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Over 10 years of non-vitamin K antagonist oral anticoagulants: highlights, challenges, and future developments

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Over the past decade, non-vitamin K antagonist oral anticoagulants have revolutionized anticoagulation therapy, offering substantial benefits over traditional vitamin K antagonists. Non-vitamin K antagonist oral anticoagulants offer reduced bleeding risks, fixed dosing without frequent monitoring, and fewer drug and dietary interactions. Their effectiveness has been demonstrated in preventing stroke in atrial fibrillation, managing venous thromboembolism, and offering new options for patients with coronary artery disease and cancer-associated thrombosis. However, challenges remain, including bleeding risks, high costs, and limited efficacy in certain patient populations. Current research is focused on addressing these limitations, with Factor XI inhibitors emerging as a promising advancement for safer anticoagulation. This review provides an overview of the clinical highlights, challenges, and future directions of anticoagulation therapy.

Introduction

In the last 15 years, anticoagulation therapy has undergone significant advances, primarily due to the introduction of the non-vitamin K antagonist oral anticoagulants (NOACs), also referred as 'direct oral anticoagulants'. Before their development, vitamin K antagonists (VKAs), such as warfarin, were the standard treatment for preventing or treating thrombo-embolic events in patients with conditions like atrial fibrillation (AF) and venous thromboembolism (VTE). However, VKAs require frequent monitoring, imply numerous dietary restrictions, and pose significant risk of bleeding, particularly intracranial haemorrhage. The advent of NOACs marked a pivotal shift in anticoagulation therapy. Drugs such as dabigatran, rivaroxaban, apixaban, and edoxaban were developed to overcome the limitations of VKAs, offering fixed dosing, fewer food and drug interactions, and a more favourable safety profile. As the result of successful large, randomized controlled trials, NOACs quickly gained acceptance in clinical practice, becoming the preferred choice for many patients and clinicians. This paper will summarize the evolution of NOACs over the past decade, focusing on their clinical highlights, but will also depict the ensued challenges and the potential future developments in this field. The journey of NOACs from their introduction to the present day has been a quite successful medical story with large clinical impact; yet, the shades in this journey are now fostering further pharmacological innovations.

The development of non-vitamin K antagonist oral anticoagulants

The development of NOACs began as a response to the significant limitations posed by VKAs, which, despite their effectiveness, require strict monitoring and have a narrow therapeutic window. Vitamin K antagonists exert their anticoagulant effect by inhibiting the synthesis of

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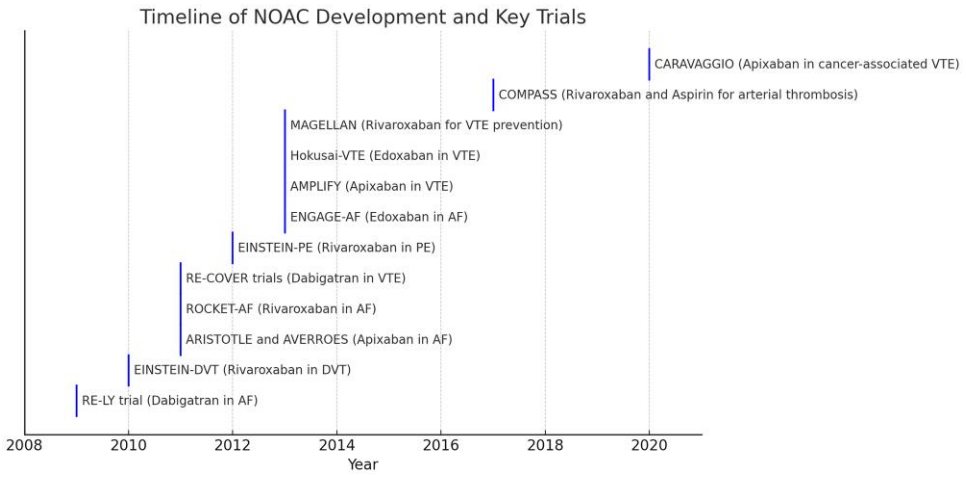

