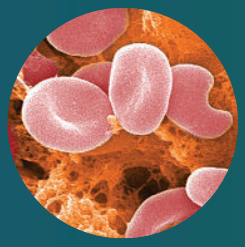

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Exploring Factor XI: A Paradigm Shift Towards Hemostasis-Sparing Anticoagulation

BIO Conference

The 2022 Biotechnology Innovation Organization (BIO) International Convention

The BIO International Convention took place in San Diego, CA, on 13–16 June 2022. BIO is the world's largest advocacy association representing member companies, state biotechnology groups, academic and research institutions, and related organizations across the United States and in 30+ countries.[1] More than 11,000 delegates from around the globe attended the BIO International Convention.[2]

The symposium, 'Exploring Factor XI: A paradigm shift towards hemostasis-sparing anticoagulation', included presentations from an expert panel of speakers comprising Rt. Hon. Lord Ajay Kakkar, Dr. Ophira Salomon, Dr. David Gailani and Ms. Mellanie True Hills. The panel encouraged delegates to consider unmet needs in anticoagulation, particularly in relation to the bleeding risk associated with current anticoagulant options. They went on to share the growing body of evidence supporting Factor XI (FXI) inhibition as a potential route to 'hemostasis-sparing' anticoagulation, including observations from individuals with congenital FXI deficiency, along with insights from the atrial fibrillation patient population who have expressed a need for 'stroke prevention without downsides.'

Anticoagulation: Who Is Not Being Treated?

Rt Hon. Professor Lord Ajay Kakkar, KBE PC
President of the Thrombosis Research Institute
London, England, UK

Key Messages

- Despite decades of progress with anticoagulation, a substantial burden of thromboembolic disease persists
- Modern anticoagulants, specifically DOACs, have been well validated in clinical trials but bleeding remains a significant concern
- Fear of bleeding, both real and perceived, underpins the ongoing under-utilization of anticoagulants in high-risk patients

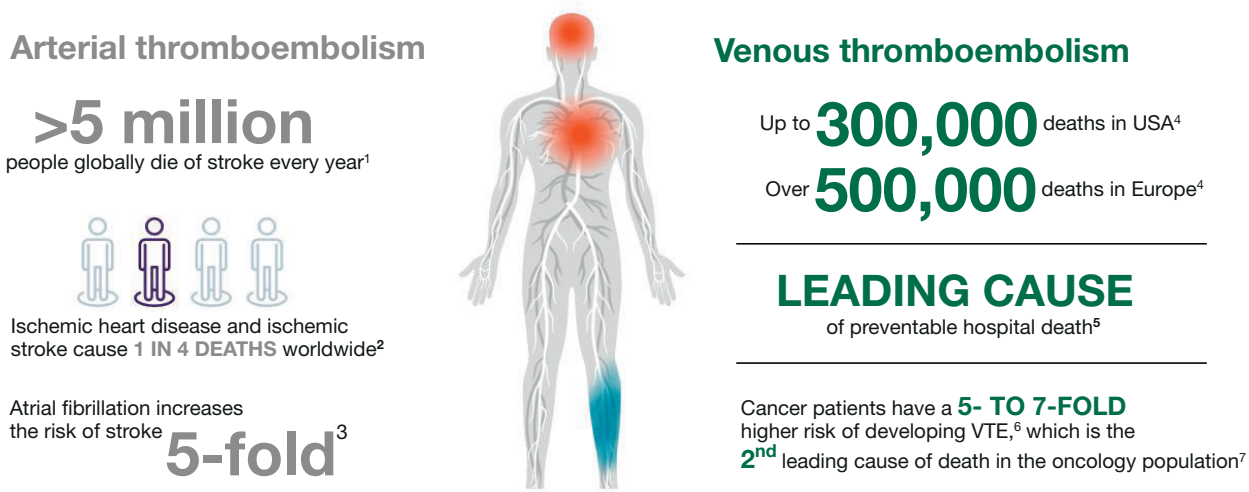
More than 1 in 4 people worldwide die from thromboembolic events.[3] Both arterial and venous thromboembolism represent a significant burden of disease with a high unmet need (Figure 1). Notably, this burden of disease persists today despite decades of research and progress in the management of thrombotic risk.

