendation: Moderate.

Delegates vote: Agree 90.95% Disagree 1.43% Abstain 7.62% (Strong Consensus).

Rationale: Warfarin is an oral anticoagulant medication commonly used to treat and prevent venous thromboembolism (VTE)[1933,1934]. Warfarin is most commonly indicated for cardiac-related issues such as minimization of embolization in patients with atrial fibrillation or heart valve replacement, and the avoidance of stroke and systemic embolization following a myocardial infarction[1934–1936]. However, warfarin is also food and drug administration (FDA)-approved for prophylaxis and treatment of VTE following surgical procedures including orthopaedic surgery[1937]. Warfarin competitively inhibits the vitamin K epoxide reductase complex 1, which activates the vitamin K available in the body. By depleting functional vitamin K reserves, warfarin reduces the synthesis of vitamin K dependent clotting Factors II, VII, IX, and X, as well as coagulation regulatory factors protein C and protein S (which also require vitamin K)[1938]. However, patient-specific factors such as drug metabolism, differences in vitamin K availability, quantity of vitamin K dependent clotting factors, concurrent diseases, drug interactions, and the pharmacokinetics of warfarin make safe and effective administration of warfarin difficult[1933,1938,1939].

One potential concern when initiating warfarin therapy is systemic hypercoagulability, which is why in most circumstances, particularly in cardiac cases, warfarin is co-administered with another anticoagulation agent such as heparin until the international normalized ratio (INR) is titrated within therapeutic range[1940–1942]. Warfarin not only impacts procoagulation Factors II, II, IX, and IX, but also protein C and protein S (which act to regulate the coagulation pathway). The potential for hypercoagulability thus arises due to the differences in half-lives of each of these proteins[1933,1943]. Protein C selectively inactivates Factors Va and VIIIa, and thus if protein C is inhibited, there is a temporary period in which a patient may enter a hypercoagulable state[1944]. The rate at which these vitamin K dependent factors decrease is governed primarily by their half-lives[1945–1947]. As both Factor VII (4 - 6 hours) and protein C (9 hours) typically have the shortest half-lives, these are the factors most rapidly impacted. In contrast, Factors II (42 - 72 hours), IX (18 - 30 hours), X (27 - 48 hours), and protein S (60 hours) take a longer time to inhibit[1933]. However, the speed at which each of these factors are affected also depends on the initial dose of warfarin. When administered as a high loading dose (30 – 40 mg) followed by lower doses, Factor VII coagulant activity decreases more rapidly than when the starting dose is 10 mg or less[1933,1947].

While based on its mechanism of action and the half-lives of vitamin K dependent coagulation and regulatory factor proteins, there is clearly the potential for hypercoagulability after the initial administration of warfarin, the clinical impact of this remains uncertain. Binymin et al., presented a case report of a patient diagnosed with atrial fibrillation who was initiated on warfarin therapy without low-molecular-weight heparin (LMWH), who was subsequently diagnosed with a deep venous thrombosis (DVT) three days after initial administration. The authors theorized that it was this unopposed warfarin dose that increased the risk of DVT[1948]. Azoulay et al., performed a case-control analysis of 70,766 patients diagnosed with atrial fibrillation, of whom 5,519 patients experienced a stroke during follow-up. They noted that warfarin was associated with a 71% increased risk of stroke in the first 30 days of use, thus proposing that unopposed use of warfarin may lead to a transient hypercoagulable state that increased the risk of stroke in patients with a diagnosis of atrial fibrillation[1949]. While warfarin has been shown to be effective for VTE prophylaxis following orthopaedic procedures, it is also known to be difficult to administer effectively. Nam et al., analyzed 184 patients who received warfarin for 4 weeks postoperatively following a primary hip and knee arthroplasty and noted that patients were in their therapeutic INR range for only 54.4% of the time during their postoperative course[1950]. Cipriano et al., compared preoperative versus postoperative initiation of warfarin therapy for VTE prophylaxis following hip and knee arthroplasty and found no difference in perioperative hemoglobin changes or VTE risk, although patients started on warfarin preoperatively reached their therapeutic range more quickly[1951].

In conclusion, while transient hypercoagulability is plausible and likely following the initial administration of warfarin, the clinical impact of this remains uncertain given the limited number of studies specifically addressing this issue.

Denis Nam, Robert L. Barrack

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81 - Is there a role for bridging with another therapeutic anticoagulant after orthopaedic surgery when warfarin is used for VTE prophylaxis?

Response/Recommendation: Patients on warfarin undergoing elective orthopaedic surgery should not routinely be bridged with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH). In patients with co-morbid conditions, such as a mechanical heart valve, where risks of thromboembolic events may outweigh the risk of bleeding, bridging may be considered.

Strength of Recommendation: Limited.

Delegates vote: Agree 91.94% Disagree 3.32% Abstain 4.74% (Strong Consensus).

Rationale: Management of patients who require long-term oral anticoagulation with warfarin due to conditions causing a high-risk for VTE is challenging in the perioperative period of elective total joint arthroplasty (TJA) surgery[1952–1955]. In order to balance the risks of VTE with cessation of warfarin, and the increased bleeding risks of continuing it, bridging chemoprophylactic agents are commonly utilized. The decision to bridge a patient is typically made by the treating surgeon based on the patient's individual risk for VTE. Although multiple studies outside of the orthopaedic literature have investigated the effect of bridge therapy in vascular and general surgery, extrapolating such data to assess a patient's individual complication risk for total knee arthroplasty (TKA) and total hip arthroplasty (THA) is difficult[1952]. Furthermore, little data is available that focuses on specific thromboembolic and bleeding related complications in patients undergoing TJA who are bridged to warfarin to help guide decision making.

Haighton et al., performed a retrospective cohort study of all patients undergoing primary THA or TKA in a 4-year period who underwent bridging therapy with either therapeutic UFH or LMWH according to a protocol and were compared to patients who received standard postoperative prophylactic LMWH postoperatively[1953]. Patients on bridging therapy had a significantly higher complication risk compared to patients receiving standard thrombosis prophylaxis. The majority of complications were bleeding-related, and no thromboembolic events were reported in either bridging group. The group concluded that the risks of bleeding and thromboembolic complications have to be carefully balanced and patients must be counseled ad monitored postoperatively.

Simpson et al., performed a similar retrospective study examining 32 patients on chronic warfarin who were bridged with heparin perioperatively and compared them to patients treated with warfarin and other chemoprophylactic agents without bridging[1954]. Patients who were bridged experienced significantly higher rates of deep infection and excessive wound drainage. Ultimately the authors' concluded that the going forward, the challenge will be to identify which patients on chronic warfarin treatment can do without therapeutic anticoagulation perioperatively. In those patients who require bridging therapy, such as those with prosthetic valves or procoagulant disorders, the goal will be to optimize the risks of thrombosis with the bleeding and infection risks of surgery. Furthermore, there are two large multi-center randomized trials being conducted to examine the safety and efficacy of bridging therapy with LMWH in high-risk and low-risk patients respectively[1954]. However, at this time it is incumbent upon the orthopaedic surgeon in conjunction with the consultants to weigh the risk of thrombosis versus bleeding and infection for each patient in order to determine the optimal perioperative anticoagulant regimen.

Jørgensen et al., studied 649 patients on vitamin K antagonist treatment undergoing THA and TKA[1956]. Of these, 430 patients were bridged, and 215 patients had their vitamin K antagonist paused. No statistically significant differences were found in regard to arterial or venous thromboembolic events or major bleeding events. However, there was a higher number of thromboembolic events in paused patients and a higher number of major bleeding events in bridged patients.

Leijtens et al., identified 13 patients receiving LMWH bridging during THA or TKA according to the American College of Clinical Pharmacy guidelines[1955]. Of these, 12 patients experienced bleeding complications with an intervention required in nine. Seven patients required a blood transfusion, nine a developed hematoma, and two periprosthetic joint infection. However, no thromboembolic were observed in any patients. This study demonstrated an alarmingly high complication rate in patients being bridged with LMWH bridging during elective TJA surgery, with all complications related to bleeding.

The study of bridging anticoagulation as it relates to THA and TKA is somewhat limited, however in the broader medical literature there have been more inquiries into its efficacy[1952]. Multiple recent studies evaluating bridging strategies have found that major bleeding occurs more frequently than VTE, and that the bleeding to thrombosis ratio is 13:1 in patients who are bridged as compared to 5:1 in those without bridging[1952]. While major bleeding may be an acceptable in order to avoid VTE, there is currently no evidence of a meaningful decrease in thromboembolic events when bridging is used. However, this data is admittedly somewhat limited as it does not stratify the VTE rates in low- vs. high-risk patients. With the known increased risk of thromboembolic events in patients without anticoagulation, it is not acceptable to abort bridging

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strategies all together, especially in patients with high-risk conditions. Rather, the decision should be on an individualized level with a multi-disciplinary effort.

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82 - Are there differences between various injectable pharmacological agents for VTE prophylaxis with regard to efficacy and safety profile?

Response/Recommendations: Compared to low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH), fondaparinux appears to have a better efficacy profile for prevention of venous thromboembolism (VTE) following orthopaedic procedures. Based on current evidence, there appears to be no difference in the safety profile of the different injectable pharmacological agents in terms of perioperative bleeding risk.

Strength of Recommendation: Moderate.

Delegates vote: Agree 91.12% Disagree 6.07% Abstain 2.80% (Strong Consensus).

Rationale: Several studies evaluating patients undergoing total hip arthroplasty (THA) have shown that using subcutaneous injection of fondaparinux for VTE prophylaxis is more effective than subcutaneous injection of LMWH or UFH in decreasing postoperative VTE[1957–1960]. The relative reduction of postoperative VTE was approximately 50% with fondaparinux 2.5 mg subcutaneous (SC) injection compared to enoxaparin based on a meta-analysis of 4 randomized trials[1958]. Studies with smaller sample sizes suggested that fondaparinux and enoxaparin were equally effective, but the studies may have been underpowered[1961,1962]. Shorr et al., used a large billing database and examined patients undergoing THA, total knee arthroplasty (TKA), and hip fracture surgery and showed that the use of fondaparinux was not only associated with lower VTE compared to enoxaparin, dalteparin, and UFH but was also more cost effective[1957]. UFH, enoxaparin, and other LMWH seem to be equally effective in terms of prevention of VTE. The studies and corresponding incidences of VTE with various injectable agents are summarized in the appendix (see Appendix Table A82-1). Some studies suggest that ultra-LMWH such as semuloparin and bemiparin, which exhibit more selective inhibition of Factor Xa, are more effective than other LMWH including enoxaparin[1963–1965]. Another potential advantage of ultra-LMWH is a better safety profile[1963,1964], which has not been proven by clinical studies reviewed and remains elusive. In fact, most of the prospective studies reviewed showed no significant differences in bleeding risk between the various injectable agents. The study by Shorr et al., consisting of more than 120,000 cases from a large database suggested that dalteparin was least associated with bleeding[1957]. Bleeding rates reported in various studies are summarized in the appendix (see Appendix Table A82-2). There was no difference in mortality after orthopaedic surgery in any of the studies using the various injectable agents for pharmacological VTE prophylaxis.

Based on the available data, it appears that fondaparinux may have better efficacy profile for prevention of VTE after orthopaedic procedures, compared to other injectable agents. However, the data is not conclusive and at this point it appears that most injectable agents have proven efficacy for reduction of VTE after surgical procedures. Clinicians should decide on the choice of injectable agents based on the clinical situation for each patient taking into account the available data.

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83 - What is the optimal timing for the start of LMWH as a VTE prophylaxis in patients undergoing orthopaedic procedures?

Response/Recommendation: The optimal timing for the initiation of low-molecular-weight heparin (LMWH) for

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venous thromboembolism (VTE) prophylaxis in patients undergoing orthopaedic procedures is 12 - 24 hours after surgery. Although high quality evidence is lacking, several studies have identified an increased risk of postoperative bleeding when LMWH is given preoperatively or immediately postoperatively. Concerns also exist for earlier initiation of LMWH in patients undergoing neuraxial anesthesia. There seems to be no benefit in starting LMWH preoperatively vs (> 12 hours) postoperatively.

