Venous thrombosis following lower-leg cast immobilization and knee arthroscopy: From a population-based approach to individualized therapy

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ABSTRACT

Venous thromboembolism (VTE) is a major complication following lower-leg cast immobilization and knee arthroscopic surgery. In this review, we aimed to give a comprehensive overview of the literature on the epidemiology, prevention and prediction of VTE in these patients.

First, the cumulative incidence of VTE was estimated by performing a meta-analysis in untreated patients only. In lower-leg cast patients with various injuries, asymptomatic VTE occurred in 18.0% (95%CI 12.9 to 23.1) and symptomatic VTE in 2.0% (95%CI 1.3 to 2.7). In knee-arthroscopy patients, asymptomatic VTE was seen in 5.9% (95%CI 3.9 to 7.9) versus a symptomatic rate of 0.6% (95%CI 0.4 to 0.7) following heterogeneous types of arthroscopic knee procedures.

Second, the efficacy of thromboprophylaxis was determined by performing a meta-analysis of all RCTs that have been performed till date. Following knee-arthroscopy, there was no clear benefit of thromboprophylaxis on the prevention of symptomatic VTE (RR 0.65, 95%CI 0.23 to 1.81), while in contrast, this seemed to prevent asymptomatic DVT. In lower-leg cast patients, thromboprophylaxis appeared to reduce symptomatic VTE (OR 0.31, 95%CI 0.13 to 0.73). However, the validity of these results may be questioned as many trials had several methodological weaknesses.

Concerning the bleeding risk (and costs) of thromboprophylaxis, treatment seems only prompted in high risk patients. Such patients could be identified based on individual risk factors such as higher age, obesity or presence of Factor V Leiden. In conclusion, we propose to use risk assessment models to identify patients at risk and to decide on individualised thromboprophylactic therapy, rather than one standard treatment for all patients.

INTRODUCTION

Patients with cast immobilization of the lower-leg or who undergo arthroscopic knee surgery are at increased risk for developing venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE). Many authors studied the occurrence of VTE following these healthcare interventions [1-5] and several clinical trials have been performed to explore whether thromboprophylaxis is effective for the prevention of VTE. [6, 7] However, regardless of all the evidence, guidelines are still ambivalent with regards to thromboprophylaxis advice.[8, 9] Recently, results from two large pragmatic randomized controlled trials (i.e. one in patients with lower-leg casting and one in patients who underwent knee arthroscopy) were published in which it was shown that thromboprophylaxis was not effective for symptomatic VTE reduction.[10] Contradictory findings in (most) previously published studies described a protective effect of thromboprophylaxis therapy.[6, 7]

In light of these recent findings, there is a necessity to integrate and translate all previously published and current research to clinical practice. For this reason, in this narrative review, we aimed to give a comprehensive overview of the literature on the epidemiology, prevention and prediction of VTE in lower-leg cast and knee arthroscopy patients.

First, the incidence of VTE following lower-leg cast immobilization and arthroscopic knee surgery was estimated. Therefore, we selected all cohort studies and clinical trials of moderate to high quality which were published till date with reliable incidence rates. We collected cumulative incidence data in all patients who did not receive thromboprophylaxis therapy (thus studies were excluded when data on thromboprophylaxis were not available). For this purpose the number of patients with a VTE and the size of the study population were extracted. Subsequently, a meta-analysis using a random effects model (using the method of DerSimonian and Laird) was performed to estimate the cumulative incidence for asymptomatic DVT and symptomatic VTE separately. Results were summarized in a forest plot showing the Estimated Proportion (ES) including 95% Confidence Interval (95%CI) of patients with a VTE in each study. Heterogeneity was assessed using the I^2 method. See *Supplement 1* for our search strategy.

Second, the efficacy of thromboprophylaxis is discussed including evidence from the most recent studies.[10-12] A meta-analysis using a random effects model (using the method of DerSimonian and Laird) was performed on the efficacy of thromboprophylaxis therapy, summarizing all clinical trials that have been performed up till now. We extracted the number of VTEs within each trial per study arm. In a forest plot we showed the Relative Risk (RR) including 95%CI for the effectiveness of thromboprophylaxis. This was done for the effectiveness on symptomatic and asymptomatic events separately. See *Supplement 1* for our search strategy.

Third, this review focusses on individualized preventive strategies. Therefore, we summarized all VTE risk factors that have been identified in knee arthroscopy and lower-leg cast patients. Additionally, we reviewed the literature for available risk prediction models that were able to assess VTE risk in these patient populations. Finally, future research perspectives are discussed, focusing on the mechanism of thrombus development following knee-arthroscopy and lower-leg casting.

Please see the table of contents below which clarifies the structure of this extensive review.

EPIDEMIOLOGY

In the general population, annually, 1.5 per 1000 patients will develop VTE, corresponding to an individual's lifetime risk after 45 years of age of about 8%.[13, 14] In this chapter we aimed to estimate the actual incidence of VTE following lower-leg cast immobilization without thromboprophylaxis. Subsequently, this was also done for patients who undergo knee arthroscopy. Thereafter the burden of VTE in both patients groups is described focussing on the impact of VTE on a population level.

Incidence of VTE following lower-leg cast immobilization

Patients with cast immobilization of the lower-leg have an increased risk for developing VTE which was already described in 1944. In that year, Gunnar Bauer showed that DVT was a very common complication (12% asymptomatic DVT) following leg injuries[15] and since then, a wide range of incidences of asymptomatic events have been published (*Figure 1*).

One of the first observational studies from Hjelmstedt and colleagues showed in 1968 that 46% of all patients with a tibial fracture developed an asymptomatic DVT (as diagnosed by phlebography).[16] Later, in 1975, a case series of six VTEs in four months was published in patients treated with cast immobilization of the lower extremities (within the Air Force orthopaedic service (USA).[27] Thereafter, multiple studies have shown an association between cast immobilization and the occurrence of VTE.[17, 28] To study whether VTE could be prevented, the first randomized controlled trial was performed in 1993.[1] 253 patients were randomized to receive a low-molecular-weight-heparin (LMWH) (126 patients) or no thromboprophylaxis (127 patients). In the control group, 21/127 (16.5%) patients developed asymptomatic VTE as compared with 6/127 (4.8%) patients in the LMWH group. A compression ultrasound was performed in all patients during plaster cast removal, and overall, only 9/253 (3.6%) patients had clinical symptoms of thrombosis. This study indicated for the first time that the frequency of asymptomatic events is much higher than that of symptomatic events, which was confirmed by another randomized controlled trial performed in 1995, that studied both the occurrence of symptomatic and asymptomatic VTE following cast immobilization for traumatic injury of the leg. In this study, lower rates were found; 4.3% of all 163 patients who received no prophylaxis developed an asymptomatic event as compared with 2.5% symptomatic events.[2]

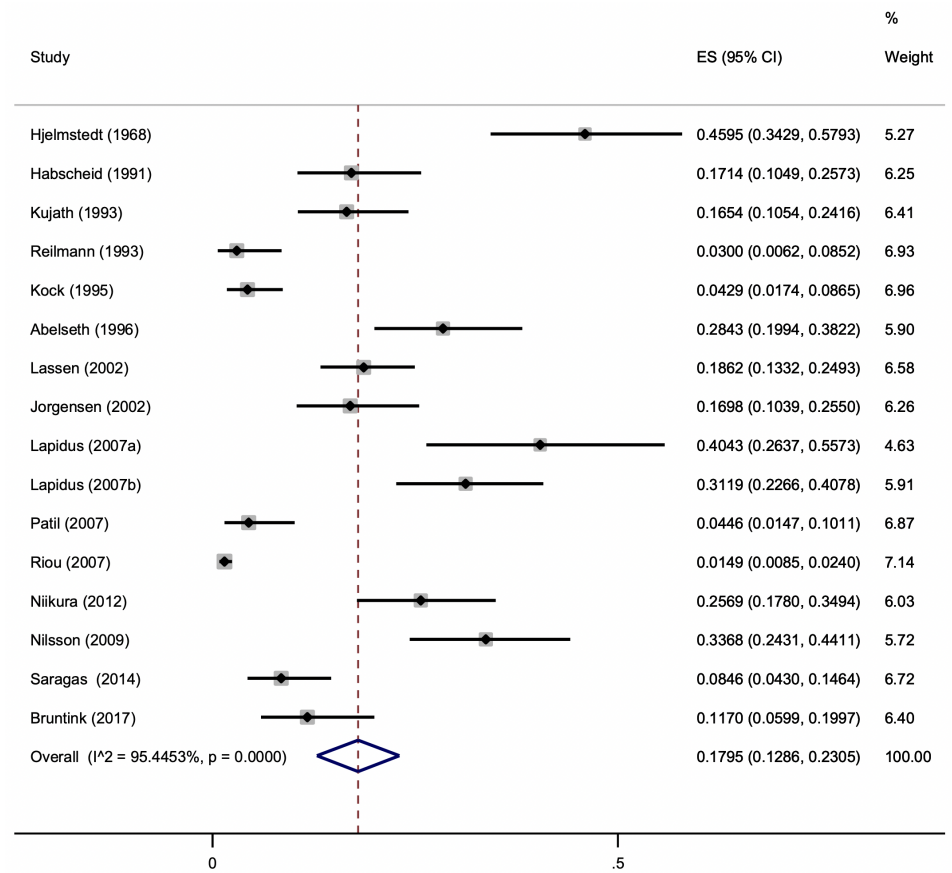

Figure 1: Incidence of asymptomatic VTE following lower-leg cast immobilization in patients without thromboprophylaxis.
ES denotes the estimated proportion of patients with a VTE in each study, thus the cumulative incidence. References: Hjelmstedt[16], Habscheid[17], Kujath[1], Reilmann[18], Kock[2], Abelseth[19], Lassen[20], Jorgensen[21], Lapidus[22], Lapidus[23], Patil[24], Niikura[25], Saragas[26], Bruntink[11].