A pivotal study published in *The Lancet* in 1960 was the first to confirm the benefits of therapeutic anticoagulation for venous thromboembolism, demonstrating a dramatic reduction in recurrence and death amongst patients with pulmonary embolism (PE) who received unfractionated heparin (UFH).[4] In the mid-1970s, UFH (at lower doses) was also shown to be useful for the prevention of fatal PEs in the peri-operative setting.[5] With regard to arterial thromboembolism, it's been known for 20-25 years that the use of oral anticoagulants, specifically vitamin K antagonists such as warfarin, can substantially reduce the risk of stroke in the high-risk atrial fibrillation (AF) population.[6] More recently, direct oral anticoagulants (DOACs) have shown even better stroke protection in AF patients than warfarin.[7]

In view of the convincing trial data on stroke prevention with oral anticoagulants in patients with AF, it's important to understand the level of adoption of these agents in routine clinical practice. The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) registry[8] (a worldwide observational study of ~57,000 AF patients that sheds light on real-world anticoagulant treatment patterns and outcomes)

A pivotal study published in *The Lancet* in 1960 was the first to confirm the benefits of therapeutic anticoagulation for venous thromboembolism, demonstrating a dramatic reduction in recurrence and death amongst patients with pulmonary embolism (PE) who received unfractionated heparin (UFH).

Figure 1. Burden of disease from thromboembolism, with a focus on mortality. Presented at the 2022 BIO International Convention.



Data sources:
[1]Wendelboe AM, Raskob GE. Global burden of thrombosis: Epidemiologic aspects. *Circ Res* 2016 ;118(9):1340-7.
[2]World Stroke Organization. Feb 2, 2022. Global stroke fact sheet. https://www.world-stroke.org/assets/downloads/WSO_Global_Stroke_Fact_Sheet.pdf. Accessed July 7, 2022.
[3]Wolf P A, Abbott R D, Kannel W B. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch. Intern. Med*. 1987;147(9): 1561–4.
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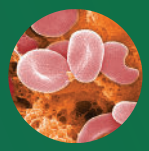
[6]Abdol Razak NB, Jones G, Bhandari M, Berndt MC, Metharom P. Cancer-associated thrombosis: an overview of mechanisms, risk factors, and treatment. *Cancers* 2018;10(10):380.
[7]National Blood Clot Alliance. Cancer and blood clots fast facts. Accessed July 7, 2022. https://www.stoptheclot.org/about-clots/cancer-and-blood-clots/cancer-and-blood-clots-fast-facts/.



has demonstrated a steady rise in the prescribing of anticoagulants, with DOACs increasingly taking the place of warfarin[9]. However, in the latest cohort, close to 30% of AF patients were still entirely untreated or receiving only antiplatelet agents,[9] which are known to be ineffective for stroke prevention in this population (Figure 2).

The primary reason for the underutilization of oral anticoagulants in this high-risk population is fear of bleeding. Patients with AF typically have a number of factors that increase their propensity for bleeding, including older age, concomitant chronic kidney disease and a history of bleeding.[10] Since currently available anticoagulants heighten bleeding risk even more, clinicians are understandably cautious about their use.

According to a separate GARFIELD-AF analysis, any form of oral anti-coagulation reduces all-cause mortality and reduces the risk of stroke but carries a 50% increase in major bleeding.[11] While DOACs perform better than warfarin with regard to both efficacy and safety, they still carry an appreciable bleeding risk, which remains a concern for today's prescribers. In a parallel observational study, the GARFIELD-VTE registry, in which ~11,000 patients presenting with acute venous thromboembolism (VTE) were followed for 3.5 years, it was shown that – despite the provision of therapeutic anticoagulation in up to 98% of these patients – the risk of recurrent VTE and bleeding remained notable.[12] Importantly, both these risks are greatly amplified in patients with cancer (both active and historic).[12] In the oncology population, the twin