Figure 1 The timeline illustrates the progression of major non-vitamin K antagonist oral anticoagulant clinical trials from 2009 to the present

multiple vitamin K-dependent coagulation factors (F) (F II, VII, IX, and X). In contrast, NOACs were designed to selectively inhibit specific targets within the coagulation cascade. Direct thrombin inhibitors (such as dabigatran) block thrombin (FIIa), while FXa inhibitors (such as rivaroxaban, apixaban, and edoxaban) directly and selectively inhibit FXa. This targeted mechanism of action results in a more predictable pharmacokinetic profile, reducing the need for frequent monitoring, which contributed to the significant advance that NOACs brought to anticoagulation therapy. Pivotal trials subsequently defined their roles in AF and VTE management, solidifying their place in clinical practice.[1] In AF, this shift began with the RE-LY trial in 2009, which demonstrated twice daily dabigatran as an effective alternative to warfarin for stroke prevention. This was followed by the ROCKET-AF trial in 2011, demonstrating once daily rivaroxaban efficacy in stroke prevention for AF patients. In the same year, the ARISTOTLE and AVERROES trials demonstrated that twice daily apixaban was superior to warfarin in reducing stroke risk with a safer bleeding profile, while also showing better efficacy and largely similar safety compared with aspirin, respectively. In 2013, the ENGAGE-AF trial supported the use of once daily edoxaban for stroke prevention in AF, further expanding the options for NOACs in AF management. Almost simultaneously, the role of NOACs in VTE management was being established through a series of landmark trials. In 2010, the EINSTEIN-DVT trial demonstrated the efficacy of rivaroxaban in the treatment of deep vein thrombosis (DVT), while the RE-COVER trial confirmed the effectiveness of dabigatran in managing VTE. The EINSTEIN-PE trial, published in 2012, validated the use of rivaroxaban in the management of pulmonary embolism (PE), broadening its clinical application. The role of apixaban in both the acute and extended phases of VTE treatment was further supported by the findings of the AMPLIFY and AMPLIFY-Extension trials, both published in 2013. That same year, the Hokusai-VTE trial demonstrated the efficacy of edoxaban with a reduced risk of major bleeding, while the MAGELLAN trial explored rivaroxaban for VTE prevention in acutely ill hospitalized patients, although the higher bleeding risk mitigated some of the benefits observed in reducing thrombo-embolic events. More recent studies have explored the role of NOACs in cancer-associated VTE with distinct focuses: the SELECT-D trial demonstrated the efficacy of rivaroxaban for treating cancer-associated VTE, the AVERT trial highlighted the role of apixaban in preventing VTE in high-risk ambulatory cancer patients, and the CARAVAGGIO trial confirmed in 2020 the safety and efficacy of apixaban as a treatment alternative to low-molecular-weight heparins (LMWHs) in patients with active cancer. In the context of arterial thrombosis, the COMPASS trial, published in 2017, demonstrated that a combination of low-dose rivaroxaban and aspirin substantially reduced major cardiovascular events in patients with stable atherosclerotic vascular disease, thereby broadening the therapeutic scope of NOACs. Concurrently, the PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI trials were pivotal in establishing the NOACs as the preferred anticoagulants for AF patients undergoing percutaneous coronary intervention (PCI) or presenting with acute coronary syndrome (ACS). Over the past 15 years, these seminal trials have not only validated the clinical benefits of the NOACs but have also established them as the cornerstone of anticoagulation therapy across a spectrum of cardiovascular conditions (*Figure 1*).

Clinical highlights of the non-vitamin K antagonist oral anticoagulants

The NOACs have shown significant advantages in numerous studies, establishing themselves as key drugs in anticoagulation therapy. One of the most significant advantages of the NOACs is their ability to reduce the incidence of intracranial haemorrhage, one of the most feared complications of VKA anticoagulation. This benefit, along with comparable or superior efficacy in preventing stroke and systemic embolism, quickly became evident in pivotal AF trials such as RE-LY, ARISTOTLE, ROCKET-AF, and ENGAGE-AF. These trials demonstrated that NOACs had a lower risk of intracranial bleeding compared with warfarin, while maintaining or surpassing efficacy in

