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Antithrombotics and new interventions for venous thromboembolism: Exploring possibilities beyond factor IIa and factor Xa inhibition

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Abstract

Direct oral anti–activated factor X and antithrombin agents have largely replaced vitamin K antagonists as the standard of care in treatment of venous thromboembolism. However, gaps in efficacy and safety persist, notably in end-stage renal disease, implantable heart valves or assist devices, extracorporeal support of the circulation, and antiphospholipid syndrome. Inhibition of coagulation factor XI (FXI) emerges as a promising new therapeutic target. Antisense oligonucleotides offer potential advantages as a prophylactic or therapeutic modality, with one dose-finding trial in orthopedic surgery already published. In addition, monoclonal antibodies blocking activation and/or activity of activated factor XI are investigated, as are small-molecule inhibitors with rapid offset of action. Further potential targets include upstream components of the contact pathway such as factor XII, polyphosphates, or kallikrein. Finally, catheter-directed, pharmacomechanical antithrombotic strategies have been developed for high- and intermediate-risk pulmonary embolism, and large randomized trials aiming to validate their efficacy, safety, and prognostic impact are about to start.

KEYWORDS
anticoagulant, catheter(s), contact system, factor XI, venous thromboembolism

Essentials

- Direct oral anticoagulants have been used as a standard of care in venous thromboembolism.
- There are gaps in their efficacy and safety in specific patient subgroups.
- Inhibition of coagulation factor XI seems to be a promising new therapeutic target.
- Factor XII, polyphosphates, kallikrein inhibition, and catheter-directed strategies are also emerging.

1 | INTRODUCTION: VENOUS THROMBOEMBOLISM AS A GROWING CHALLENGE FOR SOCIETIES

Venous thromboembolism (VTE), clinically presenting as deep vein thrombosis (DVT) or acute pulmonary embolism (PE), is the third most frequent acute cardiovascular syndrome after myocardial infarction and stroke.[1] The incidence of VTE is almost eight times higher in individuals aged ≥80 years than in the fifth decade of life,[2] and thus, as societies age worldwide, annual VTE incidence rates continue to increase over time.[3,4] Recently, an analysis of vital registration data from the World Health Organization (WHO) Mortality Database investigated the trends in annual PE-related mortality in the WHO European Region (including Central Asia), with a total population of ≈651 million.[5] Although the overall age-standardized PE-related annual mortality rate decreased from 12.7 to 6.5 deaths per 100 000 population between 2000 and 2015, PE-related mortality continues to exceed 80 deaths per 100 000 population among the elderly in many countries.[5] A further study analyzing the trends in North America revealed, for the first time, a "rebound" increase in PE-related mortality among young and middle-aged adults in the United States since 2006.[6] These facts illustrate the magnitude of the burden and multitude of challenges that, in spite of the recent advances in the prevention and treatment of thrombosis, VTE will continue to impose on populations and health care systems worldwide in the years to come.

This article reviews the current standard of care following a decade of revolution in anticoagulation, and outlines the most promising fields of ongoing research and the populations most likely to benefit from emerging antithrombotic agents and strategies in the decade to come.

2 | ANTICOAGULATION AND ANTITHROMBOTIC STRATEGY FOR VTE: THE PAST AND THE CURRENT STATE OF THE ART

For many decades and until very recently,[7,8] the standard approach to initiating anticoagulation treatment in a patient with acute VTE consisted of parenteral (subcutaneous) weight-adjusted low-molecular-weight heparin (LMWH)[9] or fondaparinux[10] administration; (intravenous) unfractionated heparin (UFH) infusion is now mainly reserved for patients presenting with hemodynamic compromise or severely reduced renal function.[11] In parallel with parenteral treatment, oral anticoagulation needs to start as soon as it is safe and feasible to do so. For over half a century, oral treatment of VTE has been synonymous with coumarin anticoagulants, that is, vitamin K antagonists (VKAs), which inhibit vitamin K epoxide reductase and thus impair the biosynthesis of functional (carboxylated) coagulation factors II, VII, IX and X (as well as two anticoagulant factors, protein C and protein S) in the liver.[12] In view of the slow onset of action of VKAs, which do not affect factors already present in the circulation, parallel administration of LMWH, fondaparinux, or UFH needs to be continued for at least 5 days and until the international normalized ratio value has been in the therapeutic range of 2.0-3.0 for 2 consecutive days.

VKAs are effective drugs, but they have a narrow therapeutic window and exhibit substantial variations in bioavailability and in interpatient as well as intrapatient dose requirement,[13] and need routine laboratory monitoring. These challenges, along with a multitude of drug-drug interactions and, in association with all the above, a persistently elevated risk for major, potentially life-threatening bleeding during chronic administration,[14,15] have limited the use of these drugs and thus the implementation of long-term secondary prevention after an index episode of VTE in clinical practice.[16] The direct oral anticoagulants (DOACs) were developed and approved in the past decade with the aim to overcome these weaknesses and deficits. DOACs are small molecules that, in contrast to UFH, LMWH, fondaparinux, and the VKAs, inhibit *directly* a single activated coagulation factor; the target is thrombin for dabigatran, and activated factor X (FXa) for apixaban, edoxaban, rivaroxaban, and betrixaban (the latter drug is approved for VTE prophylaxis in the United States). In view of their predictable bioavailability and pharmacokinetics, DOACs can be given at fixed doses without routine laboratory monitoring, a practical advantage compared to treatment with a VKA.[17] The doses, regimens, and duration of treatment tested in the phase 3 trials of DOACs for the treatment and secondary prophylaxis of VTE are summarized, along with the main efficacy and safety results of these trials, in Table 1. Meta-analyses have confirmed the noninferiority of DOACs compared to the combination of LMWH with a VKA for prevention of symptomatic or lethal VTE recurrence, along with significantly reduced rates of major, life-threatening bleeding[18]; these safety data are supported by "real-world" evidence.[15,19] In addition, DOACs have been successfully tested as part of a single-oral-drug anticoagulation strategy, which helps to avoid, in eligible, hemodynamically stable patients, the need for lead-in parenteral anticoagulation through the use of higher doses of apixaban over the first 7 days[20] or rivaroxaban over the first 3 weeks.[21,22] Finally, administration of reduced-dose apixaban or rivaroxaban for extended treatment and secondary prevention of VTE (after 6 months of therapeutic anticoagulation) may further improve the benefit-to-risk ratio of these DOACs over the long term.[23,24]