Exact timing for a specific procedure, particularly trauma patients or those at risk for VTE, should be in accordance with the chosen LMWH pharmacokinetics, surgeons/anesthesiologists' preferences, and patient comorbidities.

Strength of Recommendation: Limited.

Delegates vote: Agree 97.67% Disagree 0.93% Abstain 1.40% (Strong Consensus).

Rationale: The LMWH was first introduced in 1976 and has had almost five decades of a successful track record for VTE prophylaxis in orthopaedic surgery[1966]. The optimal timing for the first dose of LMWH prophylaxis, however, remains disputed. The risk of bleeding complications is closely linked to the timing of thromboprophylaxis. Studies evaluating the use of drains show that most blood loss occurs during the first 6 hours following surgery[1967]. The most commonly used timing is initiation of LMWH at least 12 hours preoperatively, perioperatively (2 - 6 hours), and postoperatively (12 - 24 hours)[1968].

The "ideal" time for the initiation of thromboprophylaxis should balance the optimal efficacy of the antithrombotic agent with the associated risk of bleeding[1969]. The first recommendations for the timing of prophylaxis were 2 hours preoperatively in the 1970s[1970] with low-dose unfractionated heparin (UFH) in general surgical patients. The research has shown that the timing of the start of giving anticoagulants influences the results[1971], but the ideal timings as well as dosages and ideal anti-Xa ranges for LMWH prophylaxis have yet to be established. In the 1990s and 2000s, the timing recommendations even provoked a longstanding controversy between surgeons in North America and Europe. LMWH prophylaxis is generally initiated up to 12 hours preoperatively (40 mg once daily) in some parts of Europe, to optimize antithrombotic effectiveness, whereas in North America it is mostly initiated 12 - 24 hours (30 mg twice daily) after surgery to allow hemostasis of the surgical wound[1972].

In elective orthopaedic patients, concerns exist regarding preoperative LMWH prophylaxis due to the increased risk of compressive spinal hematoma if regional or neuraxial anesthetic techniques were used[1973,1974], similar to some concerns published with early LMWH initiation in selected spine surgery patients[1975].

There are studies that support administering an LMWH for peak efficacy between 2 hours before and 8 hours after surgery[1972]. Kulshrestha et al.,[1976] opted for half of the recommended prophylactic dose of LMWH starting 8 h after surgery and switching to full prophylactic dose on the first postoperative day (enoxaparin 40 mg). Bjørnaråa et al.,[1977] recommend subcutaneous dalteparin (5,000 IU) or enoxaparin (40 mg) administered 12 hours before surgery in elective hip and knee cases and shortly after admission in emergencies and there after once daily.

Published data does not exclude the possibility that VTE will occur in some patients despite the use of prophylaxis, either because of inappropriate doses, or as a result of delayed first dose[1978].

Regarding the beginning of LMWH, in femoral neck fracture (FNF), if surgery is performed on an emergency basis (within 24 h), LMWH may be used (staring 12 h before or 12 h after). In total hip arthroplasty (THA) and total knee arthroplasty (TKA), no significant difference in efficacy and safety has been reported in the literature between preoperative and post-operative initiation of LMWH[1970,1979,1980] so the choice must be based on evidence reported in published studies as well as on what is indicated on LMWH labels, which per example in Italy require initiation of prophylaxis 12 h before surgery[1981].

Additionally, we cross matched the results of our literature search with a recent review[1968] and the most recent American Society of Hematology (ASH) guideline[1982]. In one randomized trial published in the year 2000 the relative efficacy and safety of two regimens of dalteparin given in close proximity to surgery was evaluated. The results showed lower rates of VTE with both preoperative and postoperative dalteparin compared with vitamin K antagonists (VKA) (10.7% and 13.1% vs. 24.0%, respectively; $p \leq 0.001$ for both comparisons). However, the rate of major bleeding was significantly higher with preoperative dalteparin[1983]. Another systematic review found that perioperative initiation of LMWH resulted in major bleeding rates of 5 - 7%, whereas rates were in the 1 - 3% range with preoperative and postoperative administration. The authors concluded that starting prophylaxis more than 12 hours before surgery is not more effective in preventing deep venous thrombosis (DVT) than starting 12 - 24 hours postoperatively and that despite slightly lower VTE rates associated with perioperative initiation, the increased risk of major bleeding outweighed any potential benefit[1980]. One more recent randomized trial evaluated the use of 40mg enoxaparin started either 12 or 24 hours following TKA. In 210 patients they found significantly less major bleeding (8% vs. 2% $p < 0.045$) and reduced calculated blood loss (435ml vs 387ml, $P<0.01$) when enoxaparin was started after 24 hours, with comparably high symptomatic VTE rates (5% vs. 7%)[1984].

In a registry-based study of 45,913 hip fractures reported to the Norwegian Hip Fracture Register, mortality (relative risk [RR] = 1.01, 95% confidence interval [CI] 0.97 – 1.06) and risk of reoperation (RR = 0.99, CI 0.90 – 1.08) were similar comparing preoperative and postoperative start of LMWH. Postoperative start reduced the risk of intraoperative bleeding complications compared with preoperative start. The authors conclude that the initiation of LMWH did not influence the mortality or the risk of reoperation in hip fracture patients

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treated with osteosynthesis. Postoperative start of LMWH could possibly decrease the risk of intraoperative bleeding[1985].

Based upon the limited evidence available, there is no clinical advantage in starting LMWH (> 12 hours) preoperatively vs. (> 12 hours) postoperatively. Data does show that initiating LMWH in close proximity to surgery might increase the risk of bleeding complications, particularly in orthopaedic surgery patients receiving neuraxial anesthesia.

Unfortunately, there are currently no recent randomized studies to help provide updated recommendation on timing of LMWH for specific orthopaedic surgical procedures. Even in orthopaedic trauma, besides hip fractures, there is little literature to unequivocally guide the timing of initiation of VTE prophylaxis for specific injuries in these patients in a hypercoagulable state. Timing of LMWH in these patients should be determined on a case-by-case basis depending on the patient's injuries, mobility, medical comorbidities, type of surgery, and anesthesia.

Patients undergoing elective orthopaedic surgery who would be a candidate for LMWH thromboprophylaxis, 12 - 24 hour postoperatively seems the optimal time to administer the first dose of LWWH.

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84 - Should the dose of LMWH for the prevention of VTE be weight-adjusted?

Response/Recommendation: Limited data suggests that weight-adjusted dosing of low-molecular-weight heparin (LMWH) may be of benefit in venous thromboembolism (VTE) prophylaxis for very low body weight and obese patients.

Strength of Recommendation: Limited.

Delegates vote: Agree 95.33% Disagree 2.80% Abstain 1.87% (Strong Consensus).

Rationale: While the safety and efficacy of LMWH have been studied extensively in prospective, randomized, control clinical trials, those patients of very low body weight as well as those of high body weight were excluded from studies with these agents for prophylaxis following major orthopaedic surgery[1986–1988]. Concerns regarding the use of fixed standard dosing include reduced glomerular filtration rate (GFR) and creatinine clearance (CrCL) in patients of low body weight as well as a lower volume distribution (Vd) in these individuals. Because LMWH are primarily renally excreted, increased exposure to the drug due to accumulation may result in over anti-coagulation and a reduction in safety as manifested by an increased bleeding risk in low body weight patients[1989,1990]. Conversely, in those of extremely high body weight, a larger Vd may diminish the effectiveness of the antithrombotic agent resulting in a decrease in thromboprophylactic efficacy[1991,1992]. Interestingly, obesity is also a risk factor for chronic kidney disease (CKD) and renal insufficiency[1993]. Should this occur, an obese patient with CKD on standard LMWH dosing may experience reduced renal clearance of the drug, increased exposure due to accumulation,

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and a resultant potential decrease in safety due to increased bleeding risk. Additionally, because LMWH are hydrophilic in nature and not well distributed in adipose tissue, overdosing may be a risk in those patients whose total body-weight is represented by a larger proportion of adipose tissue as opposed to an increase in lean body mass[1994,1995].

A meta-regression analysis by Zufferey et al., evaluated the possibility of a dose-effect relationship of LMWH in major orthopedic surgery patients. They reported a correlation between the dose of LMWH administered and the relative risk reduction of asymptomatic total deep venous thrombosis (DVT) observed in each of the dosing studies evaluated[1996]. A preponderance of scientific studies has used the measurement of anti-Xa levels as a surrogate for both efficacy and safety in support of the use of dose-adjusted LMWH for patients at both extremes of body weight[1997–2002]. The number of studies in support of weight-adjustment of LMWH administration have increased in the bariatric surgery literature since the introduction of the various LMWH, but limited data exist on the management of obese patients in the trauma and orthopaedic arenas.

In orthopaedic surgery, the literature is unclear as to the effectiveness of standard doses of LMWH for prophylaxis in obese patients[2003,2004]. The literature is similarly unclear as to the safety of standard doses of LMWH in patients of very low body weight, although a number of small prospective studies, as well as a trial in healthy volunteers, support a reduction in LMWH dose in patients of low body weight[1993,2005]. A number of studies have focused on different dose regimens in support of patients at the extremes of body-weight instead of adjusted dosing calculated based on weight[1993,2006–2011]. Those few prospective clinical studies were underpowered to show differences in the effectiveness of various dosing regimens on VTE events as well as bleeding events[1997,2009,2012,2013]. While weight-adjustment of LMWH has been demonstrated to be effective in achieving a target anti-Xa level, there is not a consensus on optimum anti-Xa ranges, especially in terms of a clear link between anti-Factor Xa levels and bleeding or thrombotic events[2014]. There is also no strong evidence that anti-Xa levels correlate with a reduction in the incidence of clinically important VTE events in patients undergoing orthopaedic procedures[2015]. While many studies support the benefits of weight-adjustment of LMWH administration[2016–2019], no level 1 evidence exists to support the safety and efficacy of weight-adjusted dosing of LMWH for prophylaxis against VTE in orthopaedic surgery. Further trials are needed to confirm the efficacy and safety of weight-adjusted LMWH prophylaxis in orthopaedic surgery for those patients at the extremes of body weight.

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85 - Does the administration of VTE prophylaxis to patients undergoing orthopedic procedures increase the rate of post-operative non-VTE complications?

Response/Recommendation: Administration of pharmacological venous thromboembolism (VTE) prophylaxis to patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA) increases the rate of post-operative bleeding complications. Aspirin carries the lowest risk. The literature is inconclusive for other orthopaedic procedures.

Strength of Recommendation: Strong.

Delegates vote: Agree 95.77% Disagree 1.88% Abstain 2.35% (Strong Consensus).

Rationale: Although compressive stockings and fast-track rehabilitation are effective in reducing the incidence of VTE[2020], routine pharmacological VTE prophylaxis is generally recommended[2021]. Current recommendations provide a list of procedures requiring VTE prophylaxis, focusing on THA or TKA and proximal hip fracture[2021,2022]. However, there is a general trend to extend the pharmacological VTE prophylaxis to other procedures based on perceived level of risk[2023]. Commonly used agents include: Low-molecular-weight heparin (LMWH), fondaparinux, direct-oral anticoagulant (DOAC), low-dose unfractionated heparin (UFH), adjusted-dose or low-dose vitamin K antagonist, or ASA[2021,2022].

There is no evidence in the literature that nonpharmacological VTE prophylaxis (mechanical compression, early ambulation, fast-track procedures) increases the risk of post-operative complications[2024–2027].

In contrast, the use of any pharmacological agent involves risk. Some complications such as heparin-induced thrombocytopenia are rare. Excess bleeding is the major risk which can manifest as an increase in wound discharge[2028]. Hematoma formation may require further surgery or allogeneic transfusion[2029] both of which can increase the rate of surgical site infection[2030–2033].