stroke prevention. This compelling evidence established NOACs as first-line therapy for stroke prevention in AF patients, marking a significant shift from traditional VKAs to these newer agents.[2-4] The NOACs have also emerged as a preferred therapeutic option for patients with ACS or those undergoing PCI who require oral anticoagulation. In the setting of dual or triple antithrombotic therapy (an NOAC plus a $P2Y_{12}$ inhibitor, with or without aspirin), NOACs not only reduce bleeding risk compared with VKAs but also offer the additional benefit of simplified management, such as fixed dosing and fewer drug interactions, while preserving thrombo-embolic protection.[5] In the setting of coronary artery disease (CAD), a noteworthy advancement for the NOACs has been the use of low-dose rivaroxaban in combination with aspirin for preventing major cardiovascular events in patients with stable atherosclerotic vascular disease. The results of the COMPASS trial demonstrated a significant reduction in cardiovascular events compared with aspirin alone, with an acceptable safety profile. This combination not only enhanced protection against cardiovascular outcomes but also offered a targeted approach for patients at high risk, leading to its inclusion in guidelines for secondary prevention in patients with stable CAD or peripheral artery disease, thereby expanding the clinical applications of NOACs.[6,7] Similarly, the use of NOACs has expanded to patients with bioprosthetic heart valves and AF, a setting where VKAs were traditionally the standard of care, requiring frequent monitoring and posing a higher risk of bleeding complications. The efficacy and safety of NOACs have been validated in both mitral and aortic valve positions, providing a more convenient anticoagulation option.[8] Non-vitamin K antagonist oral anticoagulants have become essential in the treatment and prevention of VTE, including DVT and PE, and have gained a prominent role in cardio-oncology for managing cancer-associated thrombosis. Their fixed dosing and oral administration improve adherence, offering a viable alternative to LMWHs, with a favourable efficacy profile in this high-risk population. Emerging evidence suggests that the NOACs may also be effective in treating intra-cardiac thrombosis, including left ventricular thrombosis.[9] Case reports and small cohort studies indicate that NOACs can significantly reduce thrombus size and lower the risk of embolic events, making them a viable therapeutic option in this challenging condition. In patients with AF, a study on edoxaban demonstrated that more than 50% of atrial thrombi resolved within 4 weeks, with efficacy comparable with VKAs in historical controls.[10] Overall, the clinical highlights of NOACs underscore their ability to prevent thrombo-embolic events effectively, coupled with a favourable safety profile and expanding indications, which have made them a preferred option across a wide range of clinical scenarios.

Challenges and limitations

Despite the significant advantages offered by NOACs, several challenges and limitations still impact their optimal use and require careful consideration in clinical practice (*Figure 2*).

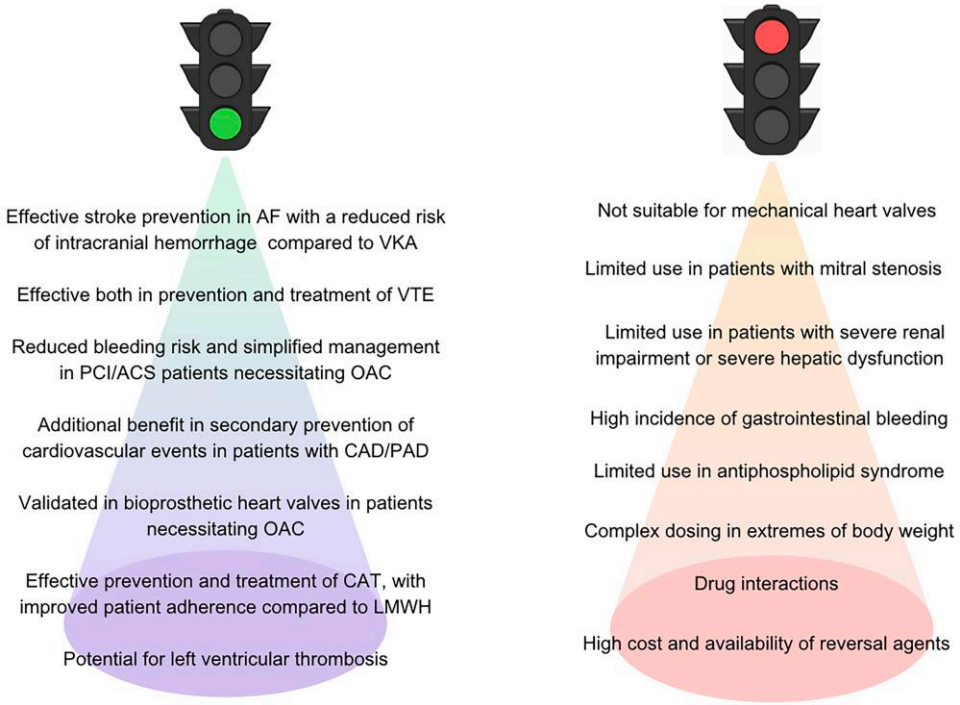

Figure 2 Clinical highlights and benefits of non-vitamin K antagonist oral anticoagulants on the left panel, including their effectiveness in stroke prevention, venous thromboembolism management, and cancer-associated thrombosis, along with their simplified dosing and reduced bleeding risk. On the right hand panel, current challenges and limitations of the non-vitamin K antagonist oral anticoagulants are shown, highlighting areas where improvements are still needed. AF, atrial fibrillation; CAD, coronary artery disease; CAT, cancer-associated thrombosis; LMWH, low-molecular-weight heparin; OAC, oral anticoagulation; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; VKA, vitamin K antagonist; VTE, venous thromboembolism.