In view of all the above, the DOACs currently represent the standard of care in the treatment and secondary prophylaxis of VTE, having displaced not only the VKAs but also, at least in part, the LMWH in the general population and in selected patients with cancer.[11,25–28]

3 | UNANSWERED QUESTIONS AND REMAINING GAPS IN THE DOAC ERA

Based on the efficacy and particularly the very good safety profile of the DOACs, as demonstrated by the large trials summarized in Table 1, current guidelines[11,25] recommend to consider an extended secondary prevention of indefinite duration in the

majority of patients after a first episode of VTE. Apart from patients who have suffered multiple episodes of VTE, potential candidates include also those with no identifiable risk factor for the index event (so-called unprovoked VTE), patients with a persistent risk factor including cancer, and those with a weak transient or reversible risk factor such as long-haul travel. However, it needs to be borne in mind that patients at high bleeding risk as based on the investigators' judgement, medical history, or chemical laboratory parameters, were excluded from the extension studies with DOACs[22–24,29]; this had also been the case for studies on extended anticoagulation with VKAs.[30,31] Although most likely less common than in the VKA era, life-threatening bleeding complications do occur among patients taking DOACs in everyday practice,[15,19,32] and we may witness an increase in their absolute numbers in the future, notably among patients with VTE who now receive lifelong secondary prophylaxis instead of the 3-month or 6-month treatment periods in the past.

This risk of bleeding in an aging population with thrombotic events may be related, among others, to a progressive decline in renal function. This caveat particularly applies to DOACs as small molecules that undergo, to a varying but in all cases significant extent, renal elimination.[17] In the phase 3 trials on VTE, and in contrast to those on stroke prevention in atrial fibrillation, the DOACs dabigatran, rivaroxaban, and apixaban were given at an unchanged (nonreduced) dose in patients with mild to moderate renal dysfunction (largely corresponding to an estimated glomerular filtration rate [eGFR] of 30–59 mL/min); only edoxaban was given at a dose reduced by 50% in this patient group. An eGFR < 25 mL/min was an exclusion criterion in the trials that tested apixaban, whereas for the trials investigating rivaroxaban, edoxaban, and dabigatran, the lowest acceptable eGFR was 30 mL/min.[11,17] At the far end of the severity spectrum, patients with end-stage renal disease on hemodialysis are a particularly vulnerable group with a high thrombotic risk but at the same time also a high bleeding risk on anticoagulation.[33] Notwithstanding some encouraging preliminary data,[34–36] the DOACs have not been able to convincingly show a favorable risk-to-benefit clinical profile in this growing population.

Clinical trials[37] as well as ex vivo studies[38] conducted soon after DOAC approval, indicated that these drugs, by targeting a single specific coagulation factor downstream of the contact pathway (which is shown on the left side of Figure 1), may possess neither adequate efficacy nor acceptable safety for treatment of patients with mechanical heart valves. This limitation is also likely to apply to patients on extracorporeal membrane oxygenation circuits as well as those carrying left ventricular assist devices, the use of which is expected to increase in the next years as part of the management of severe heart failure.

Finally, concerns have been raised on the efficacy and safety of DOACs in patients with the antiphospholipid syndrome; this is diagnosed when arterial or venous thrombotic events are accompanied by laboratory abnormalities, notably any combination of positive lupus anticoagulant and elevated titers of anticardiolipin or β2-glycoprotein I antibodies.[39] Based on the available clinical data,[40] scientific societies currently recommend that patients with triple-positive laboratory findings, or those with the antiphospholipid syndrome who have suffered arterial thromboembolism, be treated with a VKA instead of a DOAC.[11,41] Previously considered a rather marginal topic, the prognostic impact and therapeutic implications of antiphospholipid antibodies suddenly moved into the center of interest in the year 2020, following reports on the frequent detection and possible thrombogenicity of such antibodies in patients hospitalized with coronavirus disease 2019 (COVID-19).[42–44]

4 | NEW ANTICOAGULANTS TARGETING THE CONTACT SYSTEM AND FACTOR XI

Figure 1 provides a simplified schematic overview of the coagulation system to allow for visualization of current and emerging targets of anticoagulant agents. By targeting directly (as opposed to the antithrombin-mediated effects of heparin, LMWH, or fondaparinux) one of the two key proteases of the common pathway, FXa or thrombin, the DOACs have been shown to possess high anticoagulant efficacy. They also demonstrated a safer profile compared to VKAs, mostly thanks to their (more) predictable pharmacokinetics and stable anticoagulant effect. Nevertheless, bleeding does remain a concern with these drugs,[45] a fact that is to be expected in light of the central role of their target proteins for hemostasis. Consequently, attention has turned to upstream components of the so-called contact system as possibly even safer targets, at least for particular patient groups and in particular clinical situations as outlined above. Most of the existing epidemiological and experimental data point to factor XI (FXI),[46] which is activated by activated factor XII (FXIIa) and maximizes thrombin generation via the intrinsic tenase complex activated factor IX–activated factor VIII without interfering with the interaction between factor VII and tissue factor (Figure 1). The properties and main fields of investigation for inhibitors of the intrinsic coagulation pathway and more specifically of FXI, are displayed in Table 2, the focus being on their potential clinical relevance to patients with VTE. The results of two already completed and published phase 2 clinical trials on VTE prophylaxis are summarized in Table 3.