There is extensive literature for THA and TKA. While the risk of VTE events is currently decreasing, probably because of the more frequent use of fast-track procedures, the risk of bleeding remains unchanged[2036]. The risk for bleeding without VTE prophylaxis remains difficult to estimate because modified operative and recovery techniques may make the untreated bleeding event rate deriving from the placebo group of past studies[2021]. There are only few recent studies including a control group without pharmacological VTE prophylaxis[2034–2036]. The increased bleeding risk[2037,2038] may not be compensated for by the administration of tranexamic acid (TXA)[2037]. However, the routine use of TXA and more restrictive transfusion policy has dramatically decreased the need for transfusion after primary THA and TKA[2039], and the impact of VTE prophylaxis may be difficult to assess.

The risk may be further increased when potent anticoagulants drugs are administered in comparison to ASA[2040–2042], but some authors report conflicting results[2043], and the rates may be different for THA and TKA[2025]. There is little evidence that different potent anticoagulants agents other than ASA are associated with different risks of bleeding[2044,2045].

Early readmission and repeat surgery rates after primary THA or TKA are affected by the occurrence of bleeding and wound discharge[2046]. As bleeding and wound discharge are more frequent with pharmacological VTE prophylaxis, readmission and further surgery rates may be higher as well.

There is a paucity of recent literature for other orthopaedic procedures than THA and TKA, and no scientifically supported conclusion can be suggested.

Jean-Yves Jenny

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86 - Does the administration of VTE prophylaxis increase the risk for intracranial bleeding in patients undergoing orthopaedic procedures? If so, are there differences between the various prophylactic agents?

Response/Recommendation: There is a known association between the use of antithrombotic drugs and the risk of intracranial bleeding in patients receiving long-term treatment. Intracranial bleeding has been less commonly reported in patients undergoing orthopaedic procedures, probably because of the shorter time of exposure to antithrombotic drugs. The incidence of intracranial bleed seems to be higher with the use of vitamin K antagonists (VKA).

Strength of Recommendation: Limited.

Delegates vote: Agree 90.29% Disagree 1.46% Abstain 8.25% (Strong Consensus).

Rationale: Intracranial bleeding, encompassing intracerebral, subdural, and subarachnoid hemorrhages, is a potentially fatal complication of antithrombotic treatment[2047-2049]. Predisposing factors include, among others, advanced age, concomitant hypertension, and use of dual or triple antithrombotic therapies such as antiplatelet and anticoagulant drugs. This risk has been extensively studied in the population of patients with atrial fibrillation, where a reduction in the incidence of intracranial bleeding was observed with the use of the direct-oral anticoagulants (DOAC) as compared to VKA[2050]. A recent study from Denmark reported a strong association between the use of antithrombotic drugs and the risk of intracranial bleeding in the general population[2051]. This association was weakest for the use of low dose aspirin (ASA) and clopidogrel and strongest with the use of VKA. The association was weaker for the DOAC than for VKA.

The risk of intracranial bleeding is likely much lower when prophylactic doses of anticoagulant drugs are used for a limited period of time, such as after orthopaedic surgery. However, randomized controlled trials have not consistently reported specific information on the occurrence of intracranial bleeding but instead report major bleeding. The estimated risk of major bleeding with anticoagulants in patients undergoing major orthopaedic surgery is estimated around 4 cases per 1,000 procedures, with no difference between DOAC and low-molecular-weight heparin (LMWH)[2052]. This risk is slightly increased when low dose ASA is used (relative risk [RR] 2.63; 95% confidence interval [CI] 0.64 - 10.79)[2052].

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When intracranial bleeding was described in placebo-controlled trials, the incidence was very low without differences between pharmacologic prophylaxis and placebo[2053,2054]. In one study comparing warfarin and placebo in 160 elderly patients with femoral fracture there was only one occurrence of intracranial (cerebellar) bleeding in the warfarin group and none in the placebo group[2053]. In the Pulmonary Embolism Prevention (PEP) trial, in which 13,356 patients undergoing hip fracture surgery were randomized to ASA 160 mg or placebo, there were two intracranial bleeding events in the placebo arm and none in the ASA arm[2054]. In more recent trials comparing LMWH with DOAC in patients undergoing major elective orthopaedic surgery, intracranial bleeding occurred in none, and 1 case among a population of 1,146 and 2,673 treated patients, respectively[2055-2062].

Finally, no information is available on the risk of intracranial bleeding in patients with previous bleeds who are undergoing orthopaedic surgery and receiving antithrombotic prophylaxis. For these patients, decision based on individual assessment is suggested.

Walter Ageno, Daniel Caldeira

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87 - Does the administration of VTE prophylaxis increase the risk for epidural hematoma in patients undergoing orthopaedic procedures? If so, are there differences between the various agents?

Response/Recommendation: Epidural hematoma (EH) is a rare but serious complication of neuraxial anesthesia. Venous thromboembolism (VTE) prophylaxis for total joint arthroplasty (TJA) has been associated with cases of EH and low-molecular-weight heparin (LMWH) appears to carry the greatest risk of the agents currently used. EH has also been associated with the use of direct-oral acting anticoagulants (DOAC).

Strength of Recommendation: Moderate.

Delegates vote: Agree 96.17% Disagree 1.91% Abstain 1.91% (Strong Consensus).

Rationale: EH is a recognized complication of neuraxial anesthesia that is rare but potentially catastrophic. The estimated risk of neurologic complications from epidural and spinal anesthesia is approximately 1 in 150,000 patients and 1 in 220,000 patients, respectively[2063]. The addition of LMWH for thromboprophylaxis can add additional risk to patients receiving spinal or epidural anesthesia with the risk of spinal hematoma estimated at 1 in 40,800 and 1 in 3,100 North American patients[2064]. In Europe, however, this risk is estimated to be much lower (1 in 2.25 million patients) in patients receiving neuraxial anesthesia and LMWH for VTE prophylaxis owing to the reduced dose (20 - 40 mg daily) of enoxaparin versus dosing in North America (30 mg every 12 hours)[2064]. Additional factors that can increase the likelihood of spinal hematoma development include repetitive and traumatic bloody punctures during neuraxial anesthesia, placement or removal of epidural catheter during peak anticoagulant activity, and administration of concomitant medications that increase bleeding risk, such as aspirin (ASA), non-steroidal anti-inflammatory drugs (NSAID), and other anti-platelet drugs[2063].

Ozel et al.[2065], reported one case of spontaneous spinal EH ten days following total hip arthroplasty (THA) in a patient who received combined spinal-epidural. The patient received enoxaparin 40 mg twelve hours after epidural placement

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followed by transition to rivaroxaban 10 mg daily upon discharge. In this case, the symptoms spontaneously resolved, and no surgical intervention was required[2065]. Another case report documented a neuraxial hematoma following the unsuccessful attempted placement of both a spinal and epidural for a patient undergoing total knee arthroplasty (TKA)[2066]. During the first two postoperative days ASA alone for VTE prophylaxis was given, followed by therapeutic enoxaparin on postoperative day 3 when a pulmonary embolism was diagnosed. The patient developed a large EH on postoperative day 4 that led to tetraplegia despite emergent laminectomy[2066].

Larger studies have demonstrated a low incidence of EH. A 2016 phase IV, non-interventional study Xarelto® in the prophylaxis of post-surgical venous thromboembolism after elective major orthopaedic surgery of hip or knee (XAMOS) by Haas et al.[2067], compared the safety and efficacy of rivaroxaban 10 mg to standard of care (LMWH, fondaparinux, or dabigatran) in patients who underwent major orthopaedic surgery. This study reported no cases of spinal hematoma in the neuraxial anesthesia patients (n = 10,355) regardless of postoperative anticoagulant timing. Rivaroxaban was studied in four phase III trials in patients who underwent THA (RECORD 1 or 2) or TKA (RECORD 3 or 4)[2068]. The efficacy and safety of rivaroxaban 10 mg given once daily was compared to enoxaparin 40 mg daily (RECORD 1-3) or enoxaparin 30 mg twice daily (RECORD 4)[2068]. A total of 4,086 patients received rivaroxaban and 4,090 received enoxaparin among those who received either neuraxial anesthesia alone or neuraxial plus general anesthesia[2069]. There were two spinal hematomas reported, one of which required surgical intervention. This occurred in a 74-year-old patient with severe renal impairment who underwent TKA with epidural anesthesia. The catheter was removed 12 hours after receiving the last dose of enoxaparin 40 mg and subsequent enoxaparin dosing resumed six hours after the catheter was removed according to established guidelines[2069]. The other spinal hematoma occurred during spinal placement due to traumatic puncture prior to the first dose of rivaroxaban[2069].

In a case-control study by Liu et al.[2070], the efficacy and safety of preoperative versus postoperative administration of LMWH was studied in 222 patients who underwent hip fracture repair. Of the 168 patients who received neuraxial anesthesia there were no reported cases of spinal hematoma regardless of treatment arm[2070]. Singelyn et al.[2071], performed a multicenter, international, prospective study involving 5,704 patients who underwent major orthopaedic surgery, 1,553 of whom received epidural analgesia and 78 of whom received a deep peripheral nerve catheter. Fondaparinux 2.5 mg daily for VTE prophylaxis was held for 48 hours prior to epidural catheter removal and identical dosing was given to those without catheters[2071]. No neuraxial or perineural hematomas were found in the study[2071].

A case-control study by Shaieb et al.[2072], compared patients who received enoxaparin for VTE prophylaxis (n = 152) following major lower extremity orthopaedic surgery with those who did not receive VTE prophylaxis (n = 152). There were no statistically significant differences in bleeding complications but there was one documented case of neuraxial hematoma requiring surgical intervention in a patient who received epidural anesthesia[2072]. This patient received enoxaparin 30 mg twice daily postoperatively for VTE prophylaxis in addition to one dose of an NSAID prior to the development of the EH[2072].

The large trials and case reports identified have suggested that neuraxial hematomas are rare events in the setting of routine VTE prophylaxis but can occur when additional medications affecting coagulation or platelets are given or when decreased drug clearance, as in renal impairment, is present. The risk of developing an EH must be weighed against the risk of asymptomatic VTE that exists with TJA in patients without prophylaxis, which may be as high as 50%[2073]. This topic is addressed in other sections.

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88 - Does the risk of post-operative wound problems in patients undergoing orthopaedic procedures differ between various VTE prophylactic agents?

Response/Recommendation: Yes, aspirin (ASA) appears to confer a lower risk of postoperative wound problems compared to other chemoprophylactic agents.

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Strength of Recommendation: Limited.

Delegates vote: Agree 94.37% Disagree 2.82% Abstain 2.82% (Strong Consensus).

Rationale: The prevention of venous thromboembolism (VTE) following orthopaedic procedures is of paramount importance[2074,2075]. While there is a broad range of chemoprophylactic agents in the surgeon's armamentarium, emerging evidence has drawn attention to the consequences of aggressive anticoagulation regimens[2076]. Current guidelines from the American College of Chest Physicians (ACCP) and the American Academy of Orthopaedic Surgeons (AAOS) have not been able to recommend the single most optimal chemoprophylactic agent[2077,2078]. Postoperative wound complications including wound drainage and hematoma have been documented as a harbinger for periprosthetic joint infection (PJI)[2079–2082]. Furthermore, the use of more potent anticoagulation may not lead to a significant risk reduction compared to less potent regimens[2083]. Thus, it is critical to balance the risk of thrombosis against the risk of bleeding complications associated with these potent regimens. In this article, we summarize the literature evaluating the relationship between different chemoprophylaxis options and wound complications following orthopaedic procedures.

Warfarin: The association between warfarin and postoperative wound problems is well documented. Several retrospective studies have demonstrated a lower rate of wound complications in patients taking ASA when compared to warfarin[2084–2087]. A retrospective cohort study of 5,516 patients comparing persistent wound drainage in patients taking ASA and warfarin found that the warfarin group had a greater than two-fold increase in the rate of persistent wound drainage compared to ASA, although there was no difference in VTE rates[2088]. Huang et al., in a review of 30,270 patients, showed a lower incidence of PJI in their ASA cohort compared to the warfarin cohort. Warfarin was also associated with increased VTE events in this study[2085]. Other studies have also demonstrated similar results[2086,2087,2089].

