On A Scale of I to X, They're an XI…A Review of the Newest Anticoagulants, The Factor XIa Inhibitors

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Objectives:

- Discuss principles of anticoagulation therapy with brief descriptions of the clotting cascade and current anticoagulants.
- Examine the mechanism of action of the new oral anticoagulants.
- Summarize the current published literature and discuss the rationale for future larger trials.

Background:

The Centers for Disease Control and Prevention (CDC) estimate that a thrombotic event affects 900,000 Americans each year, resulting in nearly 100,000 deaths directly attributed to a blood clot[1]. Anticoagulant medications are widely prescribed to reduce the risk of thrombotic events in high-risk patients and can be found in a variety of clinical scenarios spanning the healthcare spectrum. Indications that place patients at higher risk for thrombotic events include atrial fibrillation, recent surgery, hospitalization, prolonged immobility, previous venous thromboembolic events or arterial thrombotic events, obesity (BMI > 30), pregnancy or a history/current diagnosis of cancer. While anticoagulants have shown significant benefits, they also have risks to be considered, mainly increased bleeding. Some factors that increase bleeding risk include age greater than 65 years, renal or liver dysfunction, uncontrolled hypertension, history of stroke, alcohol use and/or drug use. To mitigate this risk, while maintaining efficacy, a new class of potential anticoagulants has been developed. The following discussion will evaluate the current evidence available for the factor XIa inhibitors.

The Clotting Cascade:

There are many circumstances including illnesses, surgeries, and other medical conditions, where the body is in a balancing act between normal hemostasis (a protective mechanism used to prevent excess blood loss following injury) and pathologic thrombosis (unwanted blood clots inside blood vessels)[4]. The process of plasma coagulation in our blood is made up of multiple enzyme activation events, in which serine proteases activate proenzymes and procofactors in a process that is known as the clotting cascade[4]. The ultimate outcome of the cascade is the polymerization of fibrin and the activation of platelets, leading to a blood clot. The clotting cascade has two pathways of initiation: the tissue factor (TF) pathway (also known as the extrinsic pathway) and the contact pathway (also known as the intrinsic pathway) and can be seen in figure 1.

Initiation of the TF (extrinsic) pathway occurs when the "extrinsic" cell-surface membrane protein called tissue factor, also known as factor III or thromboplastin, is exposed to blood plasma. A common mechanism for this to happen is via trauma to the endothelium. Once the TF is exposed to the plasma, it

binds with factor VIIa forming a complex (also called the extrinsic tenase and abbreviated as TF:VIIa), which is an extremely potent activator of coagulation[4]. The TF:VIIa complex later activates two substrates in the cascade, factor IXa and factor Xa, which is where the extrinsic and intrinsic pathways come together (also known as the common pathway).

The contact (intrinsic) pathway is where this discussion will focus more time on, as this is the pathway related to the new anticoagulant class's proposed mechanism. The contact pathway is initiated by factor XII after exposure to an *ex vivo* or *in vivo* activator which leads to a conformational change and generates slight activation of XIIa[4]. Examples of *ex vivo* activators include artificial surfaces such as tests tubes, cardiopulmonary bypass machines, infusion lines used during dialysis and extracorporeal membrane oxygenation (ECMO). While there have been several proposed naturally occurring *in vivo* activators, the precise mechanisms have not been definitively identified. Some suspects include specific proteins on mammalian cell surfaces, extracellular nucleic acids, inorganic polyphosphate (polyP), misfolded proteins, glycosaminoglycans and bacterial surface proteins[4]. Also involved and required in the process are two proteins called high-molecular weight kininogen (HK) and plasma prekallikrein (PK). Factor XIIa activates PK to kallikrein, followed by further reciprocal activation of factor XII by kallikrein and PK by factor XIIa resulting in a positive feedback loop. Upon further generation of factor XIIa, the next substrate activated in the clotting cascade is factor XI to XIa which then converts factor IX to IXa. Similar to the TF pathway, a complex (also called the intrinsic tenase) is formed by factor IXa and factor VIIIa following the proteolysis of factor IX to IXa via factor XIa. This in turn activates factor X to factor Xa, which again is the common pathway where the extrinsic and intrinsic pathways meet. Table 1 below shows some commonly used anticoagulants and describes where each medication works mechanistically in the clotting cascade.