A multitude of approaches have been proposed for FXI inhibition, including polypeptides; peptidomimetic active site inhibitors; polymeric glycosaminoglycans (GAGs) and their saccharide mimetics; nonpolymeric, nonsaccharide GAG mimetics; antibodies; antisense oligonucleotides (ASOs); and aptamers.[47] Of those currently under advanced clinical investigation, ASOs, which are short nucleotide sequences complementary to specific mRNA targets, offer a number of potential advantages as prophylactic or therapeutic modalities (reviewed in Zhang et al.[48]): (i) The liver, in which FXI is primarily synthesized, is one of the most sensitive tissues for ASO therapy; (ii) second-generation ASOs exhibit dose-linear and predictable pharmacokinetics in humans; (iii) ASOs have prolonged tissue elimination half-lives and thus do not need frequent administration, facilitating patient compliance; (iv) ASOs offer a high

TABLE 1 Phase 3 randomized controlled trials, which led to the approval of DOACs for treatment and (extended) secondary prevention of VTE

Drug	Trial	Design	Treatment arms (drug regimens)
Dabigatran	RE-COVER[101]	Double-blind, double-dummy; noninferiority	Parenteral anticoagulant for ≥5 days, then dabigatran 150 mg twice daily versus parenteral anticoagulant/warfarin
	RE-COVER II[102]	Double-blind, double-dummy; noninferiority	Parenteral anticoagulant for ≥5 days, then dabigatran 150 mg twice daily versus parenteral anticoagulant/warfarin
	Extension trials		
	RE-SONATE[29]	Double-blind; superiority	Dabigatran 150 mg twice daily versus placebo
	RE-MEDY[29]	Double-blind; noninferiority	Dabigatran 150 mg twice daily versus warfarin
Rivaroxaban	EINSTEIN-DVT[22]	Open-label; noninferiority	Rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily) versus enoxaparin/warfarin
	EINSTEIN-PE[21]	Open-label; noninferiority	Rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily) versus enoxaparin/warfarin
	Extension trials		
	EINSTEIN Extension[22]	Double-blind; superiority	Rivaroxaban 20 mg once daily versus placebo
	EINSTEIN Choice[23]	Double-blind; superiority	Rivaroxaban 20 mg once daily or rivaroxaban 10 mg once daily versus aspirin 100 mg
Apixaban	AMPLIFY[20]	Double-blind, double-dummy	Apixaban (10 mg twice daily for 7 days, then 5 mg twice daily) versus enoxaparin/warfarin
	Extension trial		
	AMPLIFY Extension[24]	Double-blind; superiority	Apixaban 5 mg twice daily or apixaban 2.5 mg twice daily versus placebo
Edoxaban	Hokusai–VTE[103]	Double-blind, double-dummy; noninferiority	Enoxaparin or UFH for ≥5 days, then edoxaban (60 mg once daily; or 30 mg once daily if CrCl 30-50 mL/min or BW ≤60 kg) versus enoxaparin or UFH/warfarin

Abbreviations: A, apixaban; AMPLIFY, Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-line Therapy; BW, body weight; CrCl, creatinine clearance; CRNM, clinically relevant nonmajor (bleeding); D, dabigatran; DVT, deep vein thrombosis; E, edoxaban; PE, pulmonary embolism; R, rivaroxaban; UFH, unfractionated heparin; VTE, venous thromboembolism.

degree of target selectivity and thus greater patient safety; and (v) as second-generation ASOs are no substrates for cytochrome P450 enzymes, drug-drug interactions (eg, as in patients receiving cancer chemotherapy) may be uncommon. Following promising data on its efficacy and safety in primates,[49,50] the FXI ASO Ionis-416858 or Ionis-FXI Rx (also known as BAY-2306001) is already at an advanced stage of clinical testing (Table 2), with one dose-finding trial in orthopedic surgery already published[51] (Table 3). Another FXI ASO, Ionis-957943 or Ionis-FXI-LRX (also known as BAY-2976217), is being evaluated against placebo for prevention of stroke and acute myocardial infarction in patients with end-stage renal disease on hemodialysis (NCT04534114).

Apart from ASOs, three monoclonal antibodies blocking activation and/or activity of activated factor XI (FXIa) are at an advanced stage of clinical investigation for indications related to VTE prophylaxis, or in patients on hemodialysis (Table 2). Antibodies share with ASOs the lack of need for renal elimination and the low risk for drug-drug interactions; moreover, in contrast to ASOs, they generally have a rapid onset of effect and a half-life that may reach up to 6 weeks.[52] Their long half-life and lack of need for daily administration/intake may facilitate patient compliance, but the slow offset of the anticoagulant effect may, as with the ASOs, be a challenge in case of bleeding complications. One of the antibodies against FXI, osocimab, has already undergone evaluation in an open-label, noninferiority phase 2 trial in orthopedic surgery[53] (Table 3). Another antibody, abelacimab,[54] a subcutaneously administered IgG1 fully human monoclonal antibody that binds the catalytic domain of both FXI (zymogen) and FXIa, is being investigated against placebo in patients with atrial fibrillation (NCT04213807).

Small molecules are, in contrast to ASO or antibodies, dependent on hepatic and renal function for their metabolism and clearance; on the other hand, they offer the advantage of rapid onset

Treatment duration	Patients randomized	Efficacy outcome: VTE recurrence	Safety outcome: Bleeding
6 months	2539	Recurrent or fatal VTE: D: 2.4% compared to warfarin: 2.1%	Major bleeding: D: 1.6% compared to warfarin: 1.9%
6 months	2589	Recurrent or fatal VTE: D: 2.3% compared to warfarin: 2.2%	Major bleeding: D: 1.2% compared to warfarin: 1.7%
6 months	1343	Recurrent or fatal VTE or unexplained death: D: 0.4% compared to placebo: 5.6%	Major or CRNM bleeding: D: 5.3% compared to placebo: 1.8%
6-36 months	2856	Recurrent or fatal VTE: D: 1.8% compared to warfarin: 1.3%	Major or CRNM bleeding: D: 5.6% compared to warfarin: 10.2%
3, 6, or 12 months	3449; acute DVT	Recurrent VTE: R: 2.1% compared to warfarin: 3.0%	Major or CRNM bleeding: R: 8.1% compared to warfarin: 8.1%
3, 6, or 12 months	4832; acute PE	Symptomatic recurrent VTE: R: 2.1% compared to warfarin: 1.8%	Major or CRNM bleeding: R: 10.3% compared to warfarin: 11.4%
6-12 months	1196	Recurrent VTE: R: 1.3% compared to placebo: 7.1%	Major bleeding: R: 0.7% compared to placebo: 0
12 months	3365	Recurrent VTE: R 20 mg: 1.5% R 10 mg 1.2% compared to aspirin: 4.4%	Major bleeding: R 20 mg: 0.5% R 10 mg: 0.4% compared to aspirin: 0.3%
6 months	5395	Recurrent or fatal VTE: A: 2.3% compared to warfarin: 2.7%	Major bleeding: A: 0.6% compared to warfarin: 1.8%
12 months	2486	Symptomatic VTE or death from any cause: A 5 mg: 1.7% A 2.5 mg: 1.7% compared to placebo: 8.8%	Major bleeding: A 5 mg: 0.1%, A 2.5 mg: 0.2% compared to placebo: 0.5%
Variable, 3-12 months	8240; acute DVT and/or PE	Symptomatic recurrent VTE: E: 3.2% compared to warfarin: 3.5%	Major or CRNM bleeding: E: 8.5% compared to warfarin: 10.3%