One of the most critical limitations is the unsuitability of NOACs for patients with mechanical heart valves. The RE-ALIGN trial, which investigated dabigatran in this population, had to be terminated early due to a significantly higher risk of thrombo-embolic and bleeding events compared with warfarin. Consequently, VKAs remain the standard of care for these patients. Similarly, the use of NOACs in patients with mitral stenosis remains an area of uncertainty. The results of the INVICTUS trial, which investigated the use of rivaroxaban in patients with rheumatic heart disease and AF, found that rivaroxaban was inferior to warfarin in preventing stroke, systemic embolism, and cardiovascular death in these patients, reinforcing the continued reliance on VKAs in this population.

Another significant limitation of NOACs is their increased risk of gastrointestinal bleeding. Studies have shown that NOACs tend to cause more gastrointestinal bleeding compared with VKAs, especially in patients with pre-existing conditions such as peptic ulcer disease or in those over the age of 75. The gastrointestinal mucosal damage attributed to NOACs is thought to be due to their localized anticoagulant effect in the gastrointestinal tract, highlighting the need for careful patient selection and monitoring in high-risk groups.[11] Non-vitamin K antagonist oral anticoagulants have also shown poorer outcomes compared with VKAs in patients with the antiphospholipid syndrome who have triple positivity, a condition characterized by the presence of lupus anticoagulant, anti-cardiolipin antibodies, and antibodies against beta-2 Glycoprotein I. This group of patients, at particularly high risk for thrombo-embolic events, presents a unique challenge in anticoagulation management. Similarly, the use of NOACs is limited or impossible in patients with severe renal impairment or severe hepatic dysfunction.[12] These patients were often excluded from major clinical trials due to the heightened risk of drug accumulation and bleeding. In such populations, VKAs or dose-adjusted NOACs, with close monitoring, may be necessary, but these approaches are not always straightforward or effective. Extremes of body weight present a significant challenge in the use of NOACs. Specifically, patients with very low body weight (<50 kg) or very high body weight (>120 kg) can experience altered pharmacokinetics, which may impact the efficacy and safety of these drugs. For edoxaban, patients weighing 60 kg or less typically receive a reduced dose of 30 mg once daily. Apixaban dosing is adjusted for patients with a body weight of 60 kg or less if they also meet other criteria such as being older than 80 years or having impaired renal function. For dabigatran, dosing adjustments are generally not based on body weight, as trials included patients from 48 to 120 kg without significant differences in efficacy or safety. Similarly, rivaroxaban was studied in patients from 50 to over 120 kg, and no formal dose adjustment was required, though caution is advised at extreme body weights.[12] Drug interactions pose a challenge in the use of NOACs: while they have fewer interactions compared with VKAs, they remain susceptible to significant interactions with medications that influence P-glycoprotein and cytochrome P450 enzymes, necessitating thorough medication review and monitoring in patients on complex regimens.[12] Managing bleeding complications in patients on NOACs has been a significant concern since their introduction. Vitamin K antagonists can be reversed effectively using vitamin K or fresh frozen plasma, and their long-established use in clinical practice comes with well-defined protocols for handling bleeding. Although reversal agents, such as idarucizumab for dabigatran and andexanet alfa for FXa inhibitors, have since been developed for the NOACs, they are expensive and not universally available, which can limit timely access during emergencies and complicate the management of severe bleeding events compared with VKAs.[13] In summary, although NOACs represent a major advancement in anticoagulation therapy, their use still presents several challenges. Issues related to appropriate patient selection, bleeding risk, drug interactions, and cost must be thoughtfully addressed to maximize their benefits and ensure patient safety.