In 2000, Giannadakis and colleagues reported a series of 178 patients with lower limb injuries who required cast immobilization at low-risk for VTE.[29] Only 1.1% (2 patients) developed a symptomatic VTE and the authors concluded that due to this low absolute risk there was no indication to give thromboprophylaxis. As a result of the wide variety of reported risks and lack of studies that used venography (the gold standard for DVT diagnosis) to measure asymptomatic VTE, a new randomized clinical trial was performed to study the efficacy of thromboprophylaxis following lower-leg cast immobilization.[21] Similar asymptomatic VTE rates were found as compared with some previous studies,[1, 17, 20] as in the untreated group 18/106 (17.0%) patients developed an asymptomatic VTE. However, no symptomatic events occurred, which was contradictive with incidences of symptomatic VTE from previous studies that ranged between 1.1%-3.2%.[2, 19, 20, 28, 29] Thereafter, two other trials were performed in 2007, one in patients who underwent surgical treatment for an Achilles tendon rupture[22] and one in patients who required ankle fracture surgery concomitant to cast immobilization.[23] In the ankle fracture study, 5.5% (6/109) of all patients in the untreated group developed a symptomatic VTE as compared with 31.2% (34/109) asymptomatic events. In the Achilles tendon rupture study, of all untreated patients, 6.4% (3/47) developed symptomatic VTE versus 40.4% (19/47) asymptomatic VTE. Contradictory, an observational study that was performed within the same year, studied the incidence of asymptomatic VTE in 100 low-risk (no prophylaxis) patients with a cast immobilization because of an ankle fracture.[24] The authors only found five (5%) asymptomatic events and no symptomatic VTEs were diagnosed.

In 2008, following many small venography or ultrasound studies on asymptomatic DVT, the first large observational study was published.[30] 1789 patients with cast immobilization of the leg received thromboprophylaxis therapy (and are therefore not included in our meta-analysis) of whom only 0.50% (9/1789) developed a symptomatic VTE. A similar large observational study was published in 2014 in which 1200 patients with a lower-limb fracture were followed for three months. However, in this study, thromboprophylaxis was not administered.[31] 98% of all patients had a complete follow-up and 82% was treated with cast immobilization. Seven patients (0.58%) developed a symptomatic VTE and it was concluded that symptomatic VTE is an infrequent complication after lower-leg fractures. A slightly higher, but still low incidence (1.4%) was found by Heyes and colleagues in 945 patients with an Achilles tendon rupture treated with cast immobilization.[32]

Combining all studies in a heterogeneous group of lower-leg cast patients who did not receive thromboprophylaxis, we found a pooled absolute risk for asymptomatic events of 18.0% (95%CI 12.9 to 23.1) and a symptomatic risk of 2.0% (95%CI 1.3 to 2.7) (within approximately 3-months) (*Figures 1 and 2*).

Both surgically and conservatively treated patients, as well as patients with ankle or foot fractures or Achilles tendon ruptures were included in the abovementioned studies. The pooled analyses confirm a large difference between the occurrence of asymptomatic and symptomatic VTE following leg-cast immobilization; on average, about 10% of all asymptomatic events seem to progress into clinical disease. Moreover, the wide range of reported incidences indicates considerable heterogeneity of included patients as well as heterogeneity in diagnostic methods (for asymptomatic events)[38]. In 2015, in a large population-based case-control study, van Adrichem and colleagues reported that the

increased VTE risk following cast immobilization of the lower extremity was only present up to 3 months, resulting in an odds ratio (OR) of 56.3 (95% confidence interval [CI] 17.9–177.3) as compared with patients without plaster cast.[39] Considering an absolute risk in the general population of 1.5 per 1000 persons[14] within one year (thus about 0.0375% within 3-months), cast immobilization leads to an absolute thrombosis risk of 2.1% within 3-months (i.e. 0.0375% multiplied by an OR of 56.3). A highly similar incidence (2.0% [95%CI 1.3 to 2.7%]) was found in our meta-analysis (*Figure 2*) indicating the precision of this estimation.

Incidence of VTE following knee arthroscopy

For decades it has been well known that major orthopaedic surgery is associated with a high VTE risk which could be explained by the invasiveness of the procedure, associated immobility and the presence of additional risk factors (i.e. comorbidities in an older population). Knee arthroscopic surgery is a less invasive procedure, most patients are young (few comorbidities) and in general, patients are mobilized within the same day following surgery. Nevertheless, patients who undergo arthroscopic knee surgery are considered to be at moderate or high risk for the development of VTE.[8] An early report of this complication was published in 1977, when McGinty and colleagues investigated whether it was better to perform a partial or complete meniscectomy in 128 patients who were hospitalized for approximately 4 days.[40] In this study, one symptomatic pulmonary embolism (0.78%) and eight cases of thrombophlebitis were described. 5 years later, Dandy and Carrol reported three cases of symptomatic DVT in 1168 arthroscopic knee procedures for an incidence of 0.3%.[41]

However, these studies were not designed to study the incidence of VTE and in 1989, authors from London published the first study on DVT incidence following elective knee surgery. 48 patients underwent knee arthroscopy of whom 2 (4.2%) developed an asymptomatic DVT as diagnosed by an ascending venography that was performed in all patients following surgery.[42] Similar incidences of asymptomatic VTE were described by Williams (3.5%)[43] and Wirth (4.1%)[44].(*Figure 3*)

Subsequently, in 1995 (Roth), the first randomized clinical trial on the efficacy of thromboprophylaxis was performed. In this study 144 patients undergoing elective arthroscopic knee surgery were randomized to receive LMWH for 4 days or no treatment. In the control group, 5/61 patients (8.2%) developed asymptomatic VTE of whom 1 patient (1.6%) was found to be symptomatic. Contradictory, much higher incidences were described in another study (Demers) which venographically assessed the incidence of VTE in 184 patients.[48] Here, asymptomatic VTE was found in 34 patients (18.5%) (33 DVT, 1 PE) and symptomatic VTE was reported in 20/184 (10.9%) patients.[48]

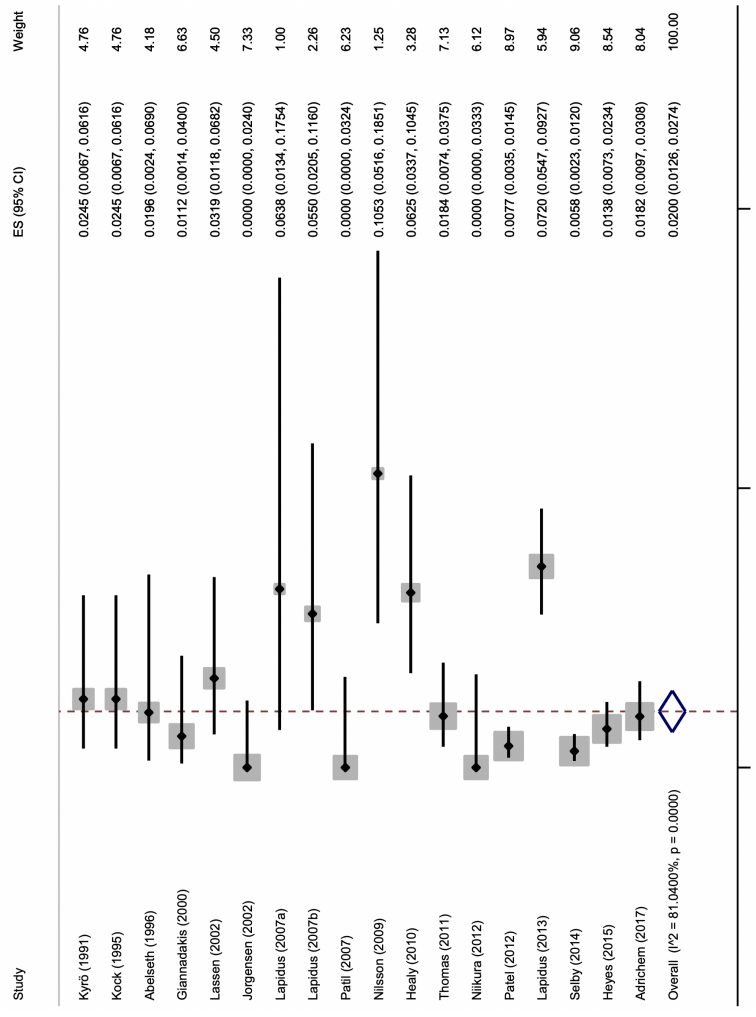

Figure 2: Incidence of symptomatic VTE following lower-leg cast in patients without thromboprophylaxis.
ES denotes the Estimated proportion of patients with a VTE in each study, thus the cumulative incidence. References: Kyrö[28], Kock[2], Abelseth[19], Giannadakis[29], Lassen[20], Jorgensen[21], Lapidus[22], Lapidus[23], Patil[24], Nilsson[33], Healy[34], Thomas[35], Niikura[25], Patel[36], Lapidus[37], Selby[31], Heyes[32], van Adrichem[10].