Figure 1: Clotting Cascade[3]:

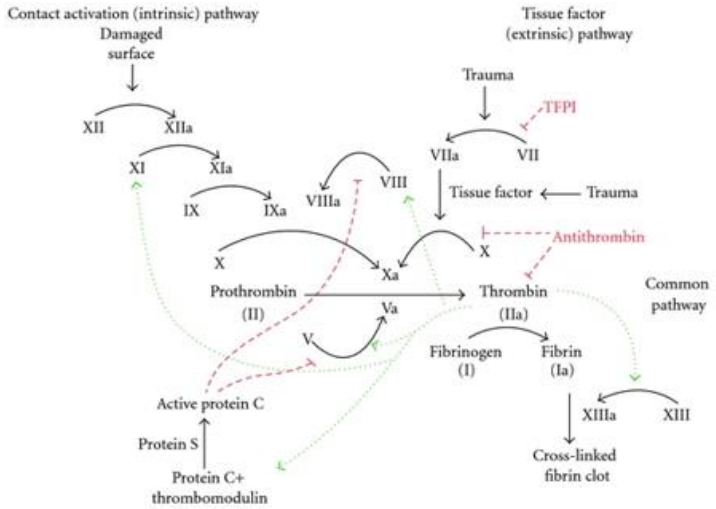

Table 1: Common Current Anticoagulant Medications

Medication Class	Medication Name(s)	Mechanism	Clinical Pearls
Vitamin K Antagonist	Warfarin	Inhibits vitamin K epoxide reductase (VKOR), which is needed for the activation of the vitamin K dependent clotting factors II, VII, IX and X, as well as protein C and S	• Administered orally • Requires frequent monitoring of INR due to its narrow therapeutic index • Effect influenced by many interactions including other medications, diet, and genetics
Heparin anticoagulant	Unfractionated heparin (UFH)	Creates a complex with antithrombin III and inactivates a variety of clotting factors downstream in the cascade, especially factors IIa (thrombin) and Xa	• IV medication that has a rapid onset and a short half-life • Monitored via activated partial thromboplastin (aPTT), activated clotting time and anti-factor Xa activity
Low molecular weight heparins (LMWH)	Enoxaparin	Similar to UFH with slight differences, including being less effective at inhibiting factor IIa and acting mostly via inhibition of factor Xa due to the smaller molecular structure	• Administered by subcutaneous injection and can be measured using anti-factor Xa levels • LMWH has a longer half-life than UFH therefore monitoring is generally not warranted except in certain conditions such as pregnancy, obesity, or renal failure
DOACs:			
Factor Xa Inhibitors	Apixaban, rivaroxaban, edoxaban	Directly inhibits factor Xa which causes inhibition of the cleavage of prothrombin to thrombin	• Administered orally • Edoxaban must be preceded by 5-10 days of parenteral anticoagulation if indication is VTE treatment • Avoid edoxaban in patients with nonvalvular atrial fibrillation and CrCl > 95 mL/minute due to reduced efficacy
Direct thrombin inhibitors	Dabigatran	Directly inhibits thrombin and therefore inhibiting cleavage of fibrinogen to fibrin	• Prodrug that is administered orally

*INR = International normalized ratio

The New Novel Anticoagulants:

New and promising anticoagulation therapies are currently being studied and work through inhibiting the intrinsic (and thrombin-feedback) pathway. Factor XIa is part of the intrinsic pathway of the clotting cascade and participates in tertiary amplification of thrombin generation. Factor XIa is thought to contribute to clot progression, which might lead to vessel occlusion and pathological manifestations of thrombosis, but, in contrast to factor IX and factor VIII, has only a minor effect on clot consolidation during hemostasis[13]. The plasma serine protease zymogen factor XI is activated to factor XIa after initiation of the contact activation pathway via factor XIIa and during the amplification phase as part of a positive feedback loop through activation by thrombin[2]. It has been demonstrated in epidemiologic studies that individuals with hereditary severe factor XI deficiency confer protection against both ischemic stroke and deep vein thrombosis (DVT) but rarely do these individuals have spontaneous bleeding[14]. Additionally, some data suggest that they have lower rates of cardiovascular events, including cardioembolic stroke[13]. Thus, it has been hypothesized that the inhibition of factor XI/XIa, by blocking the tertiary amplification of thrombin generation, might uncouple thrombosis prevention from normal hemostasis, allowing maximal anticoagulation efficacy without the increased bleeding risk[2]. This type of novel anticoagulation approach has the potential to expand the health benefits of anticoagulation therapy to a much wider set of patients (such as those at severe risk of bleeding from current therapies) in a safer and more effective manner than what is currently available.

