Trauma and thrombosis in the DOAC era: promise and peril of direct oral anticoagulant use in injured patients

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Chapter 1. General introduction

This dissertation represents my doctoral journey in content and in form. The topics covered start off broad and gradually narrow in focus. The introduction provides a necessary understanding for the specific subfield of research where I position the research that makes up my thesis. The main body consists of three parts containing the six published studies performed as part of the PhD-journey. In the Discussion chapter, interpretations and clinical implications will be provided for the studied questions, as well as suggestions for further research. It concludes with a Supplement of additional considerations that will steer my post-doctoral career.

Blood and Coagulation

Blood fascinates. It carries strong symbolic associations to life and death, ancestry and nobility, trust, generosity, and most of all to health.(1) Biomedical training teaches the many different functions blood plays in the body. Some were already known to Galen almost 1900 years ago, many others were more recently discovered.(2) Central to this thesis is blood's vital function of coagulation. This constant balancing act of prothrombotic and antithrombotic factors results in prothrombotic and antithrombotic states. These factors include soluble components present in blood, but coagulation is also dependent on the surrounding physical environment. Fluid dynamics (turbulence, venous stasis), and the composition and integrity of vessel walls are implicated in clot formation.

Normal coagulation occurs after vascular endothelium becomes damaged or altered, for instance after trauma, in malignancy or in atherosclerosis. When it comes to platelets, adhesion takes place; circulating platelets are recruited to the site by collagen-bound von Willebrand Factor (vWF) and glycoprotein Ib-V-IX complexes.(3) Second, platelets undergo morphological changes, activate prothrombotic receptors, and degranulate which releases ADP, thromboxane A2 and thrombin. The release of these factors aids in recruiting more

platelets to the damaged site.(4) In the third step, platelets aggregate, forming stable bonds with other activated platelets and creating a hemostatic plug, concluding primary hemostasis.

Concurrently, the coagulation cascade is activated resulting in an elaborate chain reaction of protease activity. This cascade is categorized into three pathways: an intrinsic pathway, which is activated when factor XII makes contact with negatively charged surfaces of polyanions, an extrinsic pathway, initiated by release of tissue factor (factor VIIa) from damaged vessel walls, from circulating microvesicles or on platelet surface, and a final common pathway, which commences with factor X activation by either the intrinsic or extrinsic pathway (**Figure 1)**.(5) The last step in the final common pathway is the enzymatic cleavage of fibrinogen (factor I) by thrombin (factor IIa) to form fibrin (factor Ia). Subsequently, fibrin molecules polymerize, forming long and stable fibers to stabilize the hemostatic platelet plug (secondary hemostasis).