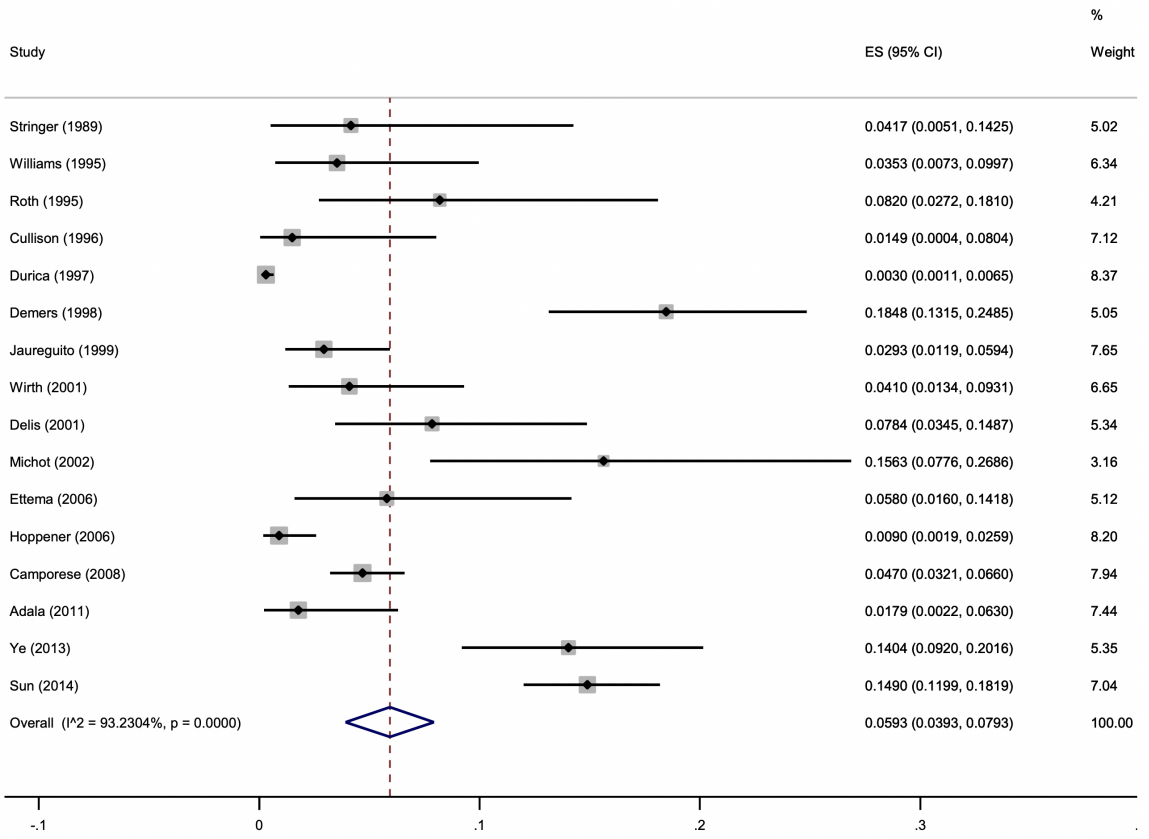

Figure 3: Incidence of asymptomatic VTE following knee arthroscopy in patients without thromboprophylaxis. ES denotes the Estimated proportion of patients with a VTE in each study, thus the cumulative incidence. References: Stringer[42], Williams[43], Roth[45], Cullison[46], Durica[47], Demers[48], Jaureguito[49], Wirth[44], Delis[50], Michot[51], Ettema[52], Hoppener[53], Camporese[54], Adala[55], Ye[56], Sun[57].

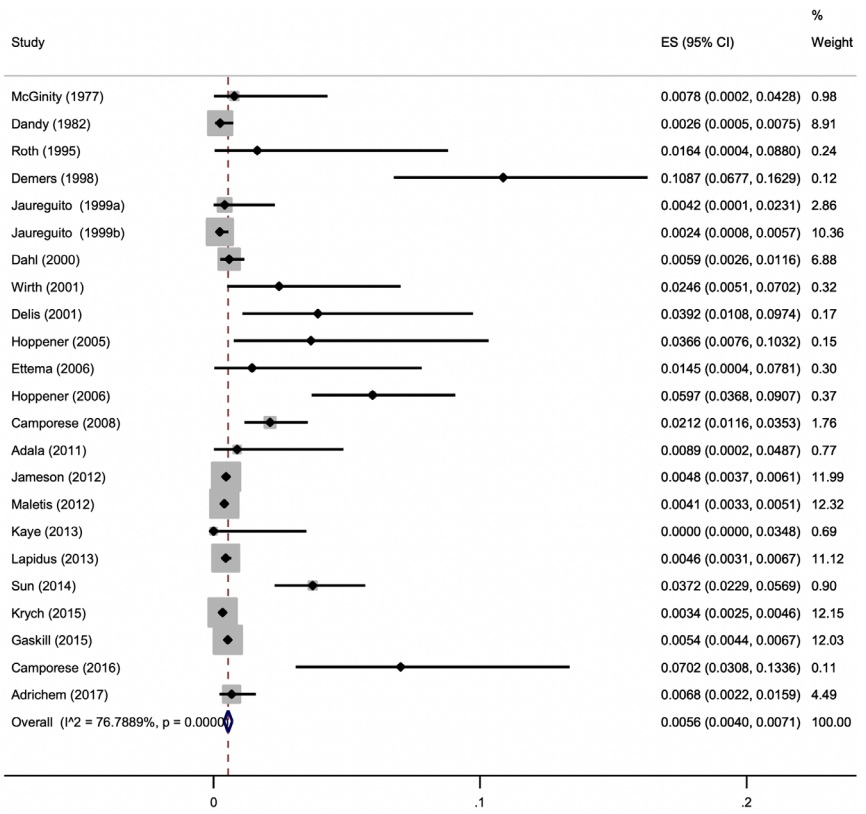

Figure 4: Incidence of symptomatic VTE following knee arthroscopy in patients without thromboprophylaxis.
ES denotes the Estimated proportion of patients with a VTE in each study, thus the cumulative incidence. References: McGinty[40], Dandy[41], Roth[45], Demers[48], Jaureguito[49], Jaureguito[49], Wirth[44], Delis[50], Hoppener[59], Ettema[52], Hoppener[53], Camporese[54], Adala[55], Jameson[58], Maletis[5], Kaye[60], Lapidus[37], Sun[57], Gaskill[4], Camporese[12], van Adrichem[10].

Possibly, more invasive procedures such as an anterior cruciate ligament [ACL] reconstruction or multiple performed procedures contributed to the higher risk as described by Demers and colleagues. Comparable results were shown by two other studies, both performed in 2014 that solely included patients who underwent cruciate ligament reconstruction. Asymptomatic VTE rates of 14.1%[56] and 14.9%[57] were observed. However, multiple large observational studies, including a wide range of knee arthroscopy types, showed low incidences for symptomatic VTE ranging from 0.3% to 0.5%.[4, 5, 37, 49, 58] As large retrospective registries were used to collect data on the occurrence of VTE, these studies are subject to information bias which could have resulted in an underestimation of the true incidence. Yet, the similar reported incidences in all of these studies suggest that VTE is not a frequent complication. (*Figure 4*)

Our meta-analysis shows that in patients undergoing knee arthroscopy, like in patients with lower-leg cast immobilization, asymptomatic VTE occurs about 10-times more than symptomatic VTE. Asymptomatic VTE was seen in 5.9% (95%CI 3.9-7.9) of all patients compared with a rate for symptomatic VTE of 0.6% (95%CI 0.4 to 0.8) following heterogeneous types of arthroscopic knee procedures in patients without chemical thromboprophylaxis (follow-up for most studies 3-months). In a large population-based case-control study, knee-arthroscopy was associated with a 16.2-fold risk for VTE within 3-months following surgery. Considering the absolute risk in the general population of about 1.5 per 1000 persons per year, this leads to an absolute risk for symptomatic VTE following arthroscopic knee surgery of 0.61% within 3-months. An almost identical incidence of symptomatic VTE was found in our meta-analysis (0.6%, 95%CI 0.4 to 0.8) which again indicates the robustness and precision of this estimate.