Early animal model studies relied on using therapy with antisense oligonucleotides (ASO) to inhibit the biosynthesis of factor XI[2]. These oligonucleotides specifically target factor XI mRNA and cause its degradation, leading to a dose-dependent decrease in factor XI levels which is a proposed mechanism to cause decreased risk of thrombosis with less risk of bleeding compared to conventional therapies. One study using ASO in baboons showed that reducing the factor XI plasma levels by as little as 50% was sufficient to cause measurable reductions in thrombus propagation, which suggested that relatively modest reductions in plasma factor XI may be sufficient to protect against at least some types of thrombosis[2]. One downfall of using the ASO-mediated inhibition that was discussed during the animal model studies was the relatively slow-onset of action as well as possibly lower antithrombotic efficacy compared to anticoagulants that target the common pathway[2]. In 2015 a second-generation ASO drug called FXI-ASO was studied in comparison to enoxaparin for efficacy and safety in a phase II, randomized trial that included 300 patients undergoing elective total knee arthroplasty (TKA)[15]. The primary outcome was venous thromboembolism (VTE), and the principal safety outcome was major or clinically relevant nonmajor bleeding. The primary efficacy outcome occurred in 36 of 134 patients (27%) who received the 200 mg dose of FXI-ASO, in 3 of 71 patients (4%) who received the 300 mg dose of FXI-ASO, and in 21 of 69 patients (30%) who received enoxaparin 40 mg daily. The 200 mg regimen was noninferior, and the 300 mg regimen was superior, to enoxaparin ($P<0.001$)[15]. Bleeding occurred in 3%, 3%, and 8% of the patients in the three study groups, respectively. Due to the long onset of action of FXI-ASO, the drug required initiation 36 days before the surgery, which was aptly noted to be a limitation of the drug therapy. However, this new study information showed efficacy in preventing VTE with potentially lower bleeding risk when compared to a commonly prescribed therapy and inspired reason to continue investigation into future drug developments for factor XIa inhibition.

Current Agents Under Investigation:

Osocimab:

One of the first new medications introduced and studied in this novel class of anticoagulants was osocimab. Osocimab is a fully human monoclonal immunoglobulin G1 antibody that binds adjacent to the active site of factor XIa and prevents it from activating factor IX[9]. After intravenous (IV) infusion in healthy volunteers, osocimab had a geometric mean time to maximum plasma concentration of one to four hours and a half-life of 30 to 44 days, thereby enabling single-dose administration for surgical thromboprophylaxis[10]. There are important differences between osocimab and the original ASO therapy. First, mechanistically osocimab inhibits factor XIa, whereas the ASO blocks hepatic synthesis of factor XI, thereby reducing the amount available for activation. Second, osocimab rapidly inhibits factor XIa activity as evidenced by the dose-dependent increase in the activated partial thromboplastin time ratios within two hours after its infusion, whereas it takes several weeks for the ASO to lower factor XI to therapeutic levels[9,15].

One of the first published studies for this new class of anticoagulants was the FOXTROT trial (Effect of Osocimab in Preventing Venous Thromboembolism Among Patients Undergoing Knee Arthroplasty) that was published in January of 2020[8]. The FOXTROT trial was a randomized, open-label, multi-center, adjudicator-blinded, phase II noninferiority trial. The study included adults who underwent TKA between October 2017 to August 2018 and followed up until January 2019. Included patients in the study were randomized to receive either single IV osocimab postoperative doses of 0.3 mg/kg, 0.6 mg/kg, 1.2 mg/kg, or 1.8 mg/kg; preoperative doses of 0.3 mg/kg or 1.8 mg/kg; or 40 mg of subcutaneous enoxaparin once daily or 2.5 mg of oral apixaban twice daily for at least 10 days or until venography. Each osocimab dose was administered as a single, 60-minute, IV infusion in a dose-blinded manner. The primary outcome investigated was VTE incidence between 10 and 13 days postoperatively and was assessed by mandatory bilateral venography performed 10 to 13 days after surgery or confirmed symptomatic DVT or pulmonary embolism (PE), with a 5% noninferiority margin compared with enoxaparin having been chosen. No statistical hypothesis was defined for the comparison with apixaban because that was considered to only be exploratory, so only 2-sided 90% confidence intervals (CI) were calculated. Six hundred patients were included in the per-protocol population used for the primary analysis. The primary outcome occurred in 18 patients (23.7%) receiving 0.3 mg/kg (P=0.14), 8 (15.7%) receiving 0.6 mg/kg (P=0.01), 13 (16.5%) receiving 1.2 mg/kg (P=0.01), and 14 (17.9%) receiving 1.8 mg/kg (P=0.02) of osocimab postoperatively; 23 (29.9%) receiving 0.3 mg/kg (P=0.42) and 9 (11.3%) receiving 1.8 mg/kg (P<0.001) of osocimab preoperatively; 20 (26.3%) receiving enoxaparin; and 12 (14.5%) receiving apixaban[8]. Major or clinically relevant nonmajor bleeding was observed in up to 4.7% of those receiving osocimab, 5.9% receiving enoxaparin, and 2% receiving apixaban. One-sided significance-level analysis showed that postoperative osocimab met criteria for noninferiority compared with enoxaparin with risk differences of 10.6% (95% CI, –1.2% to ∞) in the 0.6 mg/kg group, 9.9% (95% CI, –0.9% to ∞) in the 1.2 mg/kg group, and 8.4% (95% CI, –2.6% to ∞) in the 1.8 mg/kg group. Two-sided 90% CI analysis showed that preoperative osocimab at the 1.8 mg/kg dose level met criteria for superiority compared with enoxaparin (risk difference, 15.1% [90% CI, 4.9% to 25.2%]; P = .007). Administration of 0.3 mg/kg of osocimab did not meet the prespecified criteria for noninferiority compared with enoxaparin: postoperative risk difference, 2.6% (1-sided 95% CI, –8.9% to ∞) and preoperative risk difference, –3.6% (1-sided 95% CIs, –15.5% to ∞)[8].