and particularly offset of their effects.[46] Of these, the oral inhibitor BMS-986177, also known as JNJ-70033093, is currently being tested against enoxaparin in VTE prophylaxis in elective total knee arthroplasty, and in patients with end-stage renal disease on hemodialysis (Table 2); it is also undergoing investigation in patients with ischemic stroke or high-risk transient ischemic attack, who receive aspirin and clopidogrel for 21 days followed by aspirin thereafter (NCT03766581). Another oral small-molecule inhibitor, BAY-2433334, is being investigated against apixaban in patients with atrial fibrillation (NCT04218266) and against placebo for noncardioembolic ischemic stroke (NCT04304508) and acute myocardial infarction (NCT04304534). EP-7041, a recently introduced parenteral, potent, and selective small-molecule FXIa inhibitor, exhibits pharmacodynamic and pharmacokinetic characteristics that might be well suited for use in a critical care environment and particularly for patients on extracorporeal membrane oxygenation.[55]

5 | AGENTS TARGETING OTHER COAGULATION FACTORS

Although FXI is formally considered a component of the contact pathway and lies upstream of FX and thrombin, it is activated by thrombin, having been formed via the extrinsic pathway (following activation of factor VII [FVIIa] by tissue factor), and plays in turn an important role on amplifying thrombin generation (Figure 1). Consequently, FXI does play a relevant role in the physiology of hemostasis, and it is not surprising that its inhibition by the most effective dose of the monoclonal antibody osocimab in a phase 2 study was associated with a bleeding frequency comparable to that of enoxaparin and higher than that of apixaban[53] (Table 3). In contrast, FXII, which lies upstream and thus does not participate in this self-amplifying loop (Figure 1), may, at least theoretically, represent a safer target. On the other hand, the available experimental and

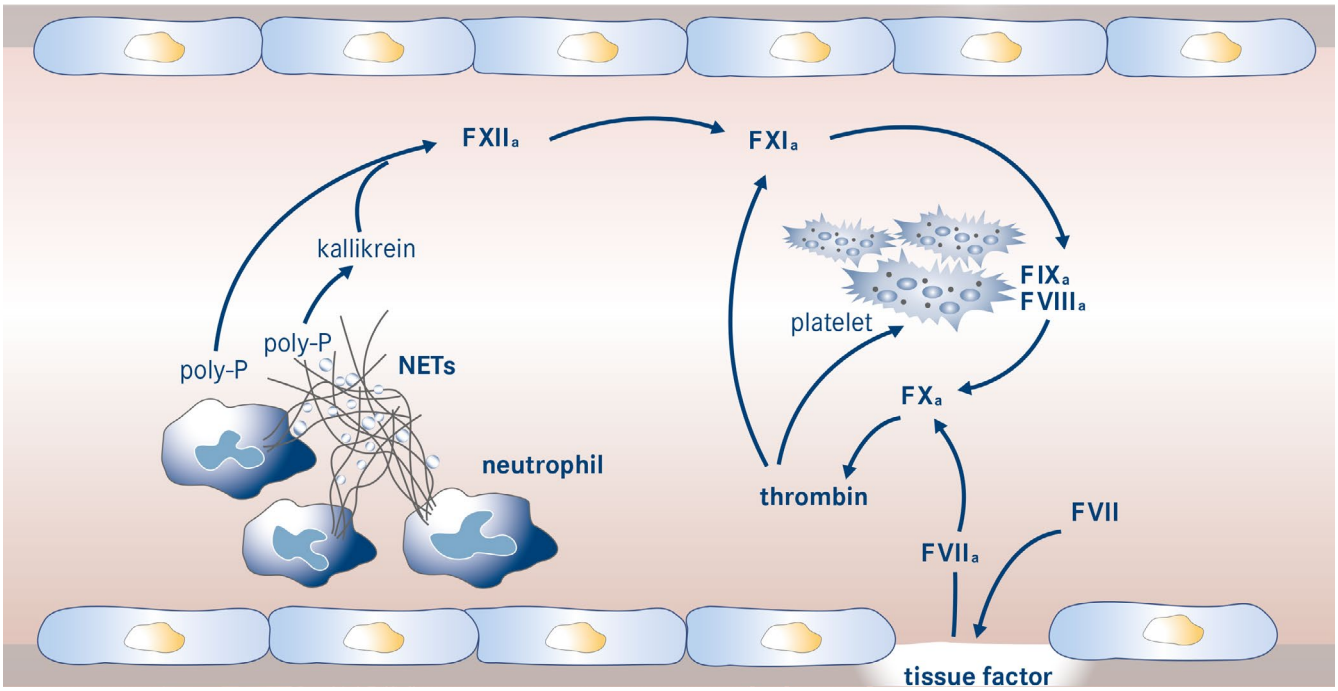

FIGURE 1 Simplified overview of the coagulation cascade, highlighting the targets of currently investigated new anticoagulants. a, activated (coagulation factor); F, (coagulation) factor; NETs, neutrophil extracellular traps; poly-P, polyphosphates; thrombin, factor IIa

epidemiological evidence (reviewed in Fredenburgh et al.[46]) does not support a role for FXII in thrombosis in humans and other primates as opposed to small mammal (rodent) models. At present, FXII inhibition is being investigated for hereditary angioedema, which is not a prothrombotic condition. Specifically, CSL-312 (garadacimab), a fully humanized IgG4 monoclonal antibody targeting FXIIa, is being tested in a phase 2 trial for subcutaneous and intravenous use (NCT03712228) in that condition. The same agent is also undergoing investigation in a phase 2 clinical study for the prevention of tracheal intubation and death from COVID-19 (NCT04409509).