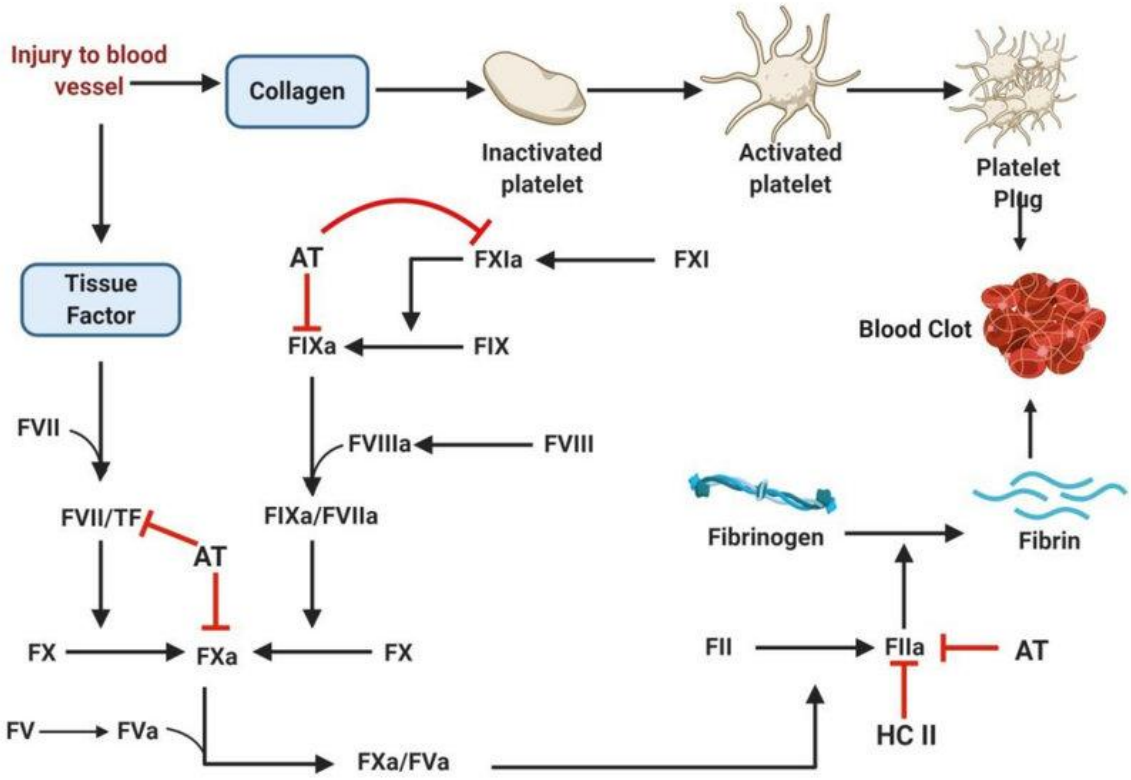

Figure 1. Coagulation cascade depicting blood clot formation. Intrinsic pathway illustrated here starting with FXI. Extrinsic (Tissue Factor) pathway starting with injury to blood vessel. Procoagulant and anticoagulant pathways are indicated in black and red, respectively. AT: antithrombin; HC II: Heparin cofactor II; TF: Tissue factor. (Figure courtesy of biorender.com)

Thrombosis

In 2019, before COVID-19, health issues caused by unwelcome formation of blood clots (i.e. thrombosis, responsible for ischemic heart disease, ischemic stroke, venous thromboembolism, among others) were responsible for an estimated 1 in 4 deaths, totaling ca. 15 of 57 million deaths annually, the highest of any cause.(6) In addition, over 3 million annual deaths were attributable to hemorrhagic causes of death, where blood fails to clot adequately, such as post-partum hemorrhage or hemorrhagic stroke. At the inception of the COVID-19 pandemic, which was responsible for 1 in 9 deaths in 2021, coagulation disorders were identified as major contributors to the disease burden and mortality.(7,8) Taken together, it is clear that inadequate coagulation poses an intimidating health burden.

Antithrombotics

Improved understanding of coagulation have led to giant strides towards effective treatment and prevention of thrombotic and hemorrhagic diseases. It is impossible to imagine modern medicine without antithrombotics, the umbrella term for *antiplatelet* and *anticoagulant* therapy. Antiplatelet agents target platelet adhesion, activation and aggregation, i.e. the way in which platelets interact with the vessel wall, other platelets, and factors altering the functionality of platelets. *Antiplatelets* are predominantly used to prevent arterial thrombosis following rupture or erosion of atherosclerosis. This thesis will focus on *anticoagulant* medication (Figure 2), which specifically targets the presence and/or activity of the various coagulation factors in the coagulation cascade. Anticoagulants are most

commonly used to treat and prevent deep venous thrombosis (DVT) and pulmonary embolism (PE), and to ischemic stroke in patients with cardiac arrhythmia, most commonly non-valvular atrial fibrillation (NVAF).