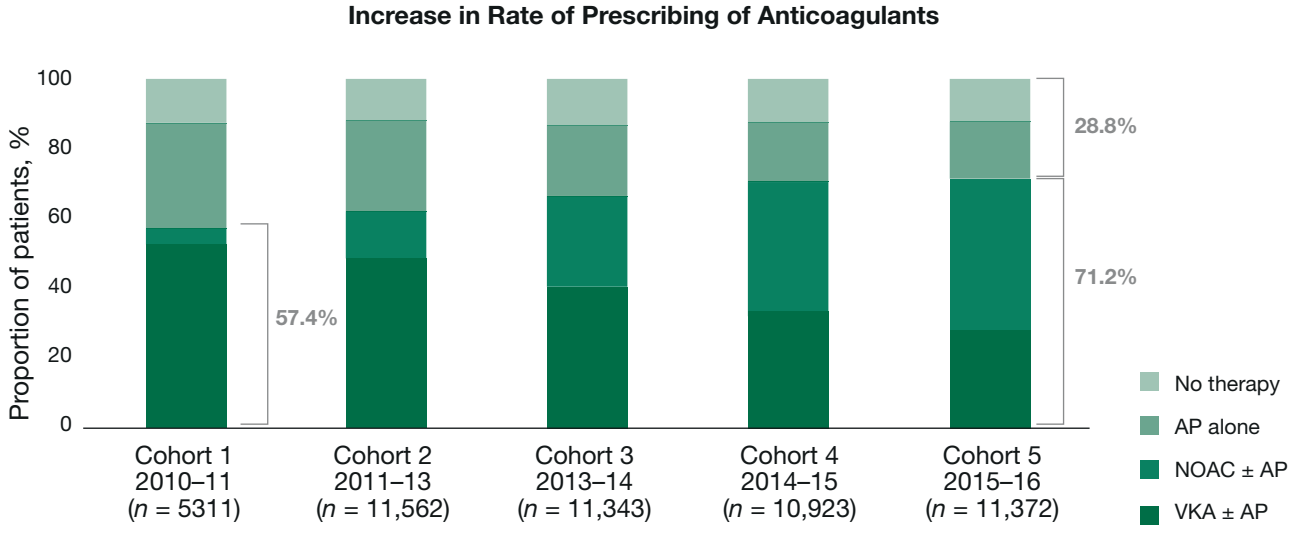
» However, in the latest cohort, close to 30% of AF patients were still entirely untreated or receiving only antiplatelet agents, which are known to be ineffective for stroke prevention in this population.

» Patients with AF typically have a number of factors that increase their propensity for bleeding, including older age, concomitant chronic kidney disease and a history of bleeding. Since currently available anticoagulants heighten bleeding risk even more, clinicians are understandably cautious about their use.

» According to a separate GARFIELD-AF analysis, any form of oral anticoagulation reduces all-cause mortality and reduces the risk of stroke but carries a 50% increase in major bleeding.

Figure 2. Trends in real-world usage of oral anticoagulants for stroke prevention in AF.

Real-world record of change: Evolution in baseline treatment for patients enrolled in sequential cohorts



Data source: *Adapted from*: Camm AJ, Accetta G, Ambrosio G, *et al*. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. *Heart* 2017;103(4):307-314.
Abbreviations: AP, antiplatelet agents; NOAC, non-vitamin-K orial anticoagulants; VKA, vitamin K antagonist

hazards of recurrent cancer-associated thrombosis (CAT) and major bleeding represent a real conundrum for clinicians, who are acutely aware of the need to protect their patients from both of these outcomes.

In clinical practice, bleeding (of any type) is not a benign occurrence. While major bleeding is associated with the greatest risk of death among participants in the GARFIELD registry, clinically relevant non-major bleeding (CRNM) and minor bleeding both carry their own heightened risk of all-cause mortality.[12] Figure 3 demonstrates how, despite the availability of DOACs, the risk of bleeding – both real and perceived – has resulted in the marked underutilization of anticoagulation among high-risk patients in several different clinical settings.[13-15]

While there is no doubt that substantial progress in anticoagulation has been made over the years – and DOACs have been well validated for their efficacy and safety – there remains a high unmet clinical need driven by the risk of bleeding. This is why the prospect of Factor XI inhibitors, with their potential to provide hemostasis-sparing anticoagulation, is so exciting.

Figure 3. Underutilization of anticoagulation in high-risk patient populations.

Risk of major bleeds remains a deterrent to optimal anticoagulant prescribing

Even with DOACs available, recent studies show no anticoagulation at all was prescribed to:

50% **of outpatients at high risk of stroke[13]** (CHA2DS2-VASc score ≥5)

42% **of surgical inpatients at risk of VTE[14]**

40% **of inpatients with pre-existing AF[15]** and a CHA2DS2-VASc score of ≥2 (even though only 5% had documented contraindications)

60% **of non-surgical inpatients at risk of VTE[14]**

What Can We Learn From Genetically FXI Deficient Patients?

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Institute of Thrombosis & Hemostasis
Sheba Medical Center, Israel

Key Messages

- Spontaneous bleeding does not occur in people with severe FXI deficiency
- Lower FXI levels (<50%) appear to protect against cardiovascular & venous thromboembolic events, while higher FXI levels are thrombogenic
- These observations indicate the potential of pharmacological FXI suppression to provide hemostasis-sparing anticoagulation

Ensuring appropriate anticoagulant treatment can considerably reduce morbidity and mortality. However, antithrombotic treatment is associated with a high risk of bleeding. Therefore, physicians must walk a fine line when deciding on a suitable antithrombotic agent, i.e., one that guarantees hemostasis without the risk of bleeding or thrombosis.