Warfarin has also been compared to no chemoprophylaxis, and this comparison has revealed an increased infection rate. Sachs et al., demonstrated the aforementioned findings, while observing no difference in VTE rates in patients with no chemoprophylaxis compared to warfarin[2084]. Warfarin use prior to total joint arthroplasty (TJA) has also been shown to be an independent risk factor for postoperative wound drainage, superficial and deep infection[2089].

The results of studies comparing warfarin to agents other than ASA have yielded varying results. Retrospective studies assessing the infection rates with low-molecular-weight heparin (LMWH) and warfarin have demonstrated higher rates of surgical site infection and reoperation at 3 months, as well as an increased time to a dry wound[2082,2090]. Colwell et al., and Francis et al., both performed randomized controlled trials (RCT) comparing ximelagatran, a direct thrombin inhibitor, and warfarin, and found a comparable rate of wound complications postoperatively following TJA[2091,2092]. In regards to bridging, Kleiner et al., found that bridging with LMWH was associated with a longer duration to a dry wound and increased cost of care following total hip arthroplasty (THA)[2093].

Other disadvantages inherent to warfarin include the need for continuous lab monitoring and delayed onset of action. Parvizi et al., demonstrated that the incidence of VTE following TJA was highest in the first week after surgery, and suggested that the delayed onset of action could be an explanation for these findings[2094].

Low-molecular-weight Heparin (LMWH): The use of LMWH has been extensively studied in the literature, often as a comparison group for other novel anticoagulants. In retrospective cohort study comparing rivaroxaban and enoxaparin in patients undergoing TJA, rivaroxaban demonstrated a near three-fold increase in wound complications (5.0% vs. 1.8%), although this did not reach significance likely due to the lack of statistical power[2095]. Kulshrestha et al., performed an RCT in total knee arthroplasty (TKA) patients comparing protocols in which enoxaparin was given routinely vs. the selective use of enoxaparin in high-risk patients and ASA in low-risk patients. Routine use of enoxaparin yielded an eight-fold increase in the incidence of wound complications postoperatively[2096]. Burnett et al compared a 10-day course of enoxaparin following TJA to their previous warfarin regimen and demonstrated a three-fold increase in reoperation rate due to wound complications[2097]. Two meta-analyses found no difference in wound complication rate between ASA and enoxaparin following TJA, although this could be due to the limited level-1 data evaluating ASA prospectively[2098,2099]. Jones et al., compared no chemoprophylaxis, ASA and enoxaparin in patients undergoing TJA and found significantly higher rates of wound drainage with ASA (odds ratio [OR] = 3.64) and enoxaparin (OR = 4.92) when compared to no anticoagulation. The ASA group had a lower incidence of wound drainage (29.9%) compared to the enoxaparin group (36.5%), and this was statistically significant[2100]. Agaba et al., reported that enoxaparin had a higher rate of incision and drainage (I&D) compared to rivaroxaban in a study of 72,670 patients undergoing THA, and noted that this rate was lower than that of the ASA and warfarin groups[2101]. More recently, another database study by Watts et al., of 85,938 TJA patients who received rivaroxaban, ASA or enoxaparin was conducted. The majority received ASA (n = 61,426), demonstrating a significant shift in practice. ASA had a lower rate of wound complications compared to enoxaparin and rivaroxaban, although the latter comparison did not reach statistical significance[2102].

Factor Xa Inhibitors: Factor Xa inhibitors are a predominant class of novel oral anticoagulants (NOAC). These drugs were introduced to avoid laboratory monitoring and the need for bridging as seen with warfarin. Current data regarding their risk of wound complications and infection remains mixed. In studies previously mentioned, Sindali et al., found a three-fold increase in wound complications with rivaroxaban, while Agaba et al., reported a higher rate of I&D with enoxaparin[2095,2101]. Brimmo et al., compared 159 patients given rivaroxaban following TJA to 480 patients given alternative chemoprophylaxis

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(322 enoxaparin, 161 ASA)[2103]. The Rivaroxaban group had a PJI incidence of 2.5% compared to 0.2% in the alternative group, which was statistically significant. In a meta-analysis of 24,385 patients, Russell et al., found a decreased risk of deep venous thrombosis (DVT) in patients on apixaban and rivaroxaban, but no difference in reoperation for postoperative wound infection when compared to enoxaparin[2104].

Direct Thrombin Inhibitors: Direct thrombin inhibitors have also had inconsistent results in the literature. In a meta-analysis comparing dabigatran with LMWH and Factor Xa inhibitors, the authors found no difference with regard to wound complication rates[2105]. Gill et al., performed a prospective study comparing dabigatran and dalteparin, noting that the reoperation rate for wound complications in the dabigatran group was 7% compared to 1% in the dalteparin group[2106]. The increased rate of wound drainage with dabigatran has also been shown in studies comparing this agent with ASA, enoxaparin and Factor Xa inhibitors[2107–2109]. In comparison to warfarin, ximelagatran showed no difference in the rate of wound complications, as discussed previously[2091,2092].

Aspirin (ASA): ASA may reduce the incidence of wound complications and PJI when compared to warfarin, Factor Xa inhibitors, LMWH and direct thrombin inhibitors, as mentioned in the above sections[2085,2096,2102,2103,2107]. ASA has also demonstrated efficacy in patients at high-risk of VTE[2083]. Notwithstanding, there is still limited prospective data evaluating the safety and efficacy of ASA, and high-level trials are currently ongoing[2110].

Conclusion: Currently, lower-level evidence suggests that ASA may be of similar efficacy to other pharmacologic agents while reducing the risk of wound complications. This data is limited by the lack of level-1 studies investigating the safety and efficacy of ASA. Future prospective studies will need to include ASA as an investigational arm while evaluating wound complications as a primary endpoint, as most RCT have only focused on the efficacy of these agents in preventing VTE events.

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89 - Should the VTE prophylaxis be altered in patients undergoing orthopaedic procedures who develop wound related problems?

Response/Recommendation: Yes. It is recommended to either hold anti-coagulation or change to a less aggressive anticoagulation agent in cases of wound related problems such as persistent wound drainage, bleeding, or hematoma formation.

Strength of Recommendation: Low.

Delegates vote: Agree 96.23% Disagree 1.89% Abstain 1.89% (Strong Consensus).

Rationale: Wound related problems in the postoperative period following orthopedic surgery can be a devastating complication leading to prolonged postoperative morbidity, lower patient-reported outcome scores, revision surgery, and higher overall health care costs[2111,2112]. Wound related problems entail a variety of complications that can occur after orthopaedic procedures, and generally include persistent wound drainage, wound infections, bleeding/hematoma formation and tissue breakdown/dehiscence. The association between bleeding, persistent wound drainage, hematoma formation and the use of therapeutic anticoagulation has been well studied after knee and hip arthroplasty[2113–2118]. A detailed description on the incidence of wound related problem per type of VTE prophylaxis is described in the consensus question: "Does the risk of post-operative wound problems in patients undergoing orthopaedic procedures differ between various VTE prophylactic agents?" Despite the clear association between wound related problems and the use of certain anticoagulants, none of the reviewed studies described which strategy should be used when wound related problems occur in patients treated with a certain type of VTE prophylaxis.

Despite the lack of direct evidence for a particular intervention, we recommend that patients who develop wound related problems after orthopedic procedures undergo tighter dosing of their vitamin K antagonist regimen to reduce an elevated international normalized ratio (INR) to optimal range if supratherapeutic, or reduce the dosage of direct-oral anticoagulants (DOAC), or change the anticoagulation regimen to a less aggressive agent such as aspirin (ASA) or possibly switching to low-molecular-weight heparin (LMWH) if there is a strong indication to maintain more potent anticoagulation over ASA[2117–2119]. The choice between LMWH or ASA should depend on the indication in which the initial anticoagulant was prescribed (e.g., atrial fibrillation, mechanical heart valve, intracardiac devices, previous thromboembolic events etc.). If possible, ASA is preferred above LMWH, as LMWH has been shown to be associated with a higher rate of wound complications compared to ASA. Kulshrestha et al., demonstrated, in a randomized controlled trial, that 7.9% of patients that underwent total knee arthroplasty and were treated with LMWH developed wound related complications compared to only 1.0% in patients treated with ASA ($p < 0.001$)[2120]. In addition, it has been demonstrated that LMWH is independently associated with prolonged wound drainage after total joint arthroplasty[2115]. If

TABLE VI Safety and Efficacy Outcomes of Anticoagulants Used in Orthopaedic Surgery

Anticoagulant Type	VTE Incidence	Incidence of Bleeding	Reference
Warfarin	21.5%	3.2%	2125
Unfractionated heparin	23.0%	3.5%	2126
Dalteparin	11.9%	1.5%	2127
Enoxaparin	13.5%	1.7%	2127
Fondaparinux	6.5%	2.7%	2128
Aspirin	0.3%	0.5%	2129

VTE=Venous thromboembolism.

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the patient was not on an anticoagulant for other reasons than primary VTE prophylaxis, temporarily discontinuation of anticoagulation should be considered if wound related problems occur. Pitto et al., demonstrated in patients undergoing knee arthroplasty that mobile mechanical compression decreases the rate of hospital readmissions related to bleeding complications, wound infection and symptomatic VTE[2121]. In addition, when persistent wound drainage is noted, physiotherapy - specifically articular range of motion - should be temporarily limited.

Switching to a less aggressive anticoagulant appears safe in terms of VTE prevention (Table VI). A meta-analysis performed by Matharu et al., indicate that ASA does not increase the risk of VTE compared to other anticoagulants[2122]. This finding is confirmed in a later meta-analysis specifically comparing ASA with rivaroxaban[2123]. Moreover, wound related problems are not identified as a risk factor to develop a VTE[2124], supporting the safety of changing to a less potent anticoagulant like ASA in this particular patient category.

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90 - Does the development of a hematoma as a result of the administration of VTE prophylaxis increase the risk of subsequent arthrofibrosis?

Response/Recommendation: There is a lack of robust data to link the use of VTE prophylaxis and arthrofibrosis. One retrospective study demonstrated an increased risk of manipulation under anesthetic/lysis of adhesions after anterior cruciate ligament reconstruction (ACLR) in patients receiving VTE prophylaxis with an agent other than aspirin (ASA), as compared to patients receiving no thromboprophylaxis.

Strength of Recommendation: Limited.

Delegates vote: Agree 88.78% Disagree 4.88% Abstain 6.34% (Strong Consensus).

Rationale: Venous thromboembolism (VTE) events are widely feared sequelae of orthopaedic surgery, and thromboprophylaxis is widely employed to reduce the incidence of VTE. Joint stiffness is a potentially devastating complication of orthopaedic surgery, and its incidence varies widely depending on the underlying diagnosis, joint involved or procedure performed[2130–2133]. The relationship between hematoma and the risk of arthrofibrosis following an orthopaedic procedure is poorly understood. Studies assessing the incidence of arthrofibrosis are complicated by the lack of a universal definition of arthrofibrosis and by the fact that not all joint stiffness is due to arthrofibrosis[2134]. Hemarthrosis and joint immobilization have been linked to joint stiffness in experimental conditions[2135], however, little is known about the relationship between hemarthrosis and arthrofibrosis in vivo, with most clinical data in this regard pertaining to bleeding diatheses such as hemophilia, which is a separate area of study[2136].

Few prospective studies report on the incidence of hematoma or hemarthrosis and compare the use of thromboprophylaxis with placebo or no intervention[2137,2138]. Therefore, it is challenging to draw firm conclusions as to whether the administration of thromboprophylaxis increases the risk of these particular adverse events. In addition, the multitude of agents and regimes available across a wide gamut of

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orthopaedic procedures further complicate the interpretation of results and generalization of the findings of the few studies in this field is impossible.