Burden of VTE following lower-leg cast and knee arthroscopy

It is estimated that each year, approximately 4 million knee arthroscopic procedures are performed worldwide[61], of which 40 000 in the Netherlands alone. For lower-leg cast, no accurate worldwide estimations are available. However, if we extrapolate the number of lower-leg cast applications in the Netherlands (35 000)[62] to the worldwide population, at least 3.5 million patients receive a lower-leg cast each year (for computational ease). Considering this high number of procedures, the burden of symptomatic VTE following these healthcare interventions in substantial. Assuming an incidence of symptomatic VTE following knee arthroscopy of 0.6% (derived from our meta-analysis), 24 800 patients will yearly develop VTE, worldwide. Likewise, assuming an incidence of symptomatic VTE following lower-leg cast of 2.0%, 70 000 patients will suffer from symptomatic VTE. Consequently, on a population level, knee arthroscopy and lower-leg cast immobilization are responsible for a population attributable fraction for VTE of 2.1% and 2.7%, respectively. This means that, of all patients who develop symptomatic VTE, a total of

4.8% is caused by leg-casting or knee arthroscopy. Furthermore, of all these patients, 11 945 patients are expected to die within 1-year following knee arthroscopy or cast-immobilization, (assuming a case-fatality rate for provoked non-cancer related VTE of 12.6%).[14] Hence, considering this high burden, it is of great importance to find the best strategy for VTE prevention in these situations.

PREVENTION

In this chapter, first the effectiveness of thromboprophylaxis in patients with lower-leg cast immobilization is discussed followed by the effectiveness following knee arthroscopy using data which have been published up to 2016. This has been done as all current guidelines and reviews are based on data up to 2016. Thereafter, we discuss all recent evidence (after 2016). Finally, we have updated results by performing our own meta-analyses on the effectiveness of thromboprophylaxis following lower-leg cast immobilization and knee arthroscopy.

The effectiveness of thromboprophylaxis following lower-leg cast immobilization

Several meta-analyses and reviews have been published regarding the effectiveness of thromboprophylaxis for the prevention of VTE following lower-leg cast immobilization.[3, 7, 63] In these meta-analyses, six randomized controlled trials were summarized of which the last one was published in 2007.[1, 2, 20-23] All trials allocated patients to either LMWH or no therapy (or placebo), however, a variety of leg-cast indications was eligible to be included (e.g. fracture, tendon ruptures, conservative or operative treatment etc.). Furthermore, all trials screened for the occurrence of *asymptomatic* DVT, either by compression ultrasound or venography. The first trial, performed in 1993, concerned 253 patients, aged >16 years, who were conservatively treated with a lower-leg cast for at least 7 days.[1] Patients were randomized between nadroparin or no treatment for 16 days. In the per-protocol analysis, after 53 post-randomization exclusions, 4.8% of all patients with prophylaxis, and 16.5% of patients without prophylaxis developed an asymptomatic DVT (defined by compression ultrasound) (risk reduction of 11.7% [95%CI 4.3% – 19.3%]). Kock et al. then published a RCT using similar inclusion criteria, in which 339 patients with a lower-leg cast were analysed.[2] Upon cast removal, a compression ultrasound and duplex scanning was performed and suspected asymptomatic events were confirmed with venography. In this trial, much lower incidences were found; 0% in the treated and 4.3% in the non-treated group developed an asymptomatic DVT (risk reduction 4.3% (95%CI 1.2% - 7.4%). Subsequently, in 2002 the first RCT using the gold standard (venography) was performed.[64] 95 patients with a planned cast immobilisation of the lower-leg for at least 3 weeks (both operated and non-operated) were eligible for inclusion and randomized between LMWH once daily or no therapy. A non-significant protective effect of prophylaxis was found (risk reduction (6.9%), RR 0.59, 95%CI 0.29 to 1.23) and no symptomatic VTE was observed. In the same year, another RCT included patients treated with cast immobilization for at least 5 weeks for either a fracture or Achilles tendon rupture (about half was treated surgically).[20] This was the first trial to use placebo injections instead of no therapy. 69 patients were excluded due to loss of follow up and in the per-protocol analysis, thromboprophylaxis prevented the development of asymptomatic DVT (RR 0.45, 95%CI 0.24 to 0.83). Furthermore, the authors observed a non-significant risk reduction

for symptomatic VTE (RR, 0.08, 95%CI 0.00 to 1.36). Finally, in 2007, Lapidus et al. performed two trials, one in patients immobilized for an Achilles tendon rupture and one in patients with a fracture.[22, 23] In the first trial, similar numbers of asymptomatic DVT were found in the treatment and control group (18/49 and 19/47, respectively),upon which the authors concluded that thromboprophylaxis was not effective. In the second trial, in patients with an ankle fracture, no significant effect of thromboprophylaxis was found for either asymptomatic or symptomatic VTE (RR 0.66; 95%CI 0.42-1.03 and OR 0.31: 95%CI 0.06-1.51, respectively).

Based on these six RCTs, several meta-analyses advise to prescribe thromboprophylaxis as the benefits (VTE prevention) outweigh the harms associated with treatment (bleeding, costs, patient burden). In a Cochrane review, a total of 1490 patients was included.[7] It was reported that thromboprophylaxis was effective for the prevention of *asymptomatic* VTE for a pooled RR of 0.49, 95%CI 0.34 to 0.72 (heterogeneity I^2 20%, p=0.29), which result was consistent for several subgroups (i.e. conservatively or operatively treated, fractures, soft-tissue injuries). Another meta-analysis which looked into several subgroups such as inclusion of the more methodologically sound trials revealed consistent results.[3] None of the meta-analyses showed an increased risk for major bleeding (major bleeding risk 0.3%[7]) associated with thromboprophylaxis therapy. However, despite these data, in the 2012 ACCP guidelines it was suggested to perform a large practical RCT which avoids screening for asymptomatic VTE due to a lack of compelling evidence.[8]

The effectiveness of thromboprophylaxis in patients following knee arthroscopy

In patients who had undergone knee-arthroscopy, 5 RCTs were performed to study the efficacy of thromboprophylaxis up until 2008.[44, 45, 51, 54, 65] In these trials, a variety of procedures such as a diagnostic arthroscopy, meniscectomy or ACL reconstruction were performed and all patients were screened for the occurrence of asymptomatic DVT, either by compression ultrasound or venography.

The first trial randomized 144 patients to LMWH for 4 days versus no treatment of whom 122 were included in the analysis.[45] 5/61 (8.2%) patients versus 1/61 (1.6%) patients developed an asymptomatic thrombotic event in the control and treated group respectively, while one symptomatic thrombosis occurred in both groups (1.6%). However, as all patients were over 60 years and no full weight bearing was allowed until the 5th day post-operative, results were less applicable to current clinical practice. In 2001, Wirth and colleagues found very similar results in elective knee arthroscopy patients with a mean age of 38 years.[44] 1/117 (0.9%) patients in the treatment group and 5/112 (4.5%) patients in the control group developed thrombosis. Whereas Roth included high risk patients,[45] Wirth focussed on low risk patients and excluded those patients with a history of VT, or those with three or

more risk factors (obesity, smoking, oral contraceptives and family history of thrombosis).[44] In 2002[51] and 2003[65], two more trials were performed into the efficacy of thromboprophylaxis. Michot randomized patients to a prophylactic dose of LMWH up to 30 days post-surgery versus no treatment. 1/66 (1.5%) patients in the LMWH group versus 10/64 (15.6%) patients in the control group developed an asymptomatic event, but no clinical events were seen. Canata and colleagues included patients scheduled for ACL reconstruction who were randomized for 6 days of LMWH therapy (n=18) versus no treatment (n=18). No asymptomatic or symptomatic events were diagnosed. Finally in 2008, the first large trial was performed by Camporese and colleagues.[54] In this assessor-blind RCT, 1761 patients were randomized to either full length graduated compression stockings for 7 days (n=660), LMWH for 7 days (n=657), or 14 days post-operatively (n=444). The 14-days LMWH group was stopped prematurely by the data safety monitoring board due to safety issues (no efficacy compared with 7-days and risk for major and minor bleeding of 4.1% [0.3% major]). In the compression stockings group, 21/660 (3.2%) patients developed the primary efficacy endpoint (death, symptomatic VTE and asymptomatic proximal DVT) versus 6/657 (0.9%) in the 7-day LMWH group (absolute risk difference -2.3% (95%CI 0.7 to 4.0). Asymptomatic distal DVT occurred in an additional 10/660 (1.5%) and 6/657 (0.9%) patients in the stocking and LMWH group respectively. From this trial is was concluded that 7-days of thromboprophylaxis reduced VTE significantly.