When thinking of the mechanisms of antithrombotic therapy, it is important to note that there is not *one* specific starting signal leading to coagulation (or perhaps it is not yet discovered). Rather, one should consider the multitude of interactions between virtually all components of the coagulation system. Moreover, one must differentiate between the various contexts in which coagulation occurs, be it arterial versus venous thrombosis, sterile or septic, in healthy or atherosclerotic vessels, locally or diffusely, et cetera. Different steps in the process of hemostasis may commence simultaneously, and combinations of the above occur.

Anticoagulant agents have a long history. Many herbal remedies are known and used in traditional/complementary medicine(9). Pharmaceutical development of anticoagulants starts formally with heparin, discovered during the first World War and commercialized in the Interbellum.(10) The early 1940's and 1950's saw the introduction of vitamin K antagonists (VKAs), which at the time were principally studied as a rodenticide.(11) For over half a century, heparin and VKAs were the only commercially available anticoagulant drugs to treat and prevent venous and arterial thrombosis. Over this period VKAs have become the mainstay of chronic oral anticoagulant therapy for patients with NVAF, the most common indication for chronic anticoagulation.

Heparin and low molecular weight heparin (LMWH) target factors IIa and Xa, the activated enzymes instigating fibrin generation in the final common pathway. Vitamin K antagonists (VKAs) antagonize the production of vitamin K dependent factors II, VII, IX and X, affecting all three pathways of the coagulation cascade. Since the discovery of these drugs, tremendous progress has been made towards optimalization of anticoagulant

therapy. The risk of ischemic stroke for NVAF patients was reduced by two thirds, and the case-mortality rate of DVT and PE decreased from circa 30% to 5%.(12–15) However, the need for routine monitoring, the number of drug-drug interactions, unpredictability of pharmacodynamics and -kinetics, and the risk of hemorrhagic side effects meant that the search for alternative anticoagulant therapy never ceased.

Direct Oral Anticoagulants

It was not until 2008, however, that a new class of anticoagulant drugs was discovered: The Direct Oral AntiCoagulants (DOAC). The category covers drugs with two pharmacological mechanisms of action; direct thrombin inhibitors (DTI, targeting factor IIa) and factor Xa (FXa) inhibitors. Both DTIs and FXa inhibitors halt the common pathway, preventing fibrinogenesis, subsequently preventing cross-linking and stabilizing of erythrocytes in the blood clot.