The need for safer anticoagulant therapy is urgent, and targeted

direct inhibition of factor XI (FXI) can produce an efficient antithrombotic effect without significantly compromising hemostasis. We know that spontaneous bleeding does not occur in patients with congenital FXI deficiency, even in those with severe deficiency (i.e., FXI activity <20% of normal). The same is true of patients with severe FXI deficiency who develop inhibitors following exposure to plasma-derived products. The situation of these patients differs from that of patients with hemophilia (A and B, FVIII and FIX deficiency, respectively), who experience hemarthrosis, soft-tissue bleeds, intracranial bleeding, gastrointestinal bleeding, etc.

FXI deficiency is most frequently diagnosed incidentally based on prolonged activated partial prothrombin time detected during a pre-surgical workup. In fact, FXI deficiency may not be diagnosed for years until a patient undergoes testing before surgery, and it is rarely diagnosed because of trauma-related bleeding or family history. What is important, however, is that bleeding in patients with severe FXI deficiency is easily managed and does not require FXI replacement or blood products. Prophylaxis with antifibrinolytic agents is usually effective for procedures associated with a mild-to-moderate risk of bleeding. For major procedures, antifibrinolytic treatment with single and low-dose rFVIIa is sufficient. As such, blood products are not required for the treatment of patients with severe FXI deficiency.

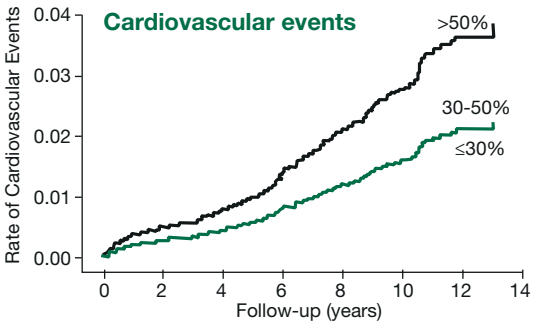
» The need for safer anticoagulant therapy is urgent, and targeted direct inhibition of factor XI (FXI) can produce an efficient antithrombotic effect without significantly compromising hemostasis.

In Israel, we know that the frequency of severe FXI deficiency among Ashkenazi Jews is 1 in 450, and that – 1 in 10 individuals carry FXI. FXI deficiency is 2 to 20 times more frequent than expected in certain populations, thus reinforcing the assumption that patients with this condition are unlikely to bleed spontaneously.[16]

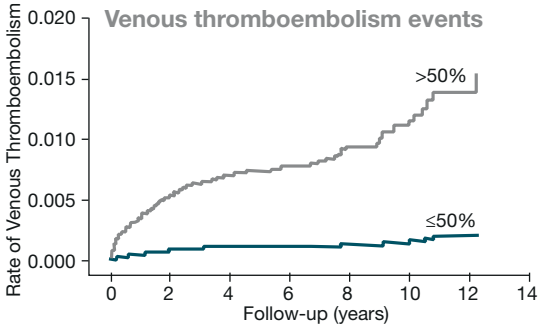
While high levels of FXI are associated with myocardial infarction, ischemic stroke, and venous thrombosis, low levels reduced the frequency of these conditions. In patients with severe FXI deficiency, FXI concentrate was found to be associated with thrombotic events, probably because of traces of FXIa. This was particularly true of elderly patients with atherosclerotic risk factors.[17] Gamma globulin, which is used in many diseases, was found to increase the risk of thromboembolic events, presumably because of contamination by traces of FXIa, which are difficult to separate chromatographically from gamma globulin.[18] Inhibition of FXI in animal models based on various modalities (knockout gene, antisense oligonucleotide, neutralizing antibodies, peptidomimetic inhibitors) protects against arterial and venous thrombosis, thus confirming the role of FXI in thrombosis.[19] Consequently, inhibiting FXI can protect against

Figure 4. Correlation between FXI levels and risk of thromboembolic events

Age-adjusted function curves of patients with normal FXI activity (>50%) and FXI deficiency (≤50%)



Age-adjusted survival function curves of patients with normal factor XI activity (>50%), mild deficiency (30%-50%), and moderate–severe deficiency (30%) for future cardiovascular events.



Age-adjusted survival function curves of patients with normal factor XI activity (>50%) and factor XI deficiency (≤50%) for future VTE events.

8958 patients with normal FXI activity (>50%) and 1232 patients with FXI deficiency (<50%)

Consistent with Loeser WD, et al., Ohio Med 1988.

Data source: *Adapted from* Preis M, Hirsch J, Kotler A, *et al*. Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. *Blood* 2017;129:1210-1215.

thrombosis without causing bleeding events.