Overall, combining all trials results, the pooled risk for any VTE (both asymptomatic and/or symptomatic) was 5.6% (95%CI 2.7 to 8.5) in patients without, and 1.6% (95%CI 0.7 to 2.4) in patients with thromboprophylaxis. Multiple meta-analyses summarized the abovementioned data:[6, 66] A Cochrane review in 2008 concluded that thromboprophylaxis was effective for the prevention of asymptomatic VTE for a relative risk of 0.16 (95%CI 0.05 – 0.52). However, when the authors only included symptomatic events, the meta-analysis failed to show a protective effect for anticoagulant therapy (RR 0.42, 95%CI 0.06 – 3.14). Thereafter, Chapelle and colleagues summarized the abovementioned 5 RCTs plus an additional trial which studied whether extended LMWH therapy (20 days) was more effective for VTE prevention than short duration (in-hospital only) therapy.[67]. Not surprisingly, the authors found a comparable risk reduction on asymptomatic proximal DVT and any symptomatic VTE as the Cochrane review (RR 0.27, 95%CI 0.15-0.49).

Guidelines for VTE prevention following lower-leg immobilization and knee arthroscopy

Despite this great body of research, in both patient groups, guidelines have been reluctant to advice in favour or against the use of thromboprophylaxis in all patients treated with lower-leg cast immobilization or knee arthroscopy. Due to extensive heterogeneity of included patients, weak methodology and limited generalizability of some studies

(underpowered for symptomatic VTE[1, 2, 20, 22, 23, 44, 45, 51, 54, 64, 65], high rates of loss to follow-up[20, 23, 64], inclusion of high-risk patients only[20, 23, 65] and many post-randomization exclusions[1]), there is no clear evidence that thromboprophylaxis is effective for symptomatic VTE prevention. For instance, the American college of chest physicians guideline from 2012 (ACCP) suggests no prophylaxis rather than pharmacologic thromboprophylaxis in patients with isolated lower-leg injuries requiring leg immobilization or following knee arthroscopy.[8] Other guidelines such as the National Clinical Guideline Centre (UK) allows treatment of high-risk patients based on an individual approach by evaluating the risks and benefits based on clinical discussion with the patient.[9].

Recent evidence on the effectiveness of thromboprophylaxis

Thus far, in all trials that involved knee arthroscopy patients, LMWH was used as the preferred drug for thromboprophylaxis. In 2016, Camporese and colleagues performed an exploratory placebo controlled clinical trial aiming to evaluate the efficacy and safety of rivaroxaban (10 mg once daily) for VTE prevention in patients following knee arthroscopy.[12]. 122 patients were assigned to rivaroxaban and 119 to placebo, all patients were followed for 3-months. From this trial it was concluded that VTE could be prevented with rivaroxaban (absolute risk reduction of 5.3% [95 %CI −11.4 to −0.8]). However, this conclusion can be questioned as the classification of outcome events was not optimal, and furthermore, the trial was not powered to determine the balance between treatment benefits and risks.[68] Moreover, although it was shown that rivaroxaban had a protective effect on the composite endpoint of all-cause mortality, symptomatic VTE, and asymptomatic proximal DVT, this conclusion was mainly driven by the effect on asymptomatic proximal DVT.

Another recently published trial by Bruntink and colleagues (2017) in lower-leg cast patients, aimed to study the effect of LMWH or fondaparinux versus no therapy on the development of asymptomatic VTE.[11] The authors showed that LMWH significantly reduced the risk of a thromboembolic event, and therefore it was suggested to prescribe thromboprophylaxis in all patients. However, we found it difficult to translate these results to clinical practice. Of all 467 randomized patients only 278 (60%) were included in the analysis, likely resulting in a significant bias. Besides, the Protect trial only studied the occurrence of asymptomatic DVT which certainly does not reflect the true effect of thromboprophylaxis on symptomatic VTE reduction.

In 2017, we published two parallel, pragmatic, multicentre, randomized, controlled, open-label trials with blinded outcome evaluation: the POT-KAST trial, which included patients undergoing knee arthroscopy, and the POT-CAST trial, which included patients treated with casting of the lower-leg.[10] In these trials, in which 1543 (POT-KAST) and

1451 (POT-CAST) patients were included, we compared the incidence of symptomatic VTE within 3-months after the procedure, and no screening for asymptomatic VTE was performed. In both trials, comparing a prophylactic dose of a LMWH with no treatment, thromboprophylaxis was not effective for the prevention of symptomatic VTE (absolute risk difference in POT-KAST, 0.3 percentage points, 95% CI, −0.6 to 1.2 and absolute risk difference in POT-CAST −0.4 percentage points, 95% CI, −1.8 to 1.0). Overall, in the knee arthroscopy trial, only 0.6% of patients developed a symptomatic VTE versus 1.6% in the lower-leg cast trial. Highly similar incidences for symptomatic VTE are found in the current meta-analysis in non-treated patients, i.e., for lower-leg cast 2.0% (95%CI 1.3 to 2.7) and knee-arthroscopy 0.6%, (95%CI 0.4 to 0.8) (*Figure 2 and Figure 4*), indicating high generalizability to clinical practice with regards to the risk population (since a similar incidence was found).

We believe a risk-benefit analysis cannot be made based on all previous trials that studied asymptomatic DVT as primary outcomes, not even if combined in a meta-analysis. In 2014, Chan and colleagues performed a large systematic review of high-quality VTE prevention trials (19 in orthopaedic patients, 5 in general surgery patients and 2 in medical patients) to examine the consistency of asymptomatic DVT to symptomatic VTE ratios within trials.[38] They found that the overall median rate for asymptomatic DVT versus symptomatic VTE was 14.5 with an extreme wide range from 2.75 to 103.86. Notably, there was poor agreement between the efficacy of thromboprophylaxis on asymptomatic DVT against symptomatic VTE. This implies that the effect of thromboprophylaxis (relative risk) on asymptomatic DVT is not consistent with the relative risk for symptomatic VTE. Consequently, decisions on the efficacy of thromboprophylaxis can only be based on trials powered for symptomatic endpoints. This viewpoint is also supported by the authors of the 9th edition of the ACCP guidelines on thromboprophylaxis.[8]

Since most guidelines and reviews (including meta-analyses on the effectiveness of thromboprophylaxis) have been performed using data which have been published up to 2016, an update is highly needed. Therefore, we summarized all data till date by performing a meta-analysis of all the abovementioned trials regardless of the methodological shortcomings. The results of these analyses will be discussed in the next section.

Updated effectiveness of thromboprophylaxis following lower-leg cast immobilization

In lower-leg cast patients, the effect of thromboprophylaxis on both asymptomatic DVT and symptomatic VTE was relatively similar. For symptomatic VTE, thromboprophylaxis reduced VTE risk: RR 0.31 (95%CI 0.13 – 0.73) (*Figure 5*). However, results from our POT-CAST trial completely opposed findings from 5 other trials. This might be explained

by the fact that identification of symptomatic events in those five trials was not optimal (i.e. not a true representation of an actual symptomatic VTE). For example, in one large trial, patients were asked about signs and symptoms of VTE before ultrasonography. One positive sign or symptom combined with a thrombus found during ultrasonography resulted in the classification of a symptomatic event. This method most likely does not represent the pattern of signs and symptoms that is present when patients seek medical advice during follow-up themselves, i.e. the truly symptomatic events.[68] This is illustrated by the high pooled incidence of symptomatic VTE in the untreated arms of 3.6% (25/703) in those 5 trials; i.e. more than of almost double as compared with the incidence in the POT-CAST trial (1.4%) or with the pooled incidence of symptomatic VTE estimated by our meta-analysis (2.0%), respectively. Another possibility is that results were overestimated due to some methodological weaknesses, for example, high rates of loss-to-follow up.[21] Furthermore, inclusion of high risk patients only (e.g. surgical patients only[37] or minimal cast duration of 5 weeks[20], could also have led to the protective effect of thromboprophylaxis on symptomatic VTE. In a recent Cochrane review on this topic a similar RR was described of (0.40, 95%CI 0.21 – 0.76) (note a slightly different RR was found compared with our own meta-analysis as this Cochrane review did not include a trial by Bruntink et al, 2017 [11]). Notably, there was no efficacy on the prevention of PE (RR 0.50, 95%CI 0.17 – 1.47), suggesting no effect on objectively confirmed symptomatic events. Although this result may be explained by a lack of power or heterogeneity of results.