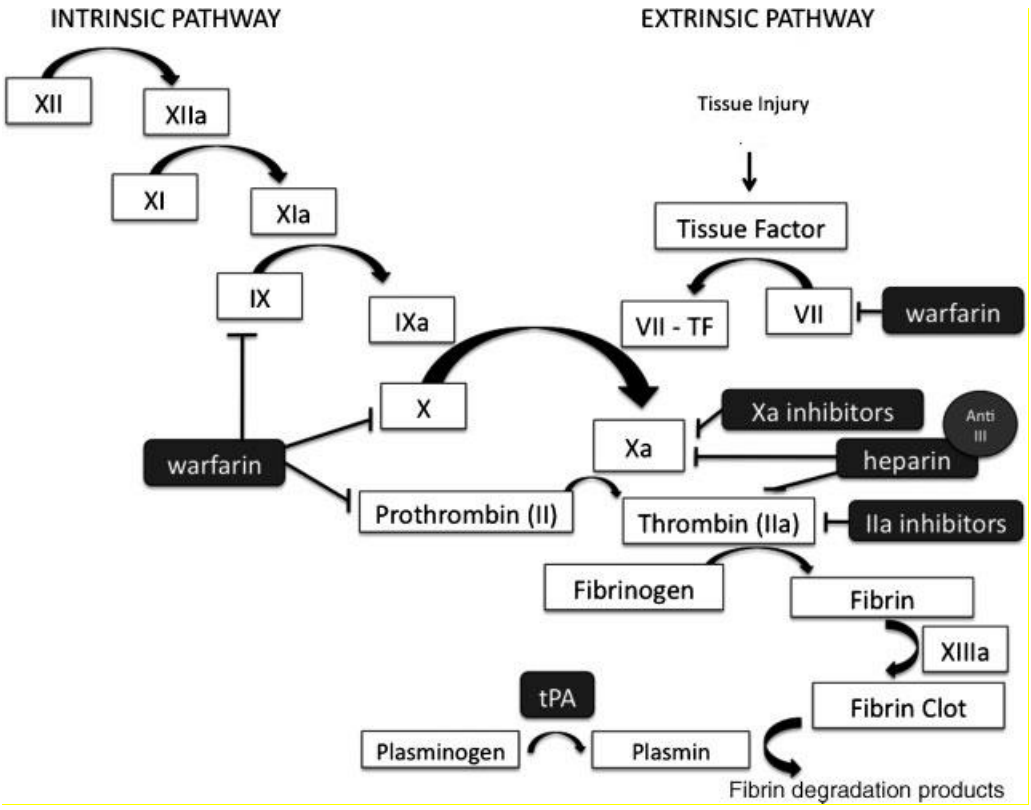

Figure 2. Coagulation cascade and anticoagulant agents and their target molecules

Multiple randomized controlled trials have since demonstrated superior effectiveness of DOACs over VKAs and low molecular weight heparin (LMWH). These trials included patients with indications such as stroke prevention in NVAF, thromboprophylaxis after hip and knee arthroplasty, and treatment of acute DVT and PE of all causes.(16–23) Moreover, these studies found DOACs to be associated with equal or lower rates of spontaneous bleeding complications. DOACs may offer more advantages still, such as more predictable pharmacodynamics and pharmacokinetics compared to VKAs, which obviates routine plasma concentration monitoring, and a favorable oral administration route compared to subcutaneous injections for LMWH.(24)

Considering these advantages, widespread use of DOACs was to be expected, and surely followed.(25–28) The introduction of a new class of anticoagulants unavoidably resulted in new clinical problems and dilemmas, such as drug-drug interactions and dosing decisions. Within the field of trauma surgery, anticoagulants pose more problems still, as aberrant coagulation is the rule and not the exception after injury.

The Influence of Physical Trauma

Injury profoundly changes the balance of pro- and antithrombotic factors. The resultant state is called trauma-induced coagulopathy (TIC).(29) Trauma patients may present with distinct hypo- and hypercoagulable phenotypes, or with mixed presentations. The natural progression of TIC can be divided into early and late stages

Directly post-trauma, the injury induces several processes to occur concurrently with negative impact on the blood’s ability to form effective clots. Various chemical factors combined impede the enzymatic reactions of the coagulation cascade, and mechanical processes prevent hemostasis. Known factors are extensive tissue injury, endothelial

dysfunction, acidosis, platelet dysfunction, coagulation factor depletion (including fibrinogen deficiency and co-factors protein C and S), dysregulated fibrinolysis, and shock. These factors may all result from trauma, depending on the extent and severity of the injury.(30) This early hypocoagulable state is associated with exsanguination, which is the most common pre-hospital cause of mortality at 44% of prehospital deaths. Exsanguination is also the number one cause of early in-hospital (<24 hours post-injury) mortality at 39% of early trauma deaths.

Prothrombotic factors gradually start to prevail after 6-24 hours. A hypercoagulable phase emerges, characterized by overactive clotting, decreased fibrinolytic activity, development of thromboemboli, and a subsequent risk of multi-organ failure.(31) In studies prospectively screening trauma patients for venous thromboembolic events, rates of up to 60% were reported.(32) Factors related to injury pattern and their treatment add further risk of thromboembolic events. Orthopedic fractures, major general surgery, spinal cord injury and associated immobilization, and major trauma have been identified as the strongest independent predictors of developing VTE.(33)

Intervention to restore coagulation is possible both during hypo- and hypercoagulable states. This thesis will focus on chemical thromboprophylaxis (CTP) and treatment of anticoagulant-associated hypocoagulable states. Optimal CTP includes appropriate patient selection, effective choice, dosing, duration and timing of administration of the pharmacologic agent. In trauma patients, the risk of thrombosis exists simultaneously with hemorrhage. Starting anticoagulant medication may exacerbate an already existing hemorrhage or re-start a prior hemorrhage. At the same time, in-hospital VTE remains the leading cause of preventable in-hospital mortality, and delaying CTP is equally undesirable.(34)

In this thesis we will study several such interventions with the overall aim of improving trauma care and reducing the burden of VTE and anticoagulant-associated bleeding in trauma patients.