FXI deficiency appears to protect against cardiovascular and venous thromboembolic events. In their 2017 study, Preis *et al.*[20] found that, after following patients with FXI deficiency at <50% of normal for several years, there was a striking difference in terms of cardiovascular protection between patients with 30-50% of normal FXI activity in blood and those with >50%. The same was true for venous thromboembolic events, that is, a protective effect was observed in patients with ≤50% (see Figure 4). These findings are consistent with those of Loesser *et al.* in 1988, who reported that Ashkenazi Jews tend to live longer because of the protective effect of FXI deficiency.[21]

» Consequently, inhibiting FXI can protect against thrombosis without causing bleeding events.

Given the above, we can see why FXI inhibition is being considered for antithrombotic treatment. We know that spontaneous bleeding does not occur in FXI–deficient patients and that FXI deficiency protects against ischemic stroke and venous thromboembolism. In addition, most patients with hereditary FXI deficiency who are undergoing surgery do not require FXI replacement but can be managed with antifibrinolytic treatment and, occasionally, the addition of rFVIIa in a single, low dose, unlike those with hemophilia A and B. Finally, in clinical trials, FXI inhibition has been associated with a substantial reduction in the frequency of venous thromboembolism compared with enoxaparin in patients undergoing total knee replacement. Therefore, we can see that the dream of hemostasis-sparing anticoagulation is on the way to becoming a reality.

What Do We Know Mechanistically About Factor FXI?

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Key Messages

- The full potential of current anticoagulant therapy is not fully realized because of the inherent risk of bleeding
- As demonstrated in preclinical models, FXI appears to play an important role in pathological thrombosis but has a limited role in hemostasis, thus attracting significant interest as a potential new anti-thrombotic target
- Clinical studies in patients undergoing total knee replacement have shown that FXI inhibition with an ASO (anti-sense oligo-nucleotide), a monoclonal antibody (abelacimab), or a small molecule active site inhibitor (milvexian) achieve anti-thrombotic efficacy that's superior to standard-of-care enoxaparin

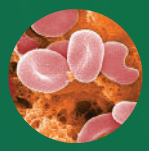
In 1977, Robert Gwyn Macfarlane, the first investigator to describe the plasma coagulation cascade in the 1960s, discussed the implications of the delicate balance between clotting at a site of blood vessel injury and maintaining blood in a liquid form where blood vessels are intact:[22]

"Our dependence on this balanced compromise is brought home when it goes wrong. Haemorrhagic disorders, though rare, have received more interest since increasing knowledge has allowed them to be accurately identified and effectively treated. However, it is thrombosis – haemostasis in the wrong place – that claims increasing attention because of its rising incidence and often fatal consequences. The key to the problem of thrombosis lies in a deeper understanding of the negative aspect of haemostasis…"

The idea that bleeding and thrombosis represent extremes on a continuum – with insufficient clotting leading to bleeding at one end and unwanted excess clotting at the other end – has dominated the development of anticoagulants for over six decades. The underlying implication in this hypothesis is that, to reduce the risk of thrombosis, it is inevitable that the risk of bleeding must rise.

Central to this concept is a plasma-based enzyme system that is required for achieving physiologic hemostasis following vessel injury. This system entails a series of reactions involving vitamin K-dependent enzymes, set off by the exposure of intravascular blood to sub-endothelial tissue factor, and culminating in the formation of

» However, it is thrombosis – haemostasis in the wrong place – that claims increasing attention because of its rising incidence and often fatal consequences.



the enzyme thrombin. For the last 60+ years, all anticoagulants have targeted this critical system, starting with heparin and warfarin, which target multiple components of the system and, more recently, DOACs that target FXa and thrombin.[23] Prescribers of current anticoagulants are highly familiar with the concept of a narrow therapeutic window (Figure 5), where the goal is to achieve 'adequate' protection from thrombosis while keeping the bleeding risk at an 'acceptable' level.[24]

The full potential of anticoagulation therapy can never be realized because it is simply too dangerous and, because of increased bleeding risk, some patients with pre-existing conditions that predispose them to bleeding cannot be treated with anticoagulation at all.[24]

In recent years, great interest has arisen in Factor XI, a coagulation enzyme that seems to play a prominent role in thrombosis – as shown by the reduced risk of thromboembolic events in the FXI deficient population – and yet appears to have only a limited role in physiological hemostasis.