In addition, a funnel plot of the RCTs shows a clear risk of publication bias towards effectiveness of thromboprophylaxis for VTE prevention (*Figure 6, left panel)*. No small trials with a negative effect (i.e. no effect) have been published while many small trials with a positive (i.e. protective effect) have. This is also true, although to a lesser extent, in RCTs in patients who underwent knee arthroscopy (*Figure 6, right panel*). Therefore, altogether, thus concerning the large difference between the efficacy on asymptomatic vs symptomatic VTE, issues regarding the classification of symptomatic events, publication bias towards efficacy, the high number needed to treat (250 based on POT-CAST) and the discomfort of daily injections and high costs, in our opinion there is no indication to provide thromboprophylaxis in all patients with lower-leg cast. However, as still about 2.0% of lower-leg cast patients develop symptomatic VTE, new preventive strategies are necessary to lower complication rates. Targeting high-risk populations could be such a preventive strategy. In this case, only high-risk patients are to be exposed to anticoagulants. In parallel, the optimal dosage and type of anticoagulants has to be determined. For example, a randomized trial that investigated the effectiveness of Fondaparinux 2.5mg once daily versus a LMWH 2850IE once daily in patients with lower-leg cast immobilization showed that Fondaparinux was much more effective than LMWH for VTE prevention.[70]

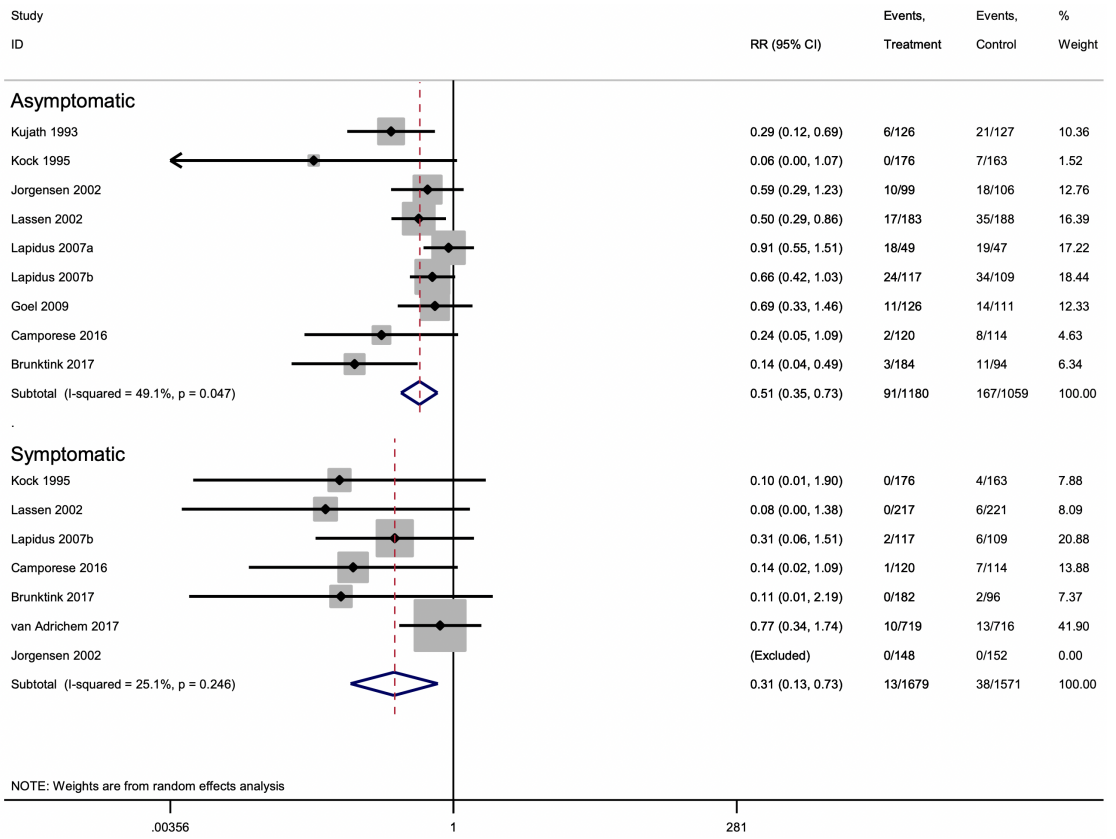

Figure 5: Effectiveness of thromboprophylaxis following lower-leg cast immobilization.
RR denotes Relative Risk. References: Kujath[1], Kock[2], Jorgensen[64], Lassen[20], Lapidus[22, 23], Goel[69], Caaporese[12], Bruntink[11], van Adrichem[10].

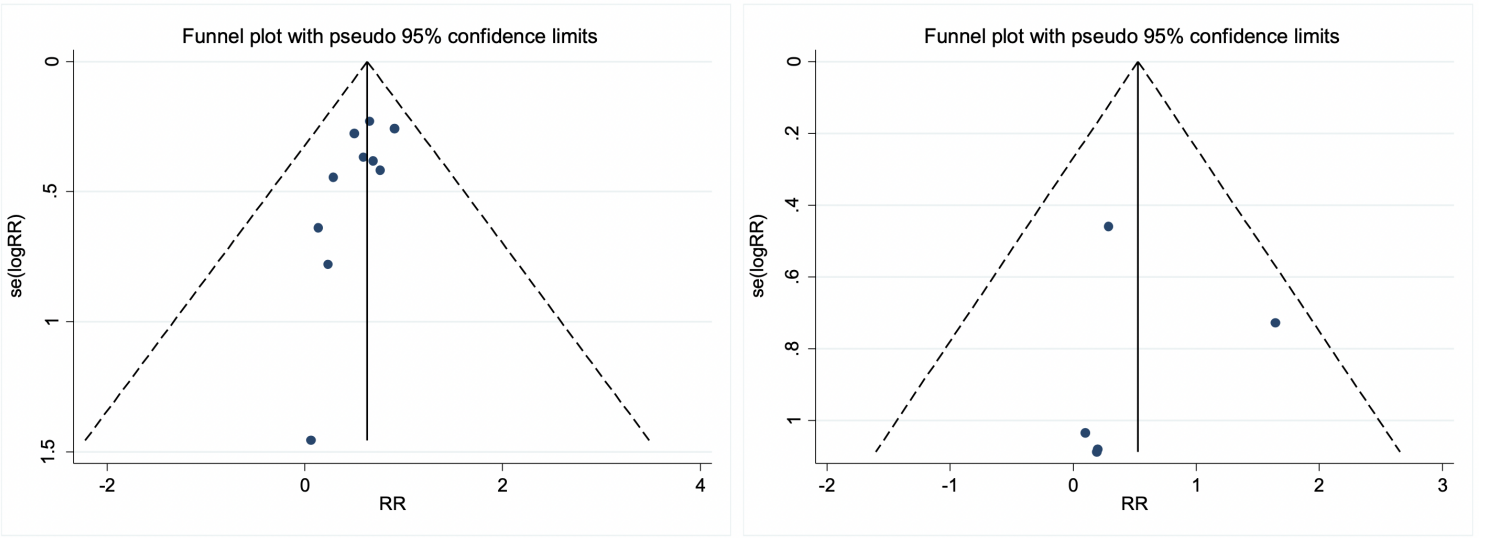

Figure 6: Funnel plot showing potential publication bias.
Funnel plot based on a meta-analysis of randomized controlled trials in patients with cast immobilization (left panel) and knee arthroscopy (right panel), note that for these analyses, symptomatic and asymptomatic endpoints are combined.

Updated effectiveness of thromboprophylaxis following knee arthroscopy

For knee arthroscopy, in light of all the previously discussed evidence, there is no clear benefit of thromboprophylaxis on the prevention of symptomatic VTE (RR 0.65, 95%CI 0.23-1.81), while conflictingly, this seems to prevent asymptomatic DVT (RR 0.23, 95%CI 0.11-0.47) (*Figure 7*). These results nicely demonstrate the poor agreement between the efficacy of thromboprophylaxis on symptomatic versus asymptomatic VTE as described by Chan and colleagues.[38] The neutral effect of thromboprophylaxis is mainly driven by two large trials, the KANT trial[54] and the POT-KAST trial[10] with contradictory findings. In our view, this could partially be explained by differences in inclusion criteria between trials. In both the KANT and POT-KAST trial, patients with a previous VTE were excluded. However, whereas the POT-KAST only included patients over 18 years, scheduled for meniscectomy, removal or loose bodies or diagnostic arthroscopies, the KANT trial also included patients who underwent anterior cruciate ligament reconstruction (39% of all patients in the control and 7-days LMWH study arm combined). Furthermore, in the KANT trial, patients were asked for signs and symptoms of VTE. Patients who reported to have 1 or more symptoms were considered symptomatic. In our view this method most likely does not represent the situation that is present when patients seek medical advice during follow-up themselves, i. e. the truly symptomatic events. The severity of these symptomatic events is therefore questionable and it is not known how many of these events would have spontaneously dissolved or progressed to real symptomatic cases.[68]

As a result of these different criteria and classification methods of symptomatic disease, the incidence of VTE differs considerably between trials; 0.6% (8/1450) in POT-KAST versus 1.4% (18/1317) in KANT. These findings might imply that high-risk patients, such as those undergoing ligament reconstruction, might actually benefit from treatment while low-risk patients can be safely withheld from thromboprophylaxis. Yet, in order to do so, high risk populations first need to be identified as such.