Polyphosphates, including DNA and RNA released from injured or dying cells or neutrophil extracellular traps, are increasingly attracting attention as activators of the contact system (Figure 1) and key mediators of immunothrombosis.[56,57] Experimental data suggest that polyphosphate inhibitors, including cationic proteins, polymers, and small molecules, may be worth pursuing as antithrombotic agents, also having a favorable safety profile.[58–60] In addition, recent studies on the structure of plasma kallikrein,[61,62] and on its contribution to FIX activation and thrombin generation independently from FXIa[63,64] have redrawn attention to this long "forgotten" protein of the contact pathway.[65] In the future, kallikrein inhibitors, currently under study for hereditary angioedema,[66] might extend our armamentarium of antithrombotic agents. Clinical evaluation of other proteases of the contact pathway downstream of FXI, namely, FVIII or FIX, is not being pursued at present. A number of antibodies, RNA aptamers, and small molecules were developed to inhibit these factors (summarized in Mackman et al.[67]), but clinical testing was terminated due to lack of efficacy or because of safety concerns.

Aspirin may have antithrombotic properties beyond classical inhibition of platelet aggregation,[68] and it was reported to exert moderate protective effects against VTE recurrence.[69,70] However, aspirin is inferior to standard anticoagulant treatment for secondary VTE prevention,[23] and its use may thus be considered only in the rare case of a patient who refuses to take or is unable to tolerate any form or oral anticoagulation.[11]

Dose-dependent tissue factor inhibition[71] may contribute, along with thrombomodulin activation[72] and stimulation of anti-inflammatory mechanisms,[73] to the antithrombotic effects of statins, and the impact of these drugs on the coagulation system may be independent, at least in part, from their lipid-lowering effects.[74] Although the use of statins has been associated with a lower incidence of first and recurrent VTE,[75,76] direct comparison with "standard-of-care" antithrombotic drugs is needed before statins can be recommended for primary or secondary VTE prevention in clinical practice. The phase 3 investigator-initiated placebo-controlled Statins for Venous Event Reduction in Patients With Venous Thromboembolism (SAVER; NCT04319627) trial is currently investigating this aspect.

6 | ANTITHROMBOTIC STRATEGIES BEYOND ANTICOAGULATION: FOCUS ON PERCUTANEOUS CATHETER-DIRECTED TECHNIQUES

Beyond anticoagulation, which is the standard of care for all patients with VTE regardless of clinical presentation and severity,

reperfusion treatment using standard-dose fibrinolysis is recommended as a life-saving option for acute PE associated with hemodynamic instability and a high risk of early death.[11] On the other hand, in apparently *stable* patients presenting with laboratory and imaging signs of right ventricular dysfunction (so-called intermediate-risk PE), standard-dose intravenous fibrinolysis, given on top of heparin anticoagulation, provided no net clinical benefit in the Pulmonary Embolism Thrombolysis (PEITHO) trial.[77] In that study, the increased incidence of life-threatening bleeding in the fibrinolysis group exceeded the achieved reduction in the risk of early hemodynamic decompensation and death.[77] At present, the question whether an appropriately selected group of patients with intermediate-high-risk PE may benefit from early reperfusion, remains to be answered.[78] Over the past years, efforts have been made to better identify such a higher-risk group based on a combination of clinical, laboratory, and imaging criteria,[79] and to explore safer reperfusion options.[80] Of the reperfusion strategies currently available (visually summarized in Figure 2), reduced-dose systemic fibrinolysis and catheter-directed thrombus suction or lysis have emerged as the most promising options.

The rationale beyond the use of a reduced-dose systemic fibrinolysis regimen has its fundament in cohort studies and in a randomized pilot trial of 118 patients, suggesting that this approach may have an acceptably low risk of (life-threatening) bleeding without loss of efficacy compared with standard-dose fibrinolysis (reviewed in Valerio et al.[80]). To test this hypothesis, the PEITHO-III randomized controlled trial (NCT04430569) will investigate whether reduced-dose systemic fibrinolysis, given in addition to low-molecular-weight heparin, is superior to heparin alone in patients with higher-risk PE as defined by a combination of clinical, imaging, and laboratory criteria. PEITHO-III will be conducted in seven European countries and is expected to recruit the first patient in early 2021.

An overview of novel catheter-directed reperfusion techniques, promising ease of use and a favorable efficacy and safety profile, is provided in Table 4. The available evidence comes from single-arm interventional studies and small randomized controlled trials with surrogate (imaging) outcomes, which compared different catheter-directed pharmacological regimens or catheter-directed techniques with standard anticoagulation.[81–84] In most of these studies, an early improvement of right-to-left ventricular diameter ratio was observed within 24-48 hours of PE diagnosis. Devices currently approved for use in acute PE include the EkoSonic endovascular system for ultrasound-assisted catheter-directed thrombolysis (Boston Scientific, Marlborough, MA, USA)[82,83] and the large-bore aspiration thrombectomy FlowTriever system (Inari Medical, Aliso Viejo, CA, USA).[84] Figures 3 and 4 illustrate two exemplary patients with acute PE and right ventricular dysfunction, who were successfully treated with catheter-directed ultrasound-assisted thrombolysis at the University Hospital of Zurich, Switzerland. However, formal approval of medical devices does not obviate the need for rigorous testing and proof of their efficacy and safety in randomized controlled trials with clinical outcomes. The recently announced HI-PEITHO study is a multicenter prospective randomized controlled trial that will be conducted in the Unites States and Europe. It will compare clinical outcomes following ultrasound-facilitated, catheter-directed thrombolysis plus standard anticoagulation with those on anticoagulation alone in a higher-risk PE population defined by inclusion criteria similar to those of PEITHO-III (mentioned above). Enrollment of the first patient is expected in 2021. Both randomized trials will also study the impact of the respective reperfusion strategies on long-term functional outcomes and complications associated with the so-called post-PE syndrome.[85]