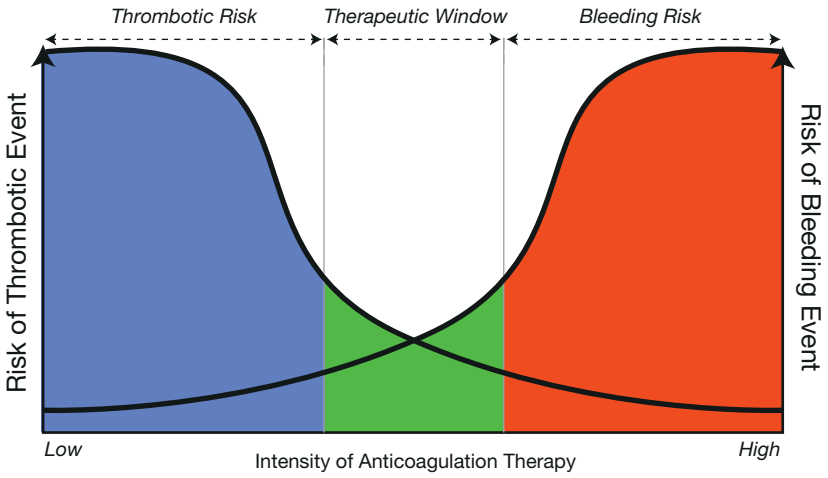
This dissociation between the pro-coagulant and the pro-thrombotic effect of FXI makes it a worthy target for exploration.[25] A series of preclinical studies demonstrated that, in FXI-deficient mice, hemostasis still occurs normally after vessel injury (similar to wild-type mice) but, importantly, clots that occlude blood vessels (thrombi) do not form.[26,27] These findings added weight to the idea that suppressing FXI could help to avoid thrombosis without an increased risk of bleeding.

Therapeutic FXI inhibitors were therefore put to the test in patients undergoing total knee arthroplasty (TKA), a clinical setting frequently used for initial assessment of new anticoagulants. This is because the surgery frequently results in small clots forming in and distal to the popliteal vein. While few patients will go on to develop clinically significant deep vein thrombosis (DVT), venograms can be utilized to detect these small clots, making an anticoagulant proof-of-efficacy study feasible with a relatively small number of participants.

One therapeutic strategy currently under investigation uses an antisense oligonucleotide (ASO) to reduce expression of FXI in the liver. In an open-label, parallel-group study,[28] 300 patients undergoing TKA were randomized to receive either a 200mg or 300mg dose of ASO. Both were compared to enoxaparin. Because of the time taken to achieve its full effect, ASO was started 4-5 weeks prior to surgery. A key feature of this study is that patients were under the full anticoagulant effect of the ASO at the time of surgery, something that isn't contemplated with warfarin or DOACs because of the high likelihood of excessive bleeding. Bilateral venography was performed 8-12 days post-surgery. Thirty percent of patients in the enoxaparin group had clots detectable by venography (none had symptomatic DVT). ASO at the 200mg dose was comparable to enoxaparin, but when the dose was increased to 300mg, few clots were detected (Figure 6). While the study was not powered to study bleeding rates, no major bleeding or clinically significant bleeds were noted in this trial.[28]

Another method for FXI inhibition currently under study involves abelacimab, a monoclonal antibody that not only inhibits the activity of FXIa (the activate form of FXI) but also binds to FXI and locks it in a zymogen (inactive precursor) conformation, preventing its conversion

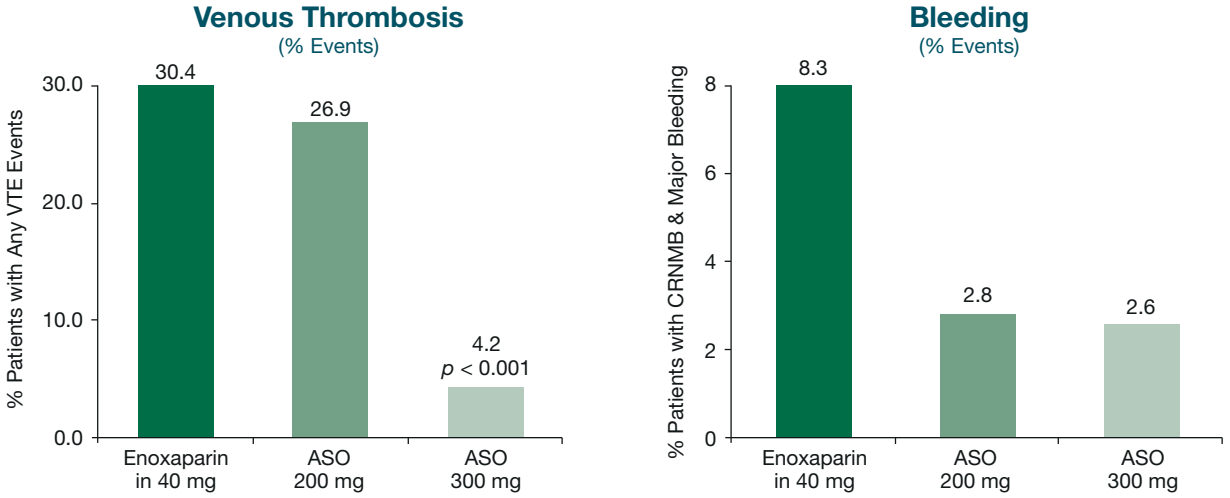
Figure 5. The narrow therapeutic window of current anticoagulation



Adapted from: Angiolillo DK, Ferreiro JL, Price MJ, *et al*. Platelet function and genetic testing. *J Am Coll Cardiol* 2013;62(17):s21-s31.