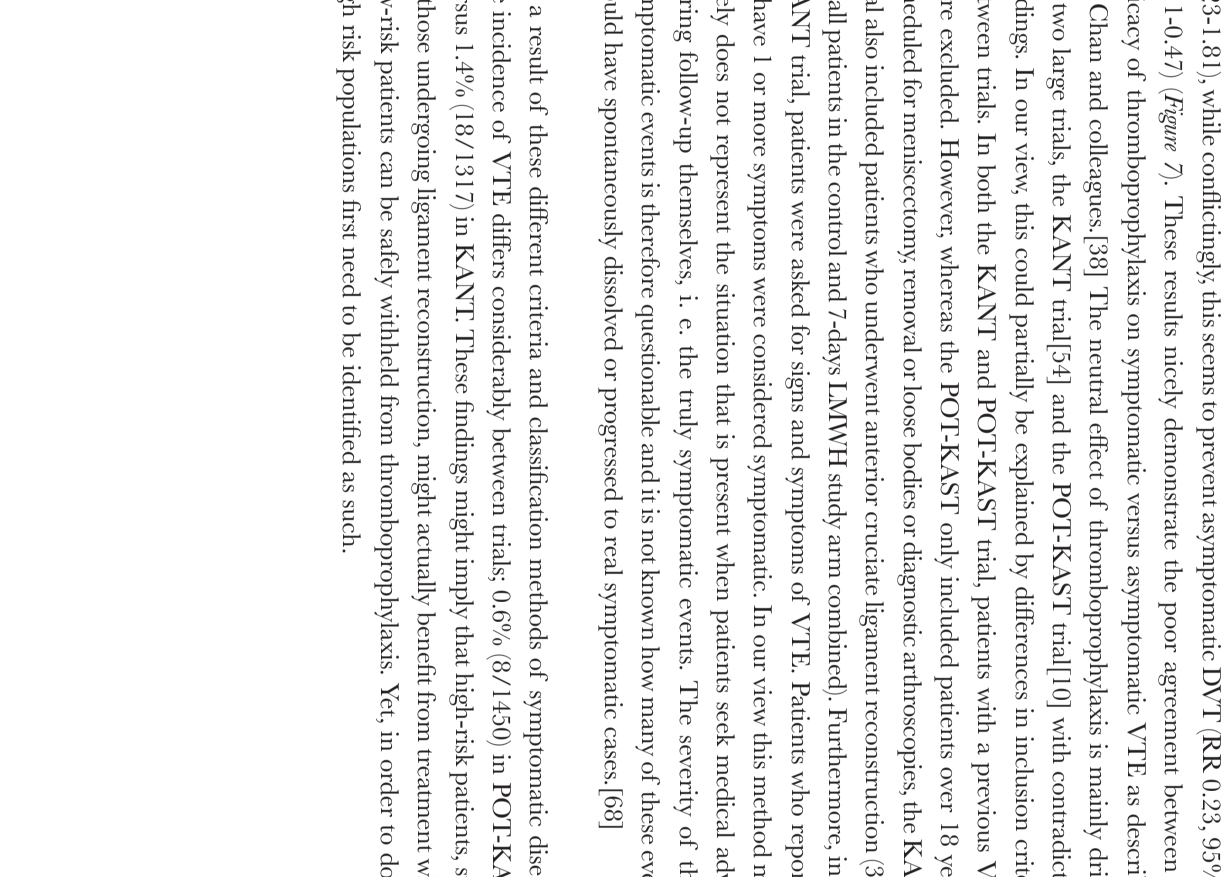

Figure 7: Effectiveness of thromboprophylaxis following knee arthroscopy.
RR denotes Relative Risk. References: Roth[45], Wirth[44], Michot[51], Camporese[54], Canata[65], van Adrichem[10].

PREDICTION

High quality epidemiological research performed over the past decades resulted in a long list of well-known risk factors for VTE.[71] Acquired risk factors such as increasing age, malignancy, obesity and comorbidity play a key role in the aetiology of VTE. Additionally, genetic factors such as Factor V Leiden mutation and blood group Non-O have contributed to our understanding in the development of VTE. Surgery, trauma and immobilization are recognized to be associated with the highest risk for VTE. Within this group of patients it is challenging to find those at the highest risk for VTE. In this chapter we aimed to give an overview of risk factors and risk assessment models (RAMs) that have been described to increase VTE risk within lower-leg cast or knee arthroscopy patients.

Risk factors for VTE in lower-leg cast patients

In cast patients, Kujath and colleagues showed already in 1993 that patients who developed thrombosis had 2.0 risk factors on average (mostly obesity and varicose veins) as compared with 1.2 risk factors in patients who did not develop thrombosis. [1] Moreover, patients who still developed thrombosis under treatment had an average of 2.7 risk factors. Healy and colleagues described that out of 13/208 patients who developed DVT following Achilles tendon ruptures, about half of all VTE patients had additional risk factors for VTE such as a positive family history, BMI > 30 kg/m2, significant medical comorbidity and planned long-distance travel. [34] A large observational study that enrolled 1200 patients stressed out that despite their large sample size, no risk factors could be identified because of the low incidence of VTE.[31] To overcome this problem, van Adrichem published results from a large population base case-control study, in which 143 cases with VTE and 23 controls, both with cast immobilization of the lower-extremity, were identified.[39] The study design and number of patients with a cast and VTE allowed the authors to study risk factors for VTE within lower-leg cast patients. Traumatic injuries were associated with higher thrombosis risks than non-traumatic injuries. Additionally, oral contraceptives (OR 18.2), obesity (OR 17.2), factor V Leiden mutation (OR 11.0), non-O blood group (20.9) showed to increase VTE risk (ORs for joint effect of cast + risk factor versus non-cast + no risk factor). Presence of multiple risk factors increased VTE risk in a dose response fashion. Several other risk factors were identified in multiple studies that we classified according to environmental, cast specific and injury specific factors (*Table 1*). For example, non-weight bearing cast was associated with a higher VTE risk in three studies[2, 22, 72] and VTE developed more often following fractures than after soft tissue injury.[1, 20]

Risk factors for VTE in knee arthroscopy patients

Despite the low VTE incidence (and thus low power for risk factor analyses) several studies did report risk factors for VTE (*Table 2*). Maletis and colleagues included 20 770 patients who underwent elective knee arthroscopy. Patients aged 50-years or older had

a 1.5-fold risk for VTE as compared with patients <50 years, furthermore, use of oral contraceptives doubled VTE risk.[5] Similarly, Gaskill and colleagues, showed that age (>35 years versus <35 years) increased VTE risk (OR 1.99)[4] Other risk factors could not be accurately identified. In 2015, van Adrichem performed a case-control study in which oral contraceptives, obesity, Factor V Leiden, and Non-O blood type were identified as risk factors for VTE within patients who underwent knee arthroscopic surgery.[75] Again, a dose-response relationship existed between the number of risk factors and the occurrence of VTE, a finding already described by Delis and colleagues in 2001 (though on asymptomatic DVT).[50] Four studies showed that for example, an increased operation time, the use of a thigh tourniquet or more invasive procedures (such as an ACL or PCL reconstruction) also increased VTE risk besides the presence of more classical VTE risk factors.

Table 1: Overview of VTE risk factors in lower-leg cast patients.

VTE risk factors in lower-leg cast patients	**Study**
Environmental	
Multiple risk factors	Kujath[1], van Adrichem[39]
Age >40 years*	Knudson[73]
Age >50 years	Riou[72]
Venous injury*	Knudson[73]
Charlson comorbidity index ≥1	Jameson[74]
Oral contraceptives	van Adrichem[39]
Obesity	van Adrichem[39]
Factor V Leiden mutation	van Adrichem[39]
Non-O blood group	van Adrichem[39]
Cast specific	
Non-weight baring cast	Kock[2], Lapidus 2007a[22], Riou[72]
Rigid immobilization	Lapidus 2007b[23], Riou[72]
Injury specific	
Fracture versus soft tissue injury	Kujath[1], Lassen 2002[20]
Major operation*	Knudson[73]
Severe injury	Riou[72]
Traumatic injury	van Adrichem[39]

*in 1602 trauma patients including lower-leg cast

Table 2: Overview of VTE risk factors in knee arthroscopy patients.

VTE risk factors in knee arthroscopy patients	Study
Environmental factors	
Increasing Age	Stringer[42], Hetsroni[76], Mauck[77], Maletis[5], Ye[56], Delis[50]
Female	Hetsroni[76], Ye[56]
Obesity (BMI>30)	Delis[50]
Varicose veins	Schippinger[78]
> 2 classical VTE risk factors	Delis[50], Krych[79]
Previous VTE	Delis[50], Krych[79]
Oral contraceptives	Delis[50], Maletis[5]
Hospitalization within 3 months before arthroscopy	Mauck[77]
Malignancy	Krych[79]
Surgery at high altitude	Cancienne[80]
Arthroscopy specific	
Operation time	Stringer[42], Jaureguito[49]
Tourniquet use	Demers 1998, Jaureguito[49]
Invasive procedures such as ACL or PCL reconstruction	Jaureguito[49], Gaskill[4]

Risk assessment models for VTE

As there is no compelling evidence that thromboprophylaxis prevents VTE in all lower-leg cast and knee arthroscopy patients, new preventive strategies have to be developed in order to prevent VTE. An appealing approach would be to use information on individual risk factors in order to fit these into a prediction model for VTE , as is done in many patients at risk for VTE, such as hospitalized medical or surgical patients. For example, surgical patients are at risk for VTE and the Caprini score has been developed to stratify these patients in a low, intermediate or high risk group. In this score, many risk factors are combined to achieve an accurate model which could be used in clinical practice for thromboprophylaxis decisions. Likewise, for medical patients, RAMs as the Geneva risk score[81], Padua prediction score[82] and Improve-7 score[83] aim to stratify patients in low or high risk groups for VTE.