Future developments

The evolution of anticoagulation therapy is now at a critical juncture, driven by the need to overcome the limitations associated with NOACs. Among the most promising advances is the inhibition of FXI, a strategy rooted in the dual aim of reducing thrombotic risk while minimizing bleeding complications.[14] The concept of targeting FXI emerged from observations in both animal studies and clinical experiences with patients who have congenital FXI deficiency. These patients feature a reduced incidence of thrombotic events with only a mild bleeding tendency, suggesting that FXI plays a more crucial role in thrombosis than in normal haemostasis. This understanding has fuelled the exploration of FXI inhibitors as a novel class of anticoagulants. Factor XI inhibitors can potentially disrupt the propagation of thrombin generation, which is central to the formation and growth of thrombi, without significantly impairing normal haemostatic processes. This unique feature makes FXI inhibitors particularly attractive for clinical applications where current anticoagulants still present limitations, especially concerning bleeding risk. Several types of FXI inhibitors are currently under development, including antisense oligonucleotides (ASOs), monoclonal antibodies (mAbs), and small molecules. Their potential spans several high-risk clinical areas where traditional anticoagulants have limitations (*Figure 3*). In orthopaedic surgeries, such as total knee arthroplasty, FXI inhibitors have shown promising results in preventing VTE. The antisense oligonucleotide IONIS-FXIRX, in a Phase 2 trial, significantly reduced VTE incidence compared with enoxaparin. Monoclonal antibodies, such as, osocimab and abelacimab, have also demonstrated efficacy in this context. Additionally, the small molecule inhibitor milvexian, studied in the AXIOMATIC-TKR trial, was found to be as effective as enoxaparin in preventing VTE, with a lower rate of major bleeding. Beyond their promising application in orthopaedic surgery, FXI inhibitors are also being investigated in other high-risk settings, such as cancer-associated thrombosis and end-stage renal disease. In cancer patients undergoing chemotherapy, abelacimab and the recombinant mAb xisomab 3G3 are being studied for the prevention of catheter-associated thrombosis. In patients with end-stage renal disease