» Prescribers of current anticoagulants are highly familiar with the concept of a narrow therapeutic window (Figure 5), where the goal is to achieve 'adequate' protection from thrombosis while keeping the bleeding risk at an 'acceptable' level.

Figure 6. ASO Factor XI inhibitor versus enoxaparin in TKA model[28]

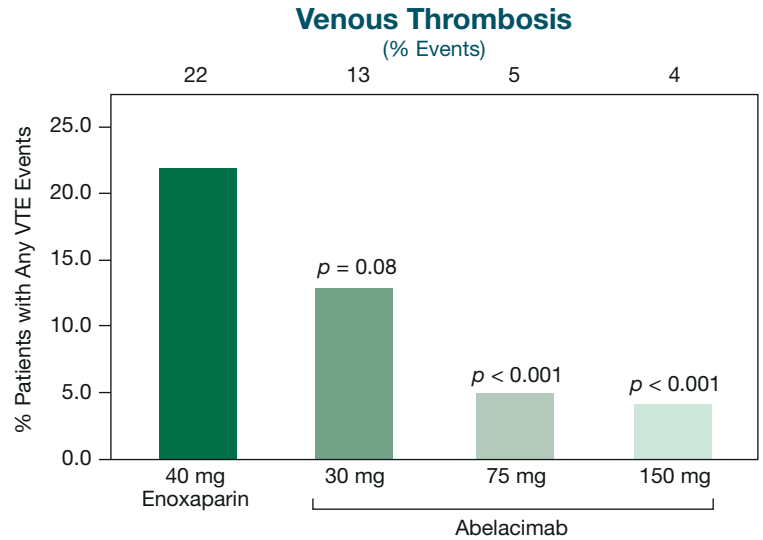


Data source: Büller HR, Bethune C, Bhanot S, *et al*. Factor XI Antisense Oligonucleotide for prevention of venous thrombosis. *N Engl J Med*. 2015;372(3):232-240.

to FXIa. In a Phase 2 efficacy study[29] 412 patients undergoing TKA were randomized to receive a single IV dose of abelacimab (30 mg, 75 mg or 150 mg) 12 hours post-operatively or 40mg of daily subcutaneous enoxaparin. All three abelacimab doses achieved rapid and durable suppression of FXI in the plasma. A clear dose response was seen, with the 150mg dose of abelacimab reducing the incidence of clots by 80% compared with enoxaparin (Figure 7). [29] As with the ASO trial, this study was not powered to demonstrate bleeding rates, but no safety signals were seen, and bleeding rates were minimal in all arms of the study.[29]

The promise of FXI as an anti-thrombotic target is based on the fact that it plays only a peripheral role in the Tissue Factor-driven process

Figure 7. Abelacimab (monoclonal antibody Factor XI inhibitor) versus enoxaparin in TKA model[29]



Data source: Verhamme P, Yi BA, Segers A, *et al*. Abelacimab for prevention of venous thromboembolism. *N Engl J Med*. 2021;385(7):609-617.[29]

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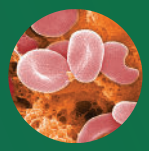
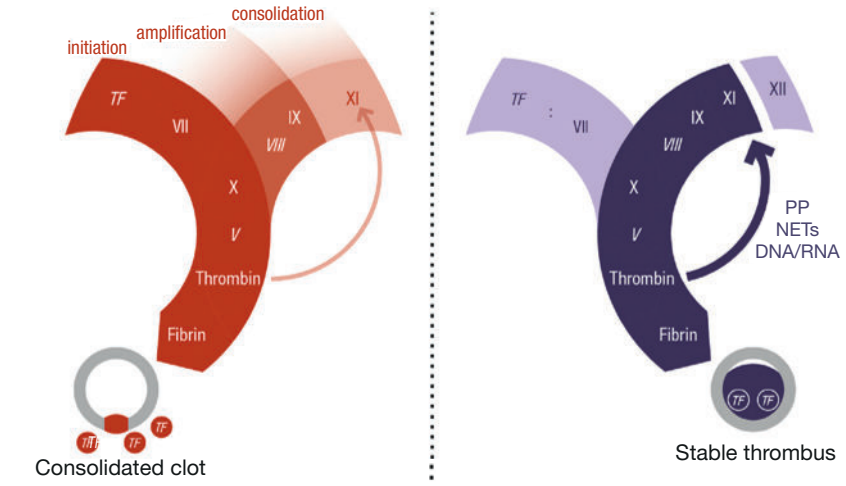