For lower-leg cast patients, few attempts have been performed to develop a RAM. However, perhaps because of the high need for such a model, two recent papers were published that summarized the current evidence on RAMs for lower-leg cast patients.[84, 85] One

model, derived from the GEMNET (UK) guideline (for the use of thromboprophylaxis in ambulatory trauma patients requiring temporary limb immobilisation), suggests patients should receive prophylactic therapy if they have one or more permanent risk factor for VTE such as hormone therapy, personal history of VTE, or recent hospital admission. [86] (*Table 3*) Similar risk factors are described in the NICE guideline[9], though, in both guidelines, risk scores were not specifically developed (or validated) for lower-leg cast related VTE. Moreover, both guidelines only give a list of risk factors and if patients have one or more, thromboprophylaxis is indicated. So no actual individual risks can be calculated and no differentiation is made (regarding thrombosis risk) within those patients with one or more additional risk factors. In 2015, using a large population-based case-control study, we derived and validated a RAM, named the L-TRiP(cast) score (Leiden-Thrombosis Risk Prediction), developed to identify lower-leg cast patients at high risk for VTE.[87] The L-TRiP(cast) score consists of classical risk factors for VTE, but also includes the type of cast (degree of immobilization) which greatly improves discriminatory capabilities. Furthermore, it was shown that biomarkers (both genetic and coagulation factors) contributed to better model performance, however, these were not included in the model to increase clinical usefulness.

For knee arthroscopy, similarly, general RAMs for surgical patients (such as a list of risk factors as provided by the NICE guideline) can be used to identify high risk patients. As in patients with lower-leg cast, our group developed a RAM for VTE risk in knee-arthroscopy patients, named the L-TRiP(ascopy) score. Notably, the best model performance was achieved by adding factor VIII activity next to 8 environmental risk factors. However, again, to improve clinical usefulness and to reduce costs FVIII was not included in the final model.

For the L-TRiP(cast) score, thromboprophylaxis is suggested if cast immobilization patients score 9 points or more corresponding to a test sensitivity of 80.0%, specificity of 60.8% and false negative rate of 0.8%. For knee arthroscopy patients, it is proposed to provide thromboprophylaxis in case patients score 8 point or more (sensitivity 82.6%, specificity 45.2% and 0.2% false negatives). However, as both risk scores (L-TRiP(cast and scopy) were not validated in a prospective study (only in other case-control studies), there is no defined cut-off that corresponds to an absolute risk threshold on which thromboprophylaxis decisions can be made. Therefore, validation in a large cohort, and perhaps model refinement to ascertain the role of biomarker testing, is highly needed.

Table 3: Overview of risk assessment models for VTE in lower-leg cast and knee arthroscopy patients.

GEMNET guideline	NICE guideline		L-TRiP(cast) score	Risk points	L-TRiP(ascopy) score	Risk points
Age >60	Age over 60 years		Age ≥ 35 and < 55 y	*2*	Age ≥ 35 and < 55 y	*1*
			Age ≥ 55 y	*3*	Age ≥ 55 y	*2*
			Male sex	*1*	Male sex	*1*
Obesity (BMI >30)	Obesity (BMI over 30 kg/m2)		BMI ≥ 25 and < 35 kg/m2	*1*		
			BMI ≥ 35 kg/m2	*2*		
Active cancer	Active cancer or cancer treatment		Cancer within the past 5 y	*3*		
Current hormone therapy (contraceptive, hormone replacement, tamoxifen)	Use of hormone replacement therapy or oestrogen-containing contraceptive therapy		Current use of oral contraceptives	*4*	Current use of oral contraceptives	*3*
Pregnant or immediately post partum			Pregnancy or puerperium	*3*		
Extensive varicosities	Varicose veins with phlebitis		Superficial vein thrombosis	*3*	Varicose veins	*1*
Any serious medical comorbidity*	One or more significant medical comorbidities**		Comorbidity***	*1*		*1*
			Pneumonia	*3*	Congestive heart failure	*1*
Personal or first-degree relative VTE history	Personal history or a first degree relative with a history of VTE		Family history of VTE (first-degree relative)	*2*	Family history of VTE -1 family member -≥2 family members	*2* *3*
Known thrombophilia	Known thrombophilias				Factor VIII activity	
					<100	*0*
					>=100 and 124	*1*
					>124	*3*
Any recent hospital admission/major surgery			Hospital admission within the past 3 mo	*2*		
			Surgery within the past 3 mo	*2*		
	Critical care admission					
			Bedridden within the past 3 mo	*2*	Bedridden within the past 3 mo	*2*
Active smoker						
	Dehydration					
			Plaster cast: complete leg	*5*	Knee arthroscopy	*4*
			Plaster cast: circular knee cast (ankle free)	*2*	Ligament reconstruction	*6*
			Plaster cast: foot	*2*		
			Plaster cast: lower-leg	*4*		
Provide thromboprophylaxis when one or more risk factors are present	*Provide thromboprophylaxis when one or more risk factors are present*		*Calculate L-TRiP(cast) score, provide thromboprophylaxis if ≥ 9†*		*Calculate L-TRiP(ascopy) score, provide thromboprophylaxis if ≥ 8††*	

* Including cardiac failure/COPD/chronic renal failure or inflammatory bowel disease
** Including heart disease, metabolic, endocrine or respiratory pathologies, acute infectious diseases or inflammatory conditions
*** Including rheumatoid arthritis, chronic kidney disease, COPD, multiple sclerosis
† Test specifics: sensitivity 80.0%, specificity 60.8% and 0.8% false negatives
†† Test specifics: sensitivity 82.6%, specificity 45.2% and 0.2% false negatives

CONCLUSION AND FUTURE PERSPECTIVES

Symptomatic VTE is a common complication following lower-leg cast immobilization or arthroscopic knee surgery. In our meta-analyses on the incidence of VTE we found an incidence of 2.0% (95%CI 1.3 to 2.7) and 0.6%, (95%CI 0.4 to 0.8), for lower-leg cast and knee-arthroscopy patients, respectively

Unquestionably, the burden of VTE following lower-leg cast immobilization or arthroscopic knee surgery is substantial. In the past decades, we[10] and others[1, 2, 11, 12, 20, 22, 23, 44, 45, 51, 54, 64, 65, 69], have tried to reduce VTE burden using a population-based approach, namely, providing all patients with thromboprophylaxis therapy. Still, despite all research there is no convincing evidence that thromboprophylaxis reduces symptomatic VTE in the total patient group. As VTE nevertheless still occurs, new treatment methods have to be explored. Identifying and treating those patients with a high risk more intensively might be such a strategy, for which reason we suggest to move forward with a more individualized approach and adjust thromboprophylaxis therapy accordingly.

A targeted approach, identifying high-risk patients who can be treated possibly with a higher dose or longer duration of therapy, might be the next step to prevent VTE. The L-TRiP(cast) and L-TRiP(ascopy) risk scores could be used for this purpose. However, to make sure the benefits of anticoagulant treatment outweigh the risks, further studies are needed to determine the optimal dose, duration and timing of therapy.

Another approach would be to concentrate on the thrombosis mechanism. While lower-leg cast and knee arthroscopy patients have a clear VTE risk, the underlying mechanisms for this increased thrombotic tendency, and eventually, development of VTE in these patients, are not well known. For example, knowledge on a patients' coagulation profile following a fracture could contribute to the development of new preventive or treatment strategies. In fact, it is actually unknown whether the fracture itself, the subsequent cast immobilization or both, significantly increase VTE risk. As there are no studies which explore the effect of fractures or the severity of lower-leg injury on coagulation factors, this could be a topic for further investigations. Likewise, in patients undergoing knee arthroscopy, little data are available on the effect of such surgery on a patients' coagulation profile. Some studies suggest that a thigh tourniquet contributes significantly to thrombus formation.[88, 89] In our view, more extensive data on this matter could potentially be valuable for clinical management. For example, it is known that for each 10IU/dl increase of factor VIII concentration, an individual's thrombosis risk increases approximately 10%. Accordingly, we could speculate that

those patients who have a strong increase in coagulation factors (after lower-leg cast or knee arthroscopy) also have a higher risk for developing VTE. Future research has to point out whether determination of individual biomarkers is prompted to individualize prophylactic strategies. Additionally, new studies, preferably RCTs powered for symptomatic events, are necessary to study new thromboprophylactic strategies.

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