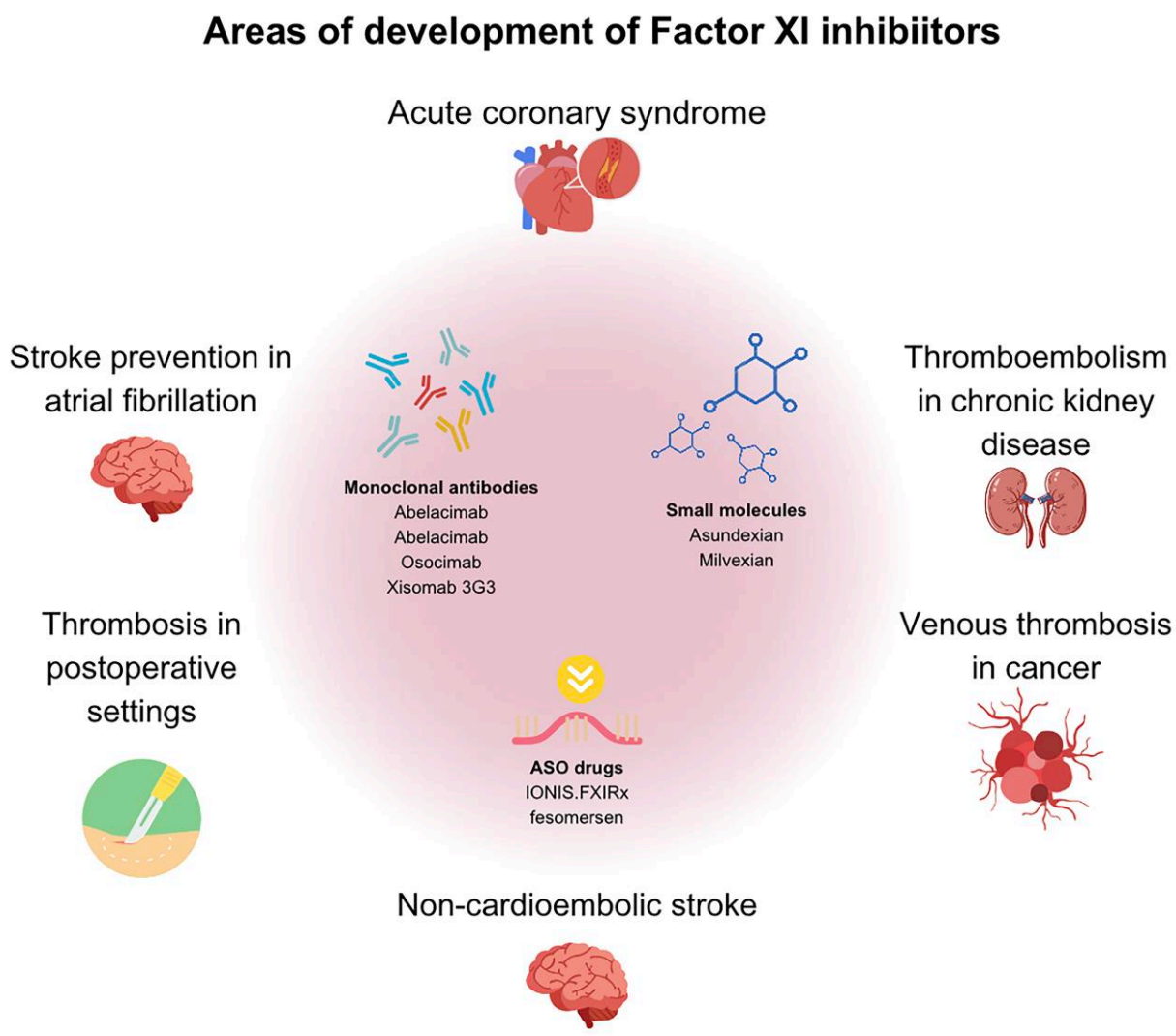

Figure 3 Future direction of anticoagulation therapy is focusing on the ongoing development of various types of Factor XI inhibitors, including antisense oligonucleotides, monoclonal antibodies, and small molecules. These agents are being explored in several high-risk clinical areas, aiming to overcome the limitations of traditional anticoagulants by providing safer and more effective options for preventing thrombotic events.

undergoing haemodialysis—a population at high risk for both thrombotic and bleeding events—the ASO IONIS-FXIRX has effectively reduced FXI activity without significantly increasing bleeding. Factor XI inhibitors are also being studied for stroke prevention in AF and secondary stroke prevention. The AZALEA-TIMI 71 Phase 2 trial demonstrated that both doses of abelacimab (90 and 150 mg monthly) were superior to rivaroxaban 20 mg daily in reducing bleeding events in patients with AF and a high CHA_2DS_2-VASc score. The trial was terminated early due to the unexpectedly significant benefit observed with abelacimab. Regarding small-molecule FXI inhibitors, although the OCEANIC-AF trial investigating asundexian has been recently discontinued due to insufficient efficacy, the LIBREXIA programme continues to evaluate milvexian across various clinical contexts, including AF, secondary stroke prevention, and post-myocardial infarction. Factor XI inhibitors are also being investigated in patients with non-cardioembolic stroke or transient ischaemic attack to assess whether, when combined with antiplatelet therapy, they can reduce the risk of recurrence. Preliminary data suggest that FXI inhibitors may offer additional protection with an acceptable safety profile, underscoring their potential expanding role in managing various thrombo-embolic conditions. Other minor but notable areas of investigation for FXI inhibitors include thromboprophylaxis in COVID-19 patients (e.g. EP-7041), prolonging central venous catheter patency, and use in extracorporeal membrane oxygenation, mechanical heart valves, and left ventricular assist devices.

Overall, FXI inhibitors represent a significant advancement in anticoagulation therapy, but their place in the medical armamentarium has still to be firmly established. By targeting a key factor that drives thrombin generation in pathological conditions without heavily impairing normal clotting, they have the potential to offer safer and more effective anticoagulation. As clinical trials progress, FXI inhibitors could redefine the standard of care, balancing thrombotic protection with minimal bleeding risks and

improving outcomes across a variety of patient populations. This hypothesis still needs, however, firm proofs of efficacy, which may vary considerably across the molecules and doses being tested, as well as therapeutic areas, both as an alternative to NOACs or—most likely—as an add-on therapy when current anticoagulants are not indicated.

Conclusions

Over the past 15 years, the NOACs have revolutionized anticoagulation therapy, offering significant improvements over traditional VKAs. Despite their success, current challenges—particularly managing bleeding risks, drug interactions, and the limitations in certain high-risk populations—have pointed towards future directions, where the most promising advance is the inhibition of FXI. This strategy is based on the dual aim of reducing thrombotic risk while minimizing bleeding complications, thus addressing gaps in anticoagulation therapy left by the NOACs. As research progresses, FXI inhibitors may offer safer and more effective treatment options, further enhancing the landscape of personalized anticoagulation care for patients at risk of thrombo-embolic events.

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Data availability

The data underlying this article are available in the article and in its online supplementary material.

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