» The promise of FXI as an anti-thrombotic target is based on the fact that it plays only a peripheral role in the Tissue Factor-driven process of physiological hemostasis, but a pivotal role in formation and growth of pathological thrombosis. Thus, it seems possible to dissociate an anti-thrombotic effect from an anti-hemostatic effect, challenging the decades-old paradigm.

of physiological hemostasis, but a pivotal role in formation and growth of pathological thrombosis (Figure 8).[30] Thus, it seems possible to dissociate an anti-thrombotic effect from an anti-hemostatic effect, challenging the decades-old paradigm.

Figure 8. Mechanisms in physiological hemostasis versus pathological thrombosis[30]



Adapted from Hsu C *et al*. *J Am Coll Cardiol*. 2021;78(6):625-631.

What Is The Patient Perspective?

Mellanie True Hills
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American Foundation for Women's Health & StopAfib.org
Decatur, Texas

Key Messages

- Living with atrial fibrillation (afib) can take a huge toll on patients and their families
- Stroke is feared most of all: patients will accept 4-5 bleeds per year to avoid a stroke. In contrast, physicians are seen as being more focused on the risk of bleeds
- Improved patient education and greater involvement in shared patient / physician decision-making would be an important step towards greater adherence with anticoagulant therapy
- Ultimately, patients want *"stroke prevention without downsides"*

Living with atrial fibrillation (afib), while being different for every patient, takes a physical, emotional, and financial toll on patients and their families. This was highlighted by responses to online forums of 1,000 people living with afib, where the overall impact of afib on quality of life was shown to be profound and patients often find it challenging to navigate their care.

While patients fear both strokes and bleeds, they fear stroke most of all, seeing it as a "fate worse than death". Patients are typically willing to accept 4-5 (non-major) bleeds to avoid a single stroke. In contrast, physicians may be perceived as being more concerned about bleeds, highlighting a potential disconnect. Nonetheless, patient adherence to anticoagulant medication can often be suboptimal, primarily because they are also worried about bleeds, feel uninformed about the need for anticoagulation or may feel uninvolved in the prescribing decision.[31]

» Patient adherence to anticoagulant medication can often be suboptimal, primarily because they are also worried about bleeds, feel uninformed about the need for anticoagulation or may feel uninvolved in the prescribing decision.

What is it like to live with atrial fibrillation (afib)?

Can be like running a marathon 24 hours/day

Is different for every patient

Can take a huge toll on you, and your family – physically, emotionally, and financially

When afib patients were asked their thoughts regarding warfarin, they expressed concerns about the frequent blood draws and narrow therapeutic window. There were also concerns about interactions with foods, supplements, and/or other medications. The biggest concern around warfarin use was the risk of bleeds associated with falls or other injuries. The concerns were slightly different in relation to DOACs. Some patients expressed concern about affordability and insurance coverage, as well as uncertainty around which of the available DOACs may be most appropriate for them. As with warfarin, bleeds were also a prevailing worry.[31]

All these concerns can lead to adherence issues, which is why transparent and empathetic patient education and shared decision-making is vitally important. When asked what can make the lives of people living with afib easier, the response was clear: "*stroke prevention without downsides*".[31]

Disclosures

Professor Lord Kakkar has received research support and personal fees from Bayer, Sanofi and Anthos Therapeutics. Dr Ophira Salomon has no conflicts of interest to report. Dr David Gailani has received funding from the US National Institutes of Health for research in the roles of FXI and other plasma proteins in thrombosis and inflammation; Consulting fees from companies with interests in targeting FXI or FXIa for therapeutic purposes (Anthos Therapeutics, Aronora, Bayer, Bristol-Myers Squibb, Ionis, Janssen, and Novartis), including Bayer, the sponsor of the PACIFIC-AF trial, but unrelated to asundexian. Dr Gailiani serves or has served on boards of clinical trials of FXIa inhibitors run by Bristol-Myers Squibb and Janssen and has received travel honoraria to attend meetings at the invitation of Anthos Therapeutics. Mellanie True Hills has no conflicts of interest to report.

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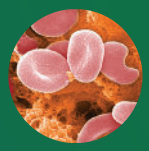

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