Five small randomized controlled trials have tested the use of catheter-directed reperfusion techniques in patients with acute (proximal) DVT for the prevention of postthrombotic syndrome.[86–90] The heterogeneity of the study populations and the fact that all studies were largely underpowered to detect statistically significant differences limit our ability to interpret their results, leaving anticoagulation as the standard therapy for acute DVT. A post hoc analysis of the Catheter Versus Anticoagulation Alone for Acute Primary (Ilio)Femoral DVT (CAVA) trial focused on the effect of ultrasound-accelerated catheter-directed thrombolysis on the development of the postthrombotic syndrome after 1 year of follow-up; although the risk was not reduced after successful thrombolysis for acute iliofemoral DVT, these patients did report an improvement in the quality of life.[91] Finally, observational data suggest that endovascular treatment of postthrombotic syndrome with stent placement might improve mid- and long-term clinical (functional) scores.[92,93] The Aspirin Plus Rivaroxaban Versus Rivaroxaban Alone for the Prevention of Venous Stent Thrombosis in Patients With Prothrombotic Syndrome (ARIVA; NCT04128956) phase 3 trial will elucidate which antithrombotic therapy may be most appropriate in this group of patients.

7 | ANNUAL CONGRESS REPORT

A number of abstracts highlighting the ongoing translational research on emerging antithrombotic drugs and strategies were presented at the 2020 Congress of the International Society on Thrombosis and Haemostasis. Prevention of carotid arterial thrombosis with the oral small-molecule FXIa inhibitor BMS-986177 was reported in animal models; the effect was present with or without combination therapy with aspirin, and no increase in bleeding complications was observed.[94] ONO-1600586, an oral direct FXIa inhibitor, demonstrated a favorable anticoagulant profile on experimental jugular vein thrombosis in animal models, with less bleeding tendency compared to rivaroxaban.[95] Comparison of the intravenous small-molecule FXIa inhibitor EP-7041 with heparin for the prevention of thrombus formation in a canine extracorporeal membrane oxygenation model showed superior anticoagulant efficacy and a better safety profile of EP-7041.[96] The reversal effect on osocimab (BAY-1213790) by activated prothrombin complex concentrate and recombinant FVIIa was demonstrated in vitro; on the other hand, (nonactivated) prothrombin complex concentrate had no reversal effect.[97] The oral small-molecule

TABLE 2 Anticoagulants currently at an advanced stage of clinical investigation in the indication of VTE, or in particular patient groups

	Antisense oligonucleotides	Antibodies
Name	**Ionis-416858 (also BAY-2306001)[50,51,104]**	**Osocimab (BAY- 1213790)[52,105]**
Targeted coagulation factor	XI	XI
Type of substance	Second-generation antisense oligonucleotide	IgG1 monoclonal antibody
Mechanism of action	Reduction of expression of the FXI mRNA in liver	Blockage of the catalytic domain of FXIa through structural reformation
Time to peak effect	4–6 wk	1–4 h
Half-life	2 wk	30–44 d
Renal elimination	Clearance does not depend on renal function	Clearance does not depend on renal function
Interactions with concomitant medication	Low risk for drug-drug interactions	Low risk for drug-drug interactions
Contraindications or caveats	Local injection reactions	Possible dosing once per month
Reversal agent available	No	Under evaluation
Clinical investigation, possibly applicable to patients with VTE (trial identifier, status)	VTE prophylaxis in ESRD on hemodialysis (NCT03358030, completed; NCT02553889, completed, presented[104])	VTE prophylaxis in ESRD on hemodialysis (NCT04523220, ongoing)

Abbreviations: CYP, cytochrome P450; ESRD, end-stage renal disease; FXI, factor XI; FXIa, activated factor XI; FXIIa, activated factor XII; TKA, total knee arthroplasty; VTE, venous thromboembolism.

TABLE 3 Published clinical trials on new anticoagulants targeting factor XI in primary prevention of VTE

Drug	Trial	Design	Treatment arms (drug regimens)
Ionis FXI-Rx (Ionis-416858, also BAY- 2306001)	FXI-ASO TKA[51]	Open-label; phase 2	ASO 200 mg or 300 mg s.c. (100 mg dose discontinued after 14 first patients) versus Enoxaparin 40 mg s.c. in elective primary unilateral TKA
Osocimab (BAY- 1213790)	FOXTROT[53]	Open-label; noninferiority; phase 2	Osocimab 0.3 or 0.6 or 1.2 or 1.8 mg/kg postoperatively i.v.; or 0.3 or 1.8 mg/kg preoperatively i.v. versus apixaban 2.5 mg twice daily or enoxaparin 40 mg in patients undergoing elective primary unilateral TKA

Abbreviations: ASO, antisense oligonucleotide; CRNM, clinically relevant nonmajor (bleeding); DVT, deep vein thrombosis; i.v., intravenously; O, osocimab (BAY 1213790); PE, pulmonary embolism; s.c., subcutaneously; TKA, total knee arthroplasty; VTE, venous thromboembolism.

		Small molecules
Abelacimab (MAA-868)[54]	**Xisomab (AB-023)[106]**	**BMS-986177/JNJ-70033093[107]**
XI	XI	XI
IgG1 monoclonal antibody	IgG2b monoclonal antibody	Small-molecule inhibitor
Blockage of the catalytic domain of FXI and FXIa through structural reformation	Recognition of apple 2 domain of FXI and FXIa Blockage of FXIIa-mediated FXI activation (no inhibition of thrombin-mediated activation of FXI)	Inhibition of the active site of FXIa
7–21 d	0.08–0.65 h	3 h
20.1–28.6 d	1.3–121.5 h	8.26-13.8 h
Clearance does not depend on renal function	Clearance does not depend on renal function	8%-20%
Low risk for drug-drug interactions	Low risk for drug-drug interactions	Drug-drug interactions related to CYP metabolism
Decreased effect in obesity	Productive cough, probably not directly related to the drug	Food may increase bioavailability
Recombinant factor VIIa (Novoseven) possible reversal agent	No	4-factor prothrombin complex concentrate (FEIBA), recombinant factor VIIa (Novoseven) under investigation[108]
VTE prophylaxis in elective unilateral TKA (EUdraCT 2019-003756-37)	Thromboprophylaxis of peripherally inserted central catheters for chemotherapy in cancer (NCT04465760, ongoing); VTE prophylaxis in ESRD on hemodialysis (NCT03612856, completed)	VTE prophylaxis in elective TKA (NCT03891524, ongoing); ESRD on hemodialysis (NCT03000673, completed)