There is a lack of scientific evidence to support or refute a link between prophylactic anticoagulation and the development of arthrofibrosis secondary to consequent bleeding events.

Venous Thromboembolic Prophylaxis and Hematoma formation: Some authors have linked the use of anticoagulant agents for VTE thromboprophylaxis with hematoma formation[2139], while others have compared rates of hematoma or bleeding events between patients receiving different chemoprophylactic regimes[2140–2144]. The endpoint of hematoma or hemarthrosis may be difficult to objectively and consistently diagnose across studies and any relationship between these and thromboprophylaxis may be conditioned by both the agent used and the procedure undertaken. Therefore, results of single studies cannot be generalized to other procedures or drugs.

Studies comparing the use of thromboprophylaxis with placebo, or no intervention provide information on the effect of thromboprophylaxis on the risk of hematoma/hemarthrosis formation. One meta-analysis of studies comparing low-molecular-weight heparin (LMWH) to placebo for thromboprophylaxis after total hip arthroplasty (THA) demonstrated a reduction in non-fatal pulmonary embolism (PE) (odds ratio [OR] = 0.14, 95% confidence interval [CI] 0.03 - 0.74, p = 0.029) at the expense of increased risk of hematoma formation (7/147 or 4.76% in the LMWH group and 0/149 in the placebo group; p = 0.015)[2139]. However, the authors recommended caution in interpreting reported results regarding hematoma formation since these figures were based on only two studies[2137,2138]. Kaye et al., randomized 170 low-risk patients undergoing knee arthroscopy to receive either ASA (325 mg once daily for 14 days) or no intervention[2145]. No VTE were recorded and there was one case of arthrofibrosis, but the authors did not state which group this occurred in. Another prospective randomized controlled trial (RCT) evaluated 76 patients undergoing hip fracture surgery to receive or not to receive prophylaxis with fondaparinux[2146]. Curiously, no information was given as to whether the "non-fondaparinux control group" received placebo, no treatment, or alternative anticoagulants. One patient suffered wound necrosis and hematoma and one developed a hematoma, both in the fondaparinux group. No other placebo-controlled studies were identified in the field of orthopaedic joint surgery, and this may relate to the ethical implications of withholding VTE prophylaxis in modern practice.

Other authors have reported the incidence of surgical site hematoma or hemarthrosis using different chemoprophylactic agents.

The RE-NOVATE RCT compared two different doses of dabigatran etexilate (220 mg or 150 mg) with enoxaparin for VTE thromboprophylaxis after THA in 3,494 patients[2141]. Post-procedural hematoma was noted in 1% of higher dose dabigatran patients, 3% of lower dose dabigatran patients and 2% of enoxaparin patients. There were eight re-operations due to bleeding. The authors concluded that oral dabigatran was as effective as enoxaparin in reducing VTE risk, with a similar safety profile.

Researchers from the RECORD programme pooled the results from four phase III RCT comparing rivaroxaban with enoxaparin for VTE prophylaxis after THA and total knee arthroplasty (TKA)[2142]. The incidence of hemarthrosis and of excessive wound hematoma was similar across the two groups.

An RCT of 900 TKA compared routine anticoagulation (4 weeks of enoxaparin) with risk stratification and selective anticoagulation (with four weeks of ASA 325 mg once daily for lower-risk patients or two weeks of enoxaparin followed by two weeks of ASA for higher-risk patients). The authors reported hemarthrosis in 6 of 706 TKA receiving LMWH and none of the 194 TKA receiving ASA[2143]. Additionally, 8 TKA in the LMWH group developed a subcutaneous hematoma with wound gaping, while none of the ASA cohort did. Patients receiving LMWH were eight times more likely to suffer wound complications (p = 0.0005). However, there may have been selection bias since this was a secondary analysis in a study primarily not designed to compare different chemoprophylactic agents.

A retrospective study of 917 patients undergoing hip fracture surgery compared patients receiving mechanical prophylaxis and one of three chemoprophylactic agents (ASA, dextran-40 or enoxaparin)[2140]. No difference in thromboembolic prophylaxis efficacy, hemorrhagic or wound complications was noted; however, use of enoxaparin (3.8%) was associated with a significant increase (p < 0.01) in wound hematoma compared with dextran-40 (1.6%) and ASA (2.4%).

Non-comparative studies have quantified the risk of hematoma for some chemoprophylactic agents[2144,2147–2149]. Lotke et al., reported a 0.3% (9 of 3,042) re-operation rate for hematoma after TKA in patients receiving ASA thromboprophylaxis (325 mg twice daily for six weeks). In addition, eight knees underwent needle aspiration for post-operative effusion or hematoma. A prospective multicenter observational study of 1,009 patients receiving bemiparin thromboprophylaxis after THA or TKA reported that 16.1% (95% CI, 13.8 – 18.5%) developed surgical wound hematoma/bruising but none required reintervention or prolonged hospitalization. There were 13 surgical site major bleeding cases, of which 3 related to joint hemarthrosis. The authors combined hematoma with bruising for analysis, so it is not possible to ascertain the true rate of hematoma formation in this study[2148]. Hosaka et al., retrospectively reviewed 935 TKR (454 receiving fondaparinux, and 481 enoxaparin)[2144] and reported that fondaparinux use resulted in documented knee enlargement (p < 0.0005) and subcutaneous knee hematoma (p = 0.035) more often than enoxaparin. A retrospective study of 113 patients receiving either enoxaparin or rivaroxaban for VTE prophylaxis after TKA reported no VTE in either group, with one hematoma in the group managed with rivaroxaban and none in the enoxaparin group[2149]. The authors of some case-reports[2150] and limited case-series[2151] have attributed post-operative hematoma

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to the use of prophylactic anticoagulation, however, it is not possible to draw conclusions from these studies.

In summary, there is weak evidence based on a small series of seven cases to suggest that LMWH thromboprophylaxis after THA may be associated with hematoma formation[2139]. Prospective RCT have reported similar efficacy and incidence of hematoma formation for enoxaparin compared to rivaroxiban[2142] and dabigatran[2141]. Data from secondary analyses in a RCT that was not designed to compare chemoprophylactic agents suggested that ASA may be associated with a lower incidence of wound complications than LMWH after TKA[2143]. Data from a single retrospective study of hip fracture surgery suggests that enoxaparin may be associated with higher rates of wound hematomata than ASA and dextran-40[2140]. One other retrospective study reported a higher incidence of hematoma with fondaparinux thromboprophylaxis as compared to enoxaparin after TKA[2144].

Arthrofibrosis in the context of thromboprophylaxis or hematoma: In a retrospective case-control study of 2,424 patients undergoing ACLR, Huleatt et al., reported that patients suffering from postoperative hematoma needing evacuation were at (3.55 times) higher risk of manipulation under anesthesia (MUA) and/or lysis of adhesions (LOA) for arthrofibrosis[2152]. Although statistically significant on univariate analysis, this did not remain significant upon regression analysis adjusting for confounding factors. The authors did not discuss the use or otherwise of thromboprophylactic agents in this cohort.

Thirteen patients in a small retrospective series of 56 TKA with post-operative stiffness had been treated for VTE with *therapeutic* dose LMWH. Three of these had developed hemarthrosis which prevented them from following the usual rehabilitation program[2153]. The authors claimed this provided some evidence that treatment of VTE with LMWH might predispose to arthrofibrosis but did not support this statement with statistical analysis or report how many patients received therapeutic dose LMWH without developing arthrofibrosis or state the incidence of arthrofibrosis with chemoprophylactic anticoagulation.

Two studies correlated the use of specific antithrombotic agents with the risk of developing arthrofibrosis postoperatively. A retrospective study of 874 TKA reported the risk of developing arthrofibrosis requiring MUA was 9%, being 8% for patients receiving standard LMWH prophylaxis and 26% in those who received therapeutic dose warfarin due to pre-existing thrombophilic tendencies or medical conditions ($p < 0.0001$). Despite finding other potential predictors of arthrofibrosis (e.g., gender), the authors did not undertake regression analysis to account for confounders.

A retrospective insurance database study of 14,081 patients undergoing ACLR identified 191 patients who underwent either MUA or LOA for arthrofibrosis post-operatively[2154]. Only 499 patients (3.5%) received pharmacologic prophylaxis post-operatively. The rate of MUA/LOA was lowest in the group with no thromboprophylaxis (1.3%), followed by those receiving ASA (1.9%) and those prescribed any agent other than ASA (4.3%). Regression analysis confirmed an increased risk of MUA/LOA for arthrofibrosis (2.6 times) following ACLR for those prescribed a thromboprophylactic agent other than ASA, compared with patients who received no thromboprophylaxis ($p = 0.004$). No statistically significant difference was demonstrated between thromboprophylaxis with ASA and either of the other groups.

In summary, one retrospective study of patients undergoing ACLR showed an apparent relationship between postoperative hematoma requiring evacuation and risk of MUA/LOA, but this was not statistically significant after adjusting for confounding factors. Two relatively small retrospective series have suggested that therapeutic anticoagulation may be associated with an increased risk of knee stiffness after TKR. One large retrospective database study did show a statistically significant relationship between intervention for arthrofibrosis and prophylactic anticoagulation with agents other than ASA, relative to patients receiving no thromboprophylaxis.

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91 - Is there a role for empirical treatment of patients with suspected, but not confirmed, VTE in the post-operative period?

Response/Recommendation: Empirical systemic treatment with anticoagulation for suspected venous thromboembolism (VTE) in the post-operative period should only be initiated when timely image-based diagnosis cannot be achieved. Early treatment reduces the risk of VTE-associated morbidity. However, the increased bleeding risk with recent surgery should also be considered. Initiation of anticoagulation is ultimately a clinical decision, and a comprehensive risk-benefit assessment should be undertaken based on individual patient factors.

Strength of Recommendation: Low.

Delegates vote: Agree 94.58% Disagree 0.99% Abstain 4.43% (Strong Consensus).

Rationale: Major orthopaedic surgery is a key risk factor for developing VTE[2155]. The risk of VTE depends on operation type, location, and individual patient factors[2156]. The 35-day cumulative risk for symptomatic VTE following total hip arthroplasty (THA), total knee arthroplasty (TKA), and hip fracture surgery is estimated to be 4.3% in the absence of pharmacological prophylaxis[2157]. A high index of suspicion for VTE in the post-operative period is therefore paramount. The American College of Chest Physicians (ACCP) and the National Institute of Health and Care Excellence (NICE) offer clear guidelines for VTE prophylaxis[2157,2158]. This has reduced the incidence of post-operative VTE[2159]. VTE diagnosis is based on clinical judgment in combination with the use of a validated pre-test probability scoring system and D-dimer to determine whether further imaging is required[2156]. Initiation of antithrombotic medication should always be weighed against the risk of bleeding, particularly in the post-operative period[2160].

A literature search was performed to review the available evidence evaluating the role for starting empirical treatment for suspected VTE in post-operative orthopaedic patients. Guidelines from the ACCP advise empirical initiation of therapeutic dose anticoagulation for suspected acute VTE in cases where there is a high clinical suspicion, or intermediate clinical suspicion when there is an expected delay in diagnostic imaging for at least 4 hours[2161]. In patients with a low clinical suspicion of acute VTE where diagnostic imaging is available within 24 hours, initiation of therapeutic anticoagulation is not advised[2161]. However, this guidance does not apply to patients following recent surgery who are at increased risk of bleeding post-operatively, and there remains no specific evidence guiding recommendation for the empirical treatment of suspected VTE in the post-operative phase, especially in the orthopaedic patient. Early initiation of therapeutic anticoagulation in the context of a suspected VTE post-operatively is therefore a risk-benefit clinical decision that should be undertaken on a case-by-case basis. This should take into consideration the adverse outcomes associated with major bleeding versus the risk of short- and long-term VTE-associated complications[2162,2163].