Thesis Outline

In Part 1, we study whether the advantages of DOACs described before apply to trauma patients as they do to patients undergoing elective orthopedic procedures. Drug choice after trauma is a distinct matter due to TIC and frequent concomitant hemorrhaging, and deserves separate study.

To mitigate the risk of VTE, CTP guidelines for trauma patients are continually improved. Efforts focus primarily on the domains of patient selection, drug type and dosing regimen, and on timing of CTP. Since the identification of the significant risk of VTE in trauma patients, clinicians have relied on LMWH and heparin in thromboprophylaxis protocols.(35) In **Chapters 2 and 3** we studied if DOACs can safely and effectively be used in subpopulation of orthopedic trauma patients with a high risk of TE events, as measured by their effects on VTE and side effects, more specifically bleeding events. .

Safety of anticoagulant therapy remains of paramount importance. Their inhibitory action on the common pathway hinders clot formation and thereby potentially leads to prolonged bleeding. This, in turn, leads to prolonged hemodynamic instability, tissue hypoxia, more severe neurological symptoms, and more frequent and higher transfusion requirements. Moreover, clinical management of DOACs requires risk assessment tools, reversal protocols, and clear prognostication. These risks and shortcomings were reported with an urgent call to action shortly after adoption of the first DOAC, dabigatran.(36)

And, while past RCTs on chronic DOAC use studied rates of spontaneous bleeding as side effects, no studies provided robust evidence on associated risks in traumatic injury. This critical aspect could therefore not be incorporated in the regulatory approval for any of the DOACs. Just two sub-analyses of randomized control trials for chronic DOAC use mentioned consequences in trauma, and with such small sample sizes that no conclusions were drawn.

The safety of pre-injury DOAC exposure in trauma patients refers to a patient's risk of poor outcomes in the event of trauma, usually compared to patients with no anticoagulation, a historical cohort, or other anticoagulant medication. Commonly used endpoints are mortality, surgical requirement, transfusion requirement, length of stay and functional outcomes.

We aimed to both study the association between DOAC exposure and outcomes, as well as the epidemiological trends in consequences of pre-injury DOAC exposure on a national scale. This was done by studying the high-risk subpopulation of patients with traumatic intracranial hemorrhage (tICH) in both an institutional registry (**Chapter 4**) and a literature study (**Chapter 5)**.

Regardless of the relative safety of DOACs, patients presenting with DOAC-associated bleeding require optimal treatment. As the difference between drug and poison is the dose, an antidote was needed against the harmful effects of DOACs. Whereas there exists robust evidence on the survival benefit of rapidly reversing the anticoagulant effects of VKAs , it is important to note that no effective reversal strategies were approved for DTIs and FXa inhibitors at the time of their regulatory approval.(37,38) Clinicians in dire straits experimented with several options, with varying success. These included dialysis, active charcoal, blood component transfusion, as well as prothrombin complex concentrates, but none of these were officially approved.

In 2015, evidence from an open-label, non-randomized study led to the approval of idarucizumab to reverse dabigatran.(39) This monoclonal antibody is an irreversible competitive antagonist for dabigatran, and is administered as a single dose effectuating complete reversal of anti-IIa activity within 10 minutes, lasting for 24 hours.(40) In 2018, andexanet alfa was approved by the FDA to reverse the effects of factor Xa inhibitors apixaban and rivaroxaban, the two most commonly prescribed DOACs. This recombinant factor Xa is also a competitive antagonist, binding with superior affinity to anti Xa inhibitors, administered as a bolus followed by continuous infusion, effectuating 95% reversal of anti Xa activity within XYZ minutes and lasting just as long as the infusion continues. Both drugs were approved under emergency authorization owing to a dire need for a reversal agent. These approvals were based primarily on pre-clinical and non-randomized clinical data with strict selection criteria.