Treatment duration	Patients randomized	Efficacy outcome: VTE recurrence	Safety outcome(s): Bleeding
36 d preoperatively to 3 d postoperatively	300 (revised protocol)	Composite of asymptomatic DVT (mandatory bilateral venography), confirmed symptomatic VTE, fatal PE, unexplained death: Ionis 200 mg: 27% Ionis 300 mg: 4% compared to enoxaparin 40 mg: 30%	Composite of major or CRNM bleeding: Ionis 200 mg: 3% Ionis 300 mg: 3% compared to enoxaparin 40 mg: 8%
Single 60-min infusion	813	Composite of asymptomatic DVT (mandatory bilateral venography), confirmed symptomatic DVT or nonfatal PE, documented fatal PE, unexplained death: Postoperatively O 0.3 mg/kg: 23.7% O 0.6 mg/kg: 15.7% O 1.2 mg/kg: 16.5% O 1.8 mg/kg: 17.9% preoperatively O 0.3 mg/kg: 29.9% O 1.8 mg/kg: 11.3% compared to Apixaban: 14.5% Enoxaparin: 26.3%	Composite of major or CRNM bleeding: Postoperatively O 0.3 mg/kg: 2.0% O 0.6 mg/kg: 0.0% O 1.2 mg/kg: 1.0% O 1.8 mg/kg: 3.0% Preoperatively O 0.3 mg/kg: 1.9% O 1.8 mg/kg: 4.7% compared to Apixaban: 2% Enoxaparin: 5.9%

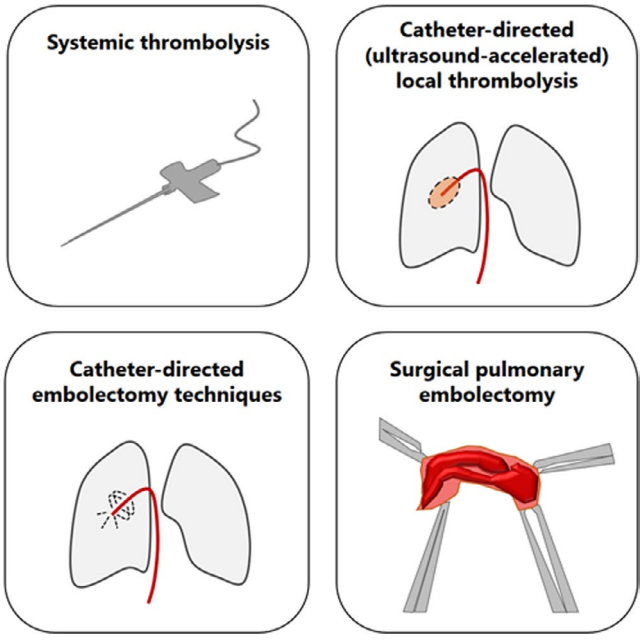

FIGURE 2 Graphical overview of the main types of available reperfusion strategies and techniques for acute pulmonary embolism

FXIa inhibitor BAY-2433334 was tested in carotid artery thrombosis and arteriovenous shunt animal models, where it demonstrated antithrombotic efficacy with no elevated bleeding risk.[98]

The first-in-human study of ONO-7684 was also reported. ONO-7684 is an oral small-molecule FXIa inhibitor, which was assessed in a phase 1 randomized double-blind placebo-controlled study on healthy individuals. It demonstrated good tolerability with mild adverse effects, a half-life of 22-28 hours, and peak concentrations that increased with food intake.[99] The safety, pharmacokinetics, and pharmacodynamics of BAY-2433334 were also evaluated in a phase 1 study on healthy men, reporting good tolerability and safety, a half-life of around 15 hours, and a decrease in peak concentrations by food intake.[100]

8 | CONCLUSIONS

In the past decade, new oral drugs directly targeting coagulation factor Xa or thrombin revolutionized the treatment of thrombotic diseases including VTE. Nevertheless, in a continuously growing population of possible candidates for long-term anticoagulation, safety concerns and unmet needs persist in the treatment of vulnerable patient groups, related, for example, to severely reduced renal function, implantable heart valves or assist devices, and extracorporeal support of the circulation. Attention has turned to components upstream of the final common pathway, with epidemiological and experimental data pointing to FXI as a promising target. Of the numerous approaches proposed for FXI inhibition, second-generation antisense oligonucleotides, several humanized monoclonal antibodies, and a

TABLE 4 Technologies for catheter-directed treatment (adapted from Hobohm et al.[109] and Valerio et al.[80])

Technique	Description	Device (company)	Evidence
Catheter-directed thrombolysis	The catheter is inserted directly into the pulmonary artery and the thrombolytic agent released close to the location of the thrombus.	Cragg-McNamara (Ev3 Endovascular); UniFuse (AngioDynamics), multi-sidehole pigtail 4-5-French catheter	Observational studies and one prospective randomized trial with surrogate outcomes
Ultrasound-assisted catheter-directed thrombolysis	A second catheter lumen contains low-energy ultrasound transducers which should loosen the clot structure to facilitate thrombolytic penetration.	EkoSonic (Boston Scientific) 5.2-French device	Prospective, single group studies and prospective randomized trials with surrogate outcomes
Catheter-directed embolectomy by fragmentation	The pigtail is inserted into the distal part of the thrombus and rotating while retracting at the proximal part.	Pigtail 5 French fragmentation plus thrombectomy with Aspirex 8/10-French	Observational studies
Catheter-directed embolectomy, rheolytic	High-pressure jet streams disrupt the thrombus, which is then trapped in a low-pressure zone and aspirated in the catheter.	AngioJet (Boston Scientific) 6-French catheter	Observational studies
Catheter-directed embolectomy by suction	The thrombus is aspirated via a pump, reintroducing excess aspirated blood via a venovenous bypass system or with mechanical clot engagement.	AngioVac (AngioDynamics) suction cannula with 26 French access; Indigo (Penumbra) 8 French vacuum-assisted aspiration system	Observational studies
Catheter-directed embolectomy by entrapment	Self-expanding nitinol disks are placed into the thrombus, ensnare it by expanding, and are retracted via a vacuum aspirator into the catheter.	FlowTriever (Inari) 20 French device	Observational studies and one single-arm phase II trial with surrogate outcomes

Note: Only EkoSonic and FlowTriever have been approved for acute pulmonary embolism. The other devices have been formally approved for other vascular sites.