Recent studies have reviewed outcomes associated with empirical treatment of suspected VTE in the absence of diagnostic imaging modalities such as duplex ultrasonography and computed tomography pulmonary angiogram (CTPA)[2164–2166], although this was not specific to the post-operative period. For example, Obi et al., outlined a protocol based on expert opinion, with initiation of therapeutic anticoagulation based on critical patient status, risk assessment by the Modified Wells' Score, and individual bleeding risk[2166]. This protocol advocated empirical treatment of suspected pulmonary embolism (PE) or deep venous thrombosis (DVT) if there was a delay in imaging > 4 hours and > 24 hours, respectively[2166].

This protocol and the ACCP guidelines are supported by data from a prospective study by Imberti et al., which reported no adverse events of PE or major bleeding at short-term follow-up after initial administration of a single weight-adjusted therapeutic dose of low-molecular-weight heparin (LMWH) in primary care patients suspected to have a DVT when confirmatory imaging study was not immediately available (within 18 hours)[2167]. A 0.7% risk of VTE-associated complications at 3-month follow-up was reported[2167]. Fronas et al., report that the initiation of treatment dose rivaroxaban followed by deferment of compression ultrasound for up to 24 hours was safe in patients with suspected lower-limb DVT (based on

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clinical assessment and a D-dimer ≥ 0.5 mg/L), with no episodes of major bleeding or complications noted at short-term follow-up of 48 hours after the last direct-oral anticoagulant (DOAC) dose[2162]. Similarly, Siragusa et al., concluded that administering treatment dose LMWH and delaying confirmatory imaging for up to 72 hours in patients with a high pre-test probability or a moderate pre-test probability score and positive D-dimer was safe[2168]. No major bleeding events were noted at ≤ 72 hours after patient referral, and a 1.2% risk of developing VTE at 3-month follow-up was observed[2168].

In a retrospective cohort study, Kim et al., found no significant difference in major or non-major bleeding, transfusion rates or length of stay at 3-month follow-up in hip fracture patients diagnosed with PE pre-operatively relative to a non-PE patient cohort with suspected VTE[2169]. Of note, 95.6% of the PE cohort received therapeutic anticoagulation post-procedure[2169], hence suggesting that peri-operative empirical treatment of VTE may be safe even if early surgery is advocated. However, peri-operative major and non-major bleeding rates remained significant, which were 21.1% and 13.3%, respectively, at 3-month follow-up in the PE cohort[2169]. Indeed, the proportion of non-PE patients administered therapeutic anticoagulation for suspected VTE pre-operatively was not reported and may have confounded the comparison in this study. Bose et al., found that the incidence of major bleeding events, recurrent VTE and death in post-operative patients initiated on treatment for PE within a 90-day period was 12%, 4% and 9%, respectively[2170], demonstrating a clear association with increased morbidity.

As the clinical signs of VTE may be unreliable[2171,2172], clinicians should always be mindful of alternative diagnoses causing respiratory decompensation, even in the presence of imaging confirmed VTE. Further studies are required to determine whether the increased bleeding risk outweighs the benefit of early treatment in cases of suspected post-operative VTE, taking into consideration the type of operation as well as individual patient factors.

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92 - What is the most appropriate method to monitor patients with confirmed post-operative VTE?

Response/Recommendation: Although it is not entirely clear whether venous thromboembolism (VTE) should be monitored after orthopaedic surgery, in selected patients suffering VTE due to persistent risk factors, the preferred method should be serial ultrasonography with or without serum D-dimer quantification.

Strength of Recommendation: Limited.

Delegates vote: Agree 91.67% Disagree 6.37% Abstain 1.96% (Strong Consensus).

Rationale: VTE includes two clinical entities, deep venous thrombosis (DVT) and, pulmonary embolism (PE).It occurs in 1 to 2 individuals per 1000 each year[2173]. VTE can be categorized broadly as either provoked or unprovoked. VTE is considered provoked when it is in conjunction with major temporary risk factors such as surgery or trauma and also be provoked by major persistent risk factors such as cancer[2174–2178]. While unprovoked are those produced in the absence of risk factors and without an identifiable cause[2174–2177]. Although a patient submitted to an orthopaedic surgery could suffer a provoked VTE secondary to a previous condition, it's more

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likely to suffer a transient provoked VTE in relation to the surgical event.

Initially, treatment of a provoked VTE from a temporary risk factor such as surgery should receive a limited course of anticoagulation[2179,2180]. In this case, the American Society of Hematology (ASH) guidelines suggest with moderated strength that after 3- to 6-months of treatment, anticoagulation should stop[2179]. Substantial literature has reported the low-risk of recurrence of a provoked VTE[2181–2186]. In this scenario, the need of monitoring patients during or after treatment, is not entirely clear. This should be in accordance with the risk of recurrence of VTE, which can occur in 1% - 3% of patients[2174–2177] after removal of the provoking factor. However, when the VTE is unprovoked, the cumulative risk of recurrence reaches 10% - 30% at 2 and 10 years, respectively[2174–2177,2187].

The monitoring of patients with a provoked VTE by transient risk factors is not required after the finalization of the primary treatment due to the improbable risk of recurrence of VTE in these individuals[2179]. Is not clear if the same condition in provoked VTE by chronic risk factors such as active cancer, inflammatory bowel disease, autoimmune disorders, chronic infections, and chronic immobility, will necessarily need extended anticoagulation, and with that, closer monitoring of the VTE[2188–2192]. The third condition would be an unprovoked VTE.

Serum D-dimer levels are easily tested and have proven to be effective in the assessment of residual thrombosis after VTE provoked by orthopaedic[2190] and non-orthopaedic procedures[2193–2195]. Despite having low specificity, they are considered useful for excluding diagnoses due to their high negative predictive values for DVT and PE[2188,2196,2197]. However, by themselves they are not an infallible tool and must be accompanied by imaging studies to confirm the presence of VTE. Kumagai et al[2190], have reported that combined D-dimer and ultrasound screening in patients with acute spinal cord injury (persistent risk factor) improved the detection of VTE, including PE, compared with D-dimer screening alone. Moreover, it is important to emphasize that the evidence is not sustainable when proposing a cut-off point or the ideal time to measure postoperative D-dimer levels. In a randomized trial, Palareti et al.[2198], included 223 individuals with an elevated D-dimer 1 month after completing 3- to 6-months of anticoagulation. In this study, participants were randomized to stop anticoagulation or to continue it for up to 18 months. They found that patients with an abnormal D-dimer level, 1 month after the discontinuation of anticoagulation had a significant incidence of recurrent VTE, which is reduced by the resumption of anticoagulation.

Ultrasonography is a less invasive procedure which besides the ability of monitoring also could diagnose recurrent VTE in selective patients. Prandoni et al., performed a randomized trial to evaluate the efficacy of tailoring the duration of anticoagulation based on recanalization or persistence of residual venous thrombosis as determined by ultrasound imaging[2189]. Their criteria for a recanalized vein were a vein thrombosis 2 mm in diameter with probe compression or 3 mm in diameter on two consecutive examinations. Participants randomized to ultrasonography received anticoagulation for an average of 4- to 5-months longer than did individuals randomized to the control group. Consequently, the investigators observed a non-significant reduction in the risk of PE in the intervention group. Unfortunately, this method is operator-dependent and the main problem in extrapolating these data to clinical practice is the criteria for determining recanalization of a thrombosed vein which can vary from one observer to another. Furthermore, ultrasound criteria to quantify residual venous thrombosis is not widely used.

The ASH guideline panel provides a conditional recommendation against the routine use of any of these modalities for all patients with VTE but acknowledges the potential utility of 1 (or more) of these approaches for management of selected patients[2179]. We agree with subjective inclination to serial ultrasonography due to its inherent capacity to confirm the potentially suspicious of VTE. However, the lack of strong evidence in relation to this topic does not allow us to recommend one over the other.

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93 - Should the post-operative rehabilitation of a patient with confirmed PE be modified?

Response/Recommendation: Following orthopaedic surgery, when a diagnosis of pulmonary embolism (PE) has been made and the patient is therapeutically anticoagulated, post-operative rehabilitation should proceed without delay. In patients who have high/intermediate risk PE, the rehabilitation, not only should address regaining function of the operated area, but also should include respiratory training and closely monitored aerobic exercise to gradually increase the pulmonary functional capacity and the patient's quality of life. This recommendation is made in the absence of evidence that an early mobilization or rehabilitation program is associated with a higher risk of adverse events (namely recurrent PE or bleeding), and that there are clear established benefits to rehabilitation. We recognize that some patients who have PE may have poor cardio-pulmonary tolerance or other medical complications, and for these patients, the exercise regimen may need to be modified based on symptoms.

Strength of Recommendation: Limited.

Delegates vote: Agree 97.55% Disagree 0.49% Abstain 1.96% (Strong Consensus).

Rationale: Rehabilitation post-orthopaedic procedures (e.g., total hip or knee arthroplasty) aims to maximize the function and independence of patients and is an essential step on the road to recovery. This consists of exercises to improve joint range of motion and strength, transfer training, gait training, and instructions on how to optimize activities of daily living. Studies performed in patients undergoing major orthopaedic surgery have consistently shown beneficial effects of exercise on functional outcomes, quality of life metrics, pain outcomes, shortening lengths of stay, and preventing post-operative complications[2199]. In current practice, it is recommended that rehabilitation begins as soon as possible after all orthopaedic surgery[2200,2201]. However, some patients may experience post-operative complications, including PE, which may incorrectly prompt healthcare teams to consider delaying rehabilitation and extending bed rest because of concerns about recurrent PE, particularly fatal PE, and bleeding while receiving anticoagulation.

Patients diagnosed with a PE following orthopaedic surgery frequently have a prolonged hospital stay and a longer rehabilitation period. However, there is a lack of randomized trials or high-quality observational studies to inform on the optimal timing and intensity of rehabilitation in patients who have PE after orthopaedic surgery, and whether these patients would benefit from cardio-pulmonary rehabilitation in the long term. One study retrospectively reviewed 325 patients who had a hip fracture and measured the length of stay, Geriatric depression scale, Modified Barthel index, and Berg balance scale score as well as 10-meter gait speed of their patients post-operatively. Fifteen patients were diagnosed with symptomatic venous thromboembolism (VTE) (six cases of both symptomatic deep venous thrombosis (DVT) and PE, four cases of symptomatic PE, and five cases of symptomatic DVT). Patients who had symptomatic VTE had a significantly more prolonged length of stay ($p = 0.012$). Interestingly, at discharge, there were no statistically significant differences between the VTE cases and non-VTE cases regarding other outcome measures. The duration of physical therapy between the two groups was similar. But due to the retrospective nature of the study, no

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information was available about the exact protocol of rehabilitation for the two mentioned groups[2202].

In the absence of high-quality evidence in the orthopaedic setting, we examined the potential risk of early mobilization and cardio-pulmonary rehabilitation in any patient who had a PE (regardless of its association with orthopaedic surgery). Considerations in patients who have a diagnosis of PE include the risk of progression to a fatal event, the risk of bleeding while on anticoagulant therapy, and on occasion, poor cardio-pulmonary tolerance that may affect adherence to an exercise program. Therapeutic anticoagulation is thought to reduce the risk of PE recurrence but increases the risk of bleeding.

For low-risk PE cases, early discharge is recommended[2203]. A randomized clinical trial evaluated the effect of outpatient rehabilitative exercise on the low-risk acute PE patient. During their six months mean follow up, they did not observe any added benefit of outpatient rehabilitation in these patients[2204].