Prescribing data indicated that factor Xa inhibitors are to be expected more commonly in the trauma bay than thrombin inhibitors.(27) It was therefore our intention to study the effectiveness and safety of andexanet alfa in the real world setting (**Chapter 6**), and to compare the available outcome data of andexanet alfa with those of its alternative prothrombin complex concentrate (**Chapter 7**).

References

1. Garraud O, Lefrère JJ. Blood and blood-associated symbols beyond medicine and transfusion: far more complex than first appears. Blood Transfus. 2014 Jan;12(1):14–21.
2. Aird WC. Discovery of the cardiovascular system: from Galen to William Harvey. J Thromb Haemost. 2011 Jul;9 Suppl 1:118–29.
3. Savage B, Almus-Jacobs F, Ruggeri ZM. Specific synergy of multiple substrate-receptor interactions in platelet thrombus formation under flow. Cell. 1998 Sep 4;94(5):657–66.
4. Yun SH, Sim EH, Goh RY, Park JI, Han JY. Platelet Activation: The Mechanisms and Potential Biomarkers. Biomed Res Int. 2016;2016:9060143.
5. Müller I, Klocke A, Alex M, Kotzsch M, Luther T, Morgenstern E, et al. Intravascular tissue factor initiates coagulation via circulating microvesicles and platelets. FASEB J. 2003 Mar;17(3):476–8.
6. Naghavi M, Ong KL, Aali A, Ababneh HS, Abate YH, Abbafati C, et al. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990–2021: a systematic analysis for the Global Burden of Disease Study 2021. The Lancet. 2024 May 18;403(10440):2100–32.
7. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers D a. MPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res. 2020 Jul;191:145–7.
8. Malas MB, Naazie IN, Elsayed N, Mathlouthi A, Marmor R, Clary B. Thromboembolism risk of COVID-19 is high and associated with a higher risk of mortality: A systematic review and meta-analysis. eClinicalMedicine [Internet]. 2020 Dec 1 [cited 2024 Jul 23];29. Available from: https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30383-7/fulltext
9. Cordier W, Steenkamp V. Herbal remedies affecting coagulation: A review. Pharmaceutical Biology. 2012 Apr 1;50(4):443–52.
10. Wardrop D, Keeling D. The story of the discovery of heparin and warfarin. Br J Haematol. 2008 Jun;141(6):757–63.
11. Copeland CE, Six CK. A tale of two anticoagulants: warfarin and heparin. J Surg Educ. 2009;66(3):176–81.
12. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007 Jun 19;146(12):857–67.
13. Dalen JE, Alpert JS. Natural history of pulmonary embolism. Prog Cardiovasc Dis. 1975;17(4):259–70.
14. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA. 1998 Feb 11;279(6):458–62.
15. Lavie CJ. Progress in Cardiovascular Diseases Statistics 2022. Prog Cardiovasc Dis. 2022;73:94–5.
16. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011 Sep 15;365(11):981–92.
17. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883–91.
18. Lassen MR, Gent M, Kakkar AK, Eriksson BI, Homering M, Berkowitz SD, et al. The effects of rivaroxaban on the complications of surgery after total hip or knee replacement: results from the RECORD programme. J Bone Joint Surg Br. 2012 Nov;94(11):1573–8.
19. Eriksson BI, Kakkar AK, Turpie AGG, Gent M, Bandel TJ, Homering M, et al. Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement. J Bone Joint Surg Br. 2009 May;91(5):636–44.