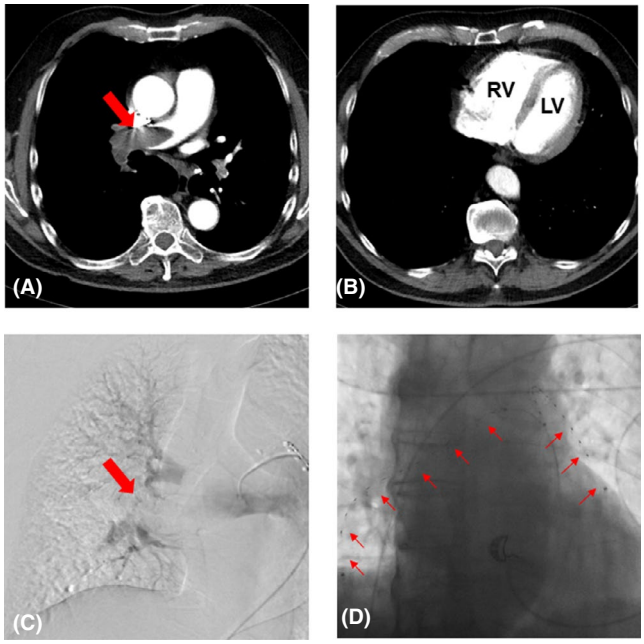

FIGURE 3 Catheter-directed thrombolysis in a patient with acute bilateral central pulmonary embolism and severe right ventricular dysfunction. (A) The arrow indicates the presence of an embolus (dark gray) in the right main pulmonary artery. (B) Right (RV) and left (LV) ventricle visualized on computed tomography pulmonary angiography, permitting measurement of the RV/LV diameter ratio. Diameter measurement should be performed at the endocardial border of each ventricle. A RV/LV ratio >1.0 was measured, indicating RV pressure overload and dysfunction. (C) Visualization of the embolus in the right pulmonary artery by pulmonary angiogram before placement of the catheters for catheter-directed thrombolysis. (D) The arrows indicate two infusion catheters with ultrasound emission in place for catheter-directed ultrasound-assisted thrombolysis

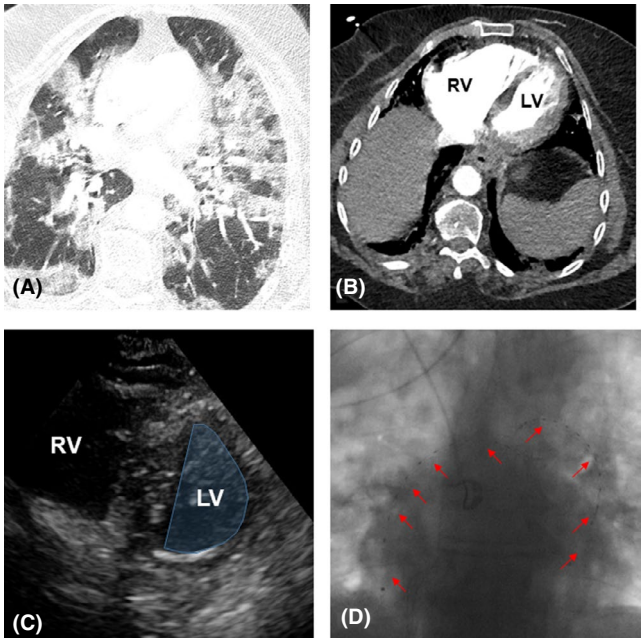

FIGURE 4 Catheter-directed thrombolysis in a patient with coronavirus disease 2019 (COVID-19) and acute bilateral pulmonary embolism associated with hemodynamic instability. (A) Computed tomography showing severe bilateral pneumonia due to COVID-19. (B) Right (RV) and left (LV) ventricle visualized on computed tomography pulmonary angiography, permitting measurement of the RV/LV diameter ratio. Diameter measurement should be performed at the endocardial border of each ventricle. A RV/LV ratio >1.0 was measured, indicating RV pressure overload and dysfunction. (C) Flattening of the interventricular septum or "D sign" on transthoracic echocardiography (parasternal short-axis view). (D) Arrows indicate two infusion catheters with ultrasound emission in place for catheter-directed ultrasound-assisted thrombolysis

number of small molecule inhibitors have completed or are still undergoing clinical testing in dose-finding, phase 2 trials. The first results are promising, and each mode of inhibition may offer advantages for specific patient groups and clinical situations. It will soon be possible to tell which of these substances will be able to enter phase 3 testing as the next critical step toward approval and clinical application. In parallel, and in view of the recognition of the critical role of FXI for amplifying thrombin generation and thus for hemostasis (indicating a remaining risk of bleeding upon FXIa inhibition), even safer targets are being sought among the upstream components of the contact pathway. Molecules of interest include FXII, polyphosphates, or kallikrein, although research is still at an earlier phase of translation in this area. Finally, catheter-directed, pharmacomechanical antithrombotic strategies beyond anticoagulation have been developed for cardiovascular emergencies such as high- and intermediate-risk PE, and large randomized trials aiming to validate their efficacy, safety, and prognostic impact are about to start. The revolution that swept antithrombosis in the 2010s will most likely be followed by a phase of targeted evolution in the decade to come; although less spectacular, this phase will be at least as interesting and relevant.

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AUTHOR CONTRIBUTIONS

AM, SB and SK designed the paper, critically reviewed the literature and reviewed and edited the final manuscript.

RELATIONSHIP DISCLOSURE

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