Regarding intermediate/ high risk PE cases, a prospective study managed 23 PE patients with 3-phase rehabilitation (phase 1 in hospital initiated within 28 days after the diagnosis of PE, phase 2 and 3 could be performed in the inpatient/ outpatient setting). Around 8.7% of their patients had a low-risk PE, 69.9% of them had a sub-massive PE (an acute PE without systemic hypotension) and 21.7% of their cases had a massive PE. They found that rehabilitation was associated with improvement in quality of life and functional capacity. During their 6-month follow up, only one case of DVT recurrence and one case of bleeding was observed[2205]. In a retrospective study, acute (within two weeks after the PE) inpatient rehabilitation, including respiratory training and heart rate monitored aerobic exercise, was applied on 422 patients. During their 3-week rehabilitation program, three cases of bleeding occurred and only one of them was clinically relevant[2206]. In a prospective study of 70 patients who had PE, similar inpatient rehabilitation was associated with 2.8% bleeding, 1.4% newly diagnosed PE, and 5.7% death in their 12-month follow up period[2207]. In a short sample controlled clinical trial (including six PE cases in the intervention group, and five PE cases in the control group), Lakoski et. al., used an outpatient rehabilitation program for patients who had subacute PE (≥ six weeks and < three months since the index injury). They demonstrated that the program was associated with increased physical fitness and insignificant weight loss of the participants. They did not observe any associated adverse events[2208]. Another study prospectively followed PE patients managed with outpatient pulmonary rehabilitation (median period of follow up 39 months). The rehabilitation was started at a median period of 19 weeks after the acute PE event. They observed that while rehabilitation led to no adverse events, it was associated with significant improvement in the 6-minute walk test[2209].

Also, a systematic review of mostly observational studies has consistently reported that early mobilization in patients who have acute PE or DVT was associated with a decrease in recurrent PE, new/progressive DVT, and did not increase the risk of recurrent PE or bleeding[2210,2211]. Consequently, the current evidence in patients who have PE do not support the concern that an early mobility and/or exercise program within one to two weeks after PE increases the risk of adverse events.

Regarding chronic PE, there are two clinical trials that studied chronic PE patients who have stable pulmonary hypertension[2212,2213]. They have demonstrated that closely monitored inpatient rehabilitation programs can improve the World Health Organization (WHO) functional class and exercise capacity. However, one study reported syncope/pre-syncope in 4.4% of patients[2213].

We recognize that there is heterogeneity in the severity of PE, and that some patients who have severe right ventricular strain and cardio-pulmonary intolerance with severe symptoms may require a modified rehabilitation program based on symptoms. Finally, to minimize the risk and consequences of falls in patients on anticoagulation therapy, we also suggest assessment of fall risk, evaluating the maximal exercise capacity before staring rehabilitation, monitoring of vital signs including heart rate, and O_2 saturation during rehabilitation, and implementation of measures (in either inpatient or outpatient) rehabilitation programs for harm minimization.

In summary, there is a lack of evidence guiding the optimal timing and intensity of rehabilitation in patients diagnosed with a PE after orthopaedic surgery. In the absence of evidence suggesting harm, we suggest that mobilization and post-operative rehabilitation proceed as rapidly as the patient's cardio-pulmonary status permits.

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94 - Should the post-operative rehabilitation of patients who have confirmed symptomatic DVT be modified?

Response/Recommendation: There is no evidence to support modifying or changing the post-operative rehabilitation protocol for a patient with symptomatic venous thromboembolism (VTE).

Strength of Recommendation: Strong.

Delegates vote: Agree 95.61% Disagree 1.95% Abstain 2.44% (Strong Consensus).

Rationale: Patients undergoing orthopaedic surgery are at risk of VTE[2214-2221]. Rehabilitation including early ambulation is of utmost importance to prevent VTE[2222,2223]. Even with multimodal thromboprophylaxis, some patients undergoing orthopaedic surgery may still develop VTE[2224-2226].

There is clinical concern that ambulation of a patient with symptomatic VTE may result in dislodgement and propagation of DVT to the lungs and potential for a fatal outcome. Thus, the question of whether the post-operative rehabilitation protocol including early ambulation in symptomatic VTE patients should be changed or not has been raised. To address the latter issue, we conducted an extensive literature search and identified 544 articles related to this issue. Of these 275 studies were identified from MEDLINE/PubMed; 237 from EMBASE; nine from the Cochrane Library; and 23 from a hand search. The detailed review of these documents did not reveal any evidence to suggest that the postoperative rehabilitation of patients with symptomatic VTE should be altered.

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95 - Is there a role for thrombolysis in the management of patients with post-operative VTE?

Response/Recommendation: Despite the lack of evidence in the literature to establish a role for thrombolysis in patients with postoperative venous thromboembolism (VTE), there is a potential role for thrombolysis among select patients. Thrombolysis should be considered, with attention to iatrogenic bleeding and hematoma risk, among postoperative patients in the following circumstances:

1. Limb threatening deep venous thrombosis (DVT) with acute limb ischemia (e.g., phlegmasia cerulea dolens).
2. For selected patients at low risk for bleeding with symptomatic DVT involving the iliofemoral veins and at higher risk for severe post thrombotic syndrome (PTS).

Strength of Recommendation: Consensus.

Delegates vote: Agree 91.50% Disagree 3.00% Abstain 5.50% (Strong Consensus).

Rationale: Treatment of VTE has seen advances with the introduction of newer anticoagulants over the years. Nevertheless, despite newer therapeutical modalities, studies have reported that up to 60% of patients with VTE suffer from PTS, with up to 10% suffering severe PTS[2227]. PTS is a chronic debilitating condition resulting from incomplete clot dissolution causing venous obstruction and valvular reflux, leading to venous hypertension[2228,2229]. These in turn may lead to limb swelling, pain, pigmentation, and development of venous ulcers.

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There is some evidence that thrombolysis reduces the risk of developing PTS in patients with VTE, thereby improving quality of life[2230,2231]. The aims of thrombolysis in acute VTE are to reduce thrombus burden, restore patency of the vein, and thereby prevent venous congestion[2230]. Options for removal of the thrombus include:

1. Systemic thrombolysis: patients receive intravenous infusion of thrombolytic agents resulting in clot lysis. Commonly used agents include streptokinase, urokinase and alteplase[2232].
2. Catheter directed thrombolysis (CDT): delivery of a thrombolytic drug through a multiple side hole catheter positioned directly into the thrombosed vein[2233]. It results in more directed thrombolysis and is used mainly for DVT alone.
3. Pharmaco-mechanical catheter directed thrombolysis (PCDT): procedures combining the use of lytic infusion for thrombolysis with adjunctive catheter-based devices to promote mechanical removal of thrombus[2233]. Adjunctive procedures include balloon maceration, catheter aspiration, suction thrombectomy, percutaneous transluminal balloon venoplasty, stent placement, intravascular ultrasound, or some combination thereof. Some of the novel technologies use mechanical thrombectomy exclusively, thereby reducing the need for lytic agents and theoretically reducing the bleeding risk.

As the effect of thrombolysis is to remove blood clots, the main concern with thrombolytic therapy in all patients, especially post-operative, is that of major bleeding. Patients should be risk stratified to determine those who would likely benefit from invasive treatment. Among the factors clinicians should consider are:

- Estimated risk of bleeding.
- Clinical severity of DVT.
- Anatomic extent of DVT.
- General medical evaluation including life-expectancy baseline ambulatory capacity and comorbidities.

To date, there have been 4 randomized clinical trials (RCT) examining the effectiveness of early thrombus removal strategies:

- TORPEDO (Thrombus Obliteration by Rapid Percutaneous Endovenous Intervention in Deep Venous Occlusion)[2234].
- CaVENT (Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis)[2235].
- ATTRACT (Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis)[2236].
- CAVA (CAtheter Versus Anticoagulation Alone for Acute Primary Iliofemoral DVT)[2237].

The RCT compared anticoagulation alone as standard treatment arm versus CDT (CaVENT and TORPEDO), PCDT (ATTRACT) or ultrasound accelerated CDT (CAVA). The important outcome measures from these trials are summarized:

1. *PTS rates:* The CaVENT and TORPEDO trials reported a significant reduction in incidence of PTS, but the ATTRACT and CAVA trials did not detect a significant difference in PTS rates between the intervention and control group, although the ATTRACT trial did report a significant reduction in moderate-severe PTS at 24 months.
2. *Major bleeding:* The CaVENT, ATTRACT and CAVA trial investigators reported an increased incidence of major bleeding in the intervention groups compared to the control groups. The TORPEDO trial investigators did not observe this in their study and postulated that it might be due to the lower doses of tissue plasminogen activator (tPA) and heparin used compared to other studies.
3. *Recurrent VTE:* The incidence of recurrent VTE was significantly reduced in the TORPEDO trial, and this benefit extended beyond 2.5 years. However, the ATTRACT trial reported no difference in recurrent VTE rates at 2-year follow-up.
4. *Quality of life (QOL):* The ATTRACT, CaVENT, and CAVA trials did not report a significant difference in quality-of-life scores between the 2 groups. Understandably, patients who had more severe PTS reported worse QOL scores.

An updated meta-analysis by Broderick, et al.[2231], comparing thrombolytic strategies against standard anticoagulation for acute DVT of the lower limb reviewed 19 randomized controlled trials with 1,943 participants. The thrombolytic strategies included systemic, loco-regional and CDT. Complete thrombolysis occurred more frequently in the thrombolysis group at early and intermediate follow-up, and no differences were found between the thrombolysis treatments at any time point. The thrombolysis group had increased bleeding complications compared to anticoagulation alone (6.7% vs. 2.2%), but no differences were detected between the different thrombolysis treatments.

It is important to note that these four trials and more recent meta-analysis all specifically excluded postoperative patients, thereby limiting applicability to postoperative orthopaedic patients. However, recent surgery is not generally considered an absolute contraindication to thrombolysis and is appropriate in the setting of active or high-risk limb ischemia. In reviewing the available literature on thrombolysis, the European Society for Vascular Surgery (ESVS) 2021 clinical practice guidelines on the management of VTE summarized by consensus that thrombolytic therapies should be limited to patients at the highest risk of developing PTS (i.e., extensive clot burden, including the iliofemoral level), with a high chance of technical success (i.e., within two weeks of onset and no obvious post-thrombotic lesions) and low bleeding risk[2233]. The American Society of Hematology (ASH) 2020 guidelines for management of VTE[2238] similarly recommended that thrombolysis should be limited to patients with proximal DVT (iliofemoral veins), limb threatening phlegmasia cerulea dolens and pulmonary embolism (PE) with hemodynamic compromise and concomitant

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cardiopulmonary disease (sub-massive PE). Additionally, due to low certainty in the evidence of effect, CDT is considered superior to systemic thrombolysis for extensive DVT[2238]. The review specifically excluded postoperative patients.

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96 - Are patients with prior history of COVID - 19 who undergo orthopaedic procedures at an increased risk of VTE? If so, should their post-operative anticoagulation regiment be altered?

Response/Recommendation: It is generally known that the severe acute respiratory syndrome-related coronavirus (SARS-CoV [COVID - 19]) infection predisposes individuals to a higher risk of thromboembolism. However, there is not sufficient data to suggest that a previous COVID - 19 infection increases the risk of venous thromboembolism (VTE) after an orthopaedic procedure. Thus, the VTE prophylaxis of patients with prior COVID - 19 does not need to be altered.

Strength of Recommendation: Limited.

Delegates vote: Agree 94.66% Disagree 1.94% Abstain 3.40% (Strong Consensus).

Rationale: It has been demonstrated that COVID - 19 infection can result in coagulopathy and thromboembolic disease[2239] with a high risk of VTE[2240]. This can be explained by the association between COVID - 19 and inflammation, increased clot firmness, and decreased clot formation time[2241]. Similar to the effects of COVID – 19[2240,2242,2243] orthopaedic injuries cause a hyperinflammatory and hypercoagulable response, increasing VTE risk. The additive effects of these factors can amplify inflammatory response to the traumatic insult and pose an even greater VTE risk, while lowering survival rates[2244]. Because of the latter concern and the potential for increased risk for mortality, some studies have proposed that elective surgical intervention be delayed in patients with active COVID - 19 infection[2245,2246]. On the other hand, there is also some data to suggest that patients who had a delay in receiving their total joint arthroplasty due to COVID - 19 protocols may be at risk of VTE[2247].