20. Mayer A, Schuster P, Fink B. A comparison of apixaban and dabigatran etexilate for thromboprophylaxis following hip and knee replacement surgery. Arch Orthop Trauma Surg. 2017 Jun;137(6):797–803.
21. Bonarelli S, Bacchin MR, Frugiuele I, Feoli MA, Facchini F, Altimari V. Dabigatran etexilate and LMWH for the prevention of venous thromboembolism in 532 patients undergoing hip surgery. Eur Rev Med Pharmacol Sci. 2015;19(5):897–903.
22. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013 Aug 29;369(9):799–808.
23. EINSTEIN–PE Investigators, Büller HR, Prins MH, Lensin AWA, Decousus H, Jacobson BF, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012 Apr 5;366(14):1287–97.
24. Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Ther Clin Risk Manag. 2015;11:967–77.
25. Navar AM, Kolkailah AA, Overton R, Shah NP, Rousseau JF, Flaker GC, et al. Trends in Oral Anticoagulant Use Among 436 864 Patients With Atrial Fibrillation in Community Practice, 2011 to 2020. Journal of the American Heart Association. 2022 Nov 15;11(22):e026723.
26. Afzal S, Zaidi STR, Merchant HA, Babar ZUD, Hasan SS. Prescribing trends of oral anticoagulants in England over the last decade: a focus on new and old drugs and adverse events reporting. J Thromb Thrombolysis. 2021;52(2):646–53.
27. Harskamp RE, Himmelreich JCL, Wong GWM, Teichert M. Prescription patterns of direct oral anticoagulants and concomitant use of interacting medications in the Netherlands. Neth Heart J. 2021 Sep 1;29(9):451–9.
28. Guelker JE, Ilousis D, Kröger K, Santosa F, Kowall B, Stang A. Increasing use of anticoagulants in Germany and its impact on hospitalization for gastrointestinal bleeding. Thrombosis Research. 2019 Sep 1;181:135–40.
29. Moore EE, Moore HB, Kornblith LZ, Neal MD, Hoffman M, Mutch NJ, et al. Trauma-induced coagulopathy. Nat Rev Dis Primers. 2021 Apr 29;7(1):1–23.
30. Kornblith LZ, Moore HB, Cohen MJ. Trauma-Induced Coagulopathy: The Past, Present, and Future. J Thromb Haemost. 2019 Jun;17(6):852–62.
31. Moore HB, Moore EE, Gonzalez E, Chapman MP, Chin TL, Silliman CC, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: The spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. J Trauma Acute Care Surg. 2014 Dec;77(6):811–7.
32. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. N Engl J Med. 1994 Dec 15;331(24):1601–6.
33. Anderson FA, Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003 Jun 17;107(23 Suppl 1):I9-16.
34. Call to Action to Prevent Venous Thromboembolism in Hospitalized Patients: A Policy Statement From the American Heart Association | Circulation [Internet]. [cited 2024 Jul 23]. Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000000769
35. Geerts WH, Jay RM, Code KI, Chen E, Szalai JP, Saibil EA, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996 Sep 5;335(10):701–7.
36. Cotton BA, McCarthy JJ, Holcomb JB. Acutely Injured Patients on Dabigatran. New England Journal of Medicine. 2011 Nov 24;365(21):2039–40.
37. Ivascu FA, Howells GA, Junn FS, Bair HA, Bendick PJ, Janczyk RJ. Rapid warfarin reversal in anticoagulated patients with traumatic intracranial hemorrhage reduces hemorrhage progression and mortality. J Trauma. 2005 Nov;59(5):1131–7; discussion 1137-1139.
38. Sarode R, Milling TJ, Refaai MA, Mangione A, Schneider A, Durn BL, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K

antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation. 2013 Sep 10;128(11):1234–43.
39. Pollack CV, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for Dabigatran Reversal. N Engl J Med. 2015 Aug 6;373(6):511–20.
40. Pollack CV, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. N Engl J Med. 2017 Aug 3;377(5):431–41.