Appropriate thromboprophylaxis is essential to prevent venous thrombotic complications associated with orthopaedic procedures, whether surgeries are elective (as hip and knee arthroplasties) or due to trauma[2248–2251]. Extended prophylaxis (for up to 45 days) can be considered for patients with elevated risk of VTE (e.g., immobility, presence of comorbidities such as active cancer or prior VTE)[2252-2254]. It is also important to include the assessment of bleeding risk in this decision. However, anticoagulant choice, dosage, and the duration in patients undergoing orthopaedic procedures who have previously been infected with COVID - 19 are not yet well studied. Several factors, such as the severity and length of the COVID - 19 infection, and the comorbidities of the individual seem to lead to a high heterogeneity of VTE presentation among this population[2255]. The issue of VTE prophylaxis for patients with COVID - 19 infection was discussed by the International Consensus Group (ICM) and in their published guidelines of July 2020, the recommendation was to administer some form of VTE prophylaxis for this patient group undergoing orthopedic procedures[2256].

In a recent study by Perazzo et al,[2257]. 16 patients with fracture of proximal femur who also had COVID - 19 infection were evaluated. The first seven patients received a single daily dose of low-molecular-weight heparin (LMWH), among whom four patients died of cardiovascular complications (four deaths). In the following nine patients with COVID - 19 and proximal femoral fracture, the dose of LMWH was doubled. There was only one death in that group. None of the patients died of VTE

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related complications and the sample size was so small that no conclusive deductions could be drawn from the study.

In a review paper, some investigators attempted to evaluate the potential implications of commonly prescribed medications in orthopaedic surgery for COVID - 19 patients, including VTE prophylaxis[2258]. In one letter, some authorities recommended that injectable VTE prophylaxis be used in lieu of oral anticoagulant[2259]. The authors felt that patients with COVID - 19 infection exhibited high variability in prothrombin time and international normalized ratio (INR) due to the issues with vitamin K metabolism in patients with acute viral infection. They also felt that patients with COVID - 19 receiving other oral anticoagulants may be exposed to under/over treatment caused by significant pharmacological interferences. Similar recommendations were made by other authorities in a follow-up publication[2260]. There is some data to suggest that aspirin may be useful in preventing critical illness associated with COVID – 19[2261] and it is also stipulated that oral anticoagulants may help decrease the hyperinflammatory effects of COVID - 19 in general[2262].

In conclusion, and based on current data, there is no need to change the VTE prophylaxis of patients with prior COVID - 19 undergoing orthopedic procedures. The decision to choose one agent versus other should rely on the risk-benefit ratio for these patients like others.

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97 - Does the risk for VTE increase after COVID - 19 vaccination?

Response/Recommendation: The risk of venous thromboembolism (VTE) in individuals receiving the severe acute respiratory syndrome-related coronavirus (SARS-CoV [COVID - 19]) vaccination is similar to the general population. A rare but drastic side effect of adenoviral COVID - 19 vector vaccines is the development of venous thrombosis at unusual sites, such as the brain or abdomen, accompanied by thrombocytopenia. Because the mechanism is still unclear and

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similarity was observed with heparin-induced thrombocytopenia (HIT), treatment of such thrombus should include non-heparin anticoagulants and intravenous immunoglobulin.

Strength of Recommendation: Limited.

Delegates vote: Agree 91.58% Disagree 0.99% Abstain 7.43% (Strong Consensus).

Rationale: Vaccination against COVID - 19 has proven its efficacy in preventing infection contraction and spreading, and has significantly reduced the risk of severe illness, hospitalization, and mortality[2263-2265]. Diversity of technology landscapes were developed to create vaccines that offer a way out of the COVID - 19 crisis. Most platforms utilized the virus spike protein and its variants as the main antigen of COVID - 19 infection. These projects involved nucleic acid technologies (nucleoside-modified messenger RNA and DNA), non-replicating viral vectors, peptides, recombinant proteins, live attenuated viruses, and inactivated viruses approaches[2266]. Though generally safe and efficacious, some temporary adverse effects have been reported including pain at the injection site, myalgia, headaches, fatigue, and tiredness, which is not uncommon with an inoculant that stimulates the immune system and usually resolves in a few days. However, few reports addressed a rare but devastating complication of thrombotic events in combination with thrombocytopenia observed after the administration of COVID - 19 vaccination[2267-2269].

The thrombotic disorder was described to be clinically similar to severe HIT, which is caused by anti-PF4/heparin antibodies and occurs almost 5 - 24 days after the 1st dose of vaccination[2270,2271]. Vaccine-induced prothrombotic immune thrombotic thrombocytopenia (VIPTT) were found to be associated with unusual sites of thromboembolism, such as cerebral venous sinus thrombosis in (CVST) or abdominal venous thromboses. Apprehension remains relative to the safety of two vaccines that were associated with most cases of thrombosis; Vaxzevria (previously AstraZeneca) and Janssen vaccines (Johnson and Johnson; also known as J&J)[2272]. Both vaccines contain recombinant adenoviral vectors based on a chimpanzee adenovirus (Vaxzevria) or a human adenovirus (Janssen vaccine) that encodes the SARS-CoV-2 spike protein immunogen. It is well known that adenovirus binds to platelets and that this interaction causes platelet activation which can initiate the thrombosis process[2273]. The American Society of Hematology and the Expert Hematology Panel (UK) suggest four diagnostic criteria in patients presenting within 4 - 30 days after vaccination with thrombotic symptoms. This includes receipt of a COVID - 19 vaccine (Janssen/Vaxzevria) 4 to 30 days previously; thrombosis (often cerebral or abdominal); thrombocytopenia; and positive PF4-HIT test using enzyme-linked immunosorbent assay (ELISA)[2274,2275]. While fewer cases were reported to have thrombotic events after the lipid nanoparticle encapsulated mRNA vaccine (Moderna and Comirnaty), no reports were found about thrombocytopenia after these vaccines[2275].

The majority of the large-scale studies consisting of individuals receiving COVID - 19 vaccination have reported that the thrombotic risk associated with vaccination was not elevated relative to the risk in the general population[2276,2277]. Huh et al., used the Korean claim database to determine the incidence of VIPTT among 8'548,231 patients vaccinated with Vaxzevria and it was found to be 0.23/1'000,000[2278]. In a multinational study of 21,720 persons receiving the Comirnaty (Pfizer/BioNTech) vaccine, half of them followed for 2 months and reported no deep venous thrombosis (DVT) or pulmonary embolism (PE)[2279]. Shazley et al., reported on a patient who developed DVT and PE which culminated in disseminated intravascular coagulation (DIC) in a COVID - 19 positive patient following the administration of the J&J vaccine[2280]. Smadja et al., assessed clinical features of venous and arterial thrombotic events after injection of three COVID - 19 vaccines (Comirnaty, Moderna, and Vaxzevria). They recorded more arterial thrombosis occurring with mRNA vaccines compared to venous thrombosis. For Vaxzevria, the proportion of venous and arterial thromboses was more evenly distributed[2272].

An observed-to-expected analysis performed by the marketing authorization holder reported that the number of DVT or PE cases observed was indeed significantly lower than expected, suggesting no causal association between VTEs and Vaxzevria[2281]. This interpretation however needs to be taken cautiously due to concerns related to quality, sensitivity, and appropriate stratification in the report.

Although the main pathogenic mechanisms behind the rare thrombotic phenomenon known to occur after COVID - 19 vaccination have not yet been identified, both host factors (thrombosis history, specific haplotypes, smoking and taking specific medications) and vaccine-related factors might be involved, with pathology being at least in part related to the vaccine-triggered autoimmune reaction[2263]. Furthermore, COVID - 19 infection has been proven to be prothrombotic[2282], it is unclear whether the patients who developed VTE after vaccination were infected with COVID - 19 (i.e., asymptomatic) prior to or immediately before immunity developed.

Based on the reports available, the rate of VTE in individuals receiving COVID - 19 vaccination appears to be similar to the general population.

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98 - Do clinical practice guidelines set the standard of care for VTE prophylaxis?

Response/Recommendation: The development of the current clinical practice guidelines (CPG) which followed the Delphi method, thus removing the potential for bias, may set the "standard of care" in venous thromboembolism (VTE) prophylaxis in orthopaedic surgery, since for the first time, they cover all subspecialties in orthopaedics.

Strength of Recommendation: Moderate.

Delegates vote: Agree 93.27% Disagree 2.40% Abstain 4.33% (Strong Consensus).

Rationale: The issue of VTE prophylaxis after orthopaedic procedures has been the subject of discussions in and outside courtrooms. Numerous lawsuits are filed on an annual basis against the medical community, when a patient undergoing a surgical (orthopaedic) procedure develops VTE, fatal or otherwise. The question that attracts attention in the courtroom is whether standard of care related to this issue was followed by the defending physician. The broader questions that we must ask is what is the "standard of care" for VTE prophylaxis after orthopaedic procedures, and if the standard varies depending on the particular condition being operated on, and also who determines the standard of care for a physician? Some might say the treating physician is the one to determine the standard of care. After all he/she is the one who has undergone extensive medical training, conducted medical research and is the one to treat the patient. Others might argue it is the payor/insurance company who decides what care will be reimbursed and hence sets the standard of care. While some argue that CPG determine the standard of care. But medical malpractice lawyers know that in the courtroom, the jury ultimately decides the standard of care.

The jury obviously gets plenty of assistance from experts on both sides of the case who tell them how the doctor violated or upheld the standard of care. The experts may point to the presence of CPG. However, before CPG can be used in the court of law, it must be determined admissible by a judge. There is no set standard on how CPG are used in medical malpractice cases. CPG are the definition of inadmissible hearsay, as the author of the guidelines is not available for cross examination in most cases. However, many courts rule that CPG fall under the learned treatise exception to the hearsay rule. It is important to note that judges make this determination on a case-by-case basis[2283].

Once the CPG have been deemed admissible, either side can use them to support their argument that a provider violated or upheld the standard of care. In the only review this author could find, Hymans et al., did a computerized search of the US Courts from 1980 - 1994. They found 37 uses of CPG by either side. In those cases, they were successfully used in 28 cases, 22 times by the patient's attorney and only 6 times by the physician's attorney. There were 9 unsuccessful uses of the CPG, 7 by the patient's attorney and 2 by the defense. When used successfully, the CPG were generally from strong, evidence-based sources like the American Medical Association, the American Hospital Association, the American College of Obstetrics and Gynecology or similar authorities[2284].

While there is a strong argument that, in the courtroom, the CPG have more often been used as a sword than a shield, that does not take into consideration what happens before the case gets to the courtroom. Cases are likely rejected by attorneys because there are strong CPG in place that would protect the doctor in court. And doctors' attorneys may be using the CPG to file dispositive motions that dismiss cases before they get to court.

As you consider the use of VTE CPG in the courtroom, know that once the judge determines their admissibility the jury will determine their weight. Both will likely be based upon the strength of the evidence behind the guideline and the group presenting it. When both are strong, the CPG will be used to prosecute the doctors who have violated those guidelines and thus protect the patient. The reverse is also true in that CPG may provide ample protection to physicians who were aware of them and followed them during the treatment of the patient.

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The current CPG on VTE are unique in many ways. They are produced by an extremely well known and recognized experts in the field of VTE from around the world. The delegates were selected using a vigorous process and specialties beyond orthopaedic surgery such as hematology, anesthesia, cardiology, internal medicine, infectious diseases, oncologists, and others were included. The development of the current CPG has followed an established and respected process, namely the Delphi method, that removes the potential for prejudice and bias. The content has been reviewed by numerous experts in the field and has also undergone the vigorous scrutiny imposed by the publishing journal. Finally, these CPG are extremely useful, as for the first time, they cover all subspecialties in orthopaedics.

Heather Hansen

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Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/G903).

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Update

This article was updated on June 17, 2022 because of a previous error. On page 33, in the section entitled "17 - Does administration of tranexamic acid (TXA) to patients undergoing orthopaedic procedures increase the risk of subsequent VTE?", and in the note on page 161, the name "Armin Arish" now reads "Armin Arshi."

An erratum has been published: J Bone Joint Surg Am. 2022 Aug 3;104(15):e69.