The results of the FOXTROT trial showed that for patients undergoing TKA, postoperative 0.6 mg/kg, 1.2 mg/kg, and 1.8 mg/kg doses of osocimab met criteria for noninferiority compared with enoxaparin, and the preoperative 1.8-mg/kg dose of osocimab met criteria for superiority compared with enoxaparin for

the primary outcome of incidence of VTE at 10 to 13 days postoperatively. Postoperative administration of osocimab was associated with rates of clinically relevant bleeding ranging from 1% with the 0.3 mg/kg dose to 4.7% with the 1.8 mg/kg dose with all but one bleed in the clinically relevant nonmajor category. The highest dose of osocimab (1.8 mg/kg) may have been associated with more bleeding when given preoperatively than when given postoperatively, whereas the lowest dose (0.3 mg/kg) was not. There were no clinically relevant bleeding events after study-drug administration with the 0.6 or 1.2 mg/kg doses of osocimab, whereas there were such events with enoxaparin and apixaban. Therefore, osocimab doses between 0.6 and 1.2 mg/kg appear to be the most promising to carry forward into future trials[8]. Further studies are needed to establish dosing, efficacy and safety of osocimab relative to standard thromboprophylaxis however, this study suggested that upstream inhibition of factor XIa prevents thrombosis to a similar extent as downstream inhibition at the level of factor Xa or thrombin[8].

Abelacimab:

Abelacimab is a fully human monoclonal immunoglobulin G1 antibody that binds to the catalytic domain of both factor XI (zymogen, inactive precursor) and factor XIa. Structural studies of the drug show that abelacimab traps factor XI and factor XIa in an inactive, zymogen-like conformation, which is thought to explain the drugs equally high binding affinity for both forms of the enzyme[12]. With the factors locked into the zymogen-like conformation, this prevents further activation by factor XIIa or thrombin. The IV infusion of abelacimab almost immediately reduces the functional factor XI level in a dose-dependent manner[12]. Based on preclinical findings that showed the drug had robust and sustained anticoagulant activity in mice (assessed by activated partial thromboplastin time) without any evidence of bleeding, a first-in-human study was conducted in healthy subjects and revealed that single subcutaneous doses of abelacimab were safe and well tolerated[12]. The drug resulted in dose- and time-dependent robust and sustained prolongation of activated partial thromboplastin time and factor XI suppression for up to four weeks or longer, which supported further clinical investigation as a potential once-monthly anticoagulant therapy[12].

The next study conducted was the ANT-005 TKA trial (Abelacimab for Prevention of Venous Thromboembolism) published in July of 2021[11]. The ANT-005 TKA trial was a phase II, prospective, open-label, parallel-group trial. The study included 412 patients who underwent TKA between June 2020 to November 2020. Patients were randomly assigned in a 1:1:1:1 ratio to receive one of three regimens of abelacimab (30 mg, 75 mg, or 150 mg) as a single IV infusion over a period of 30 to 60 minutes in a dose-blinded manner or enoxaparin 40 mg subcutaneously once daily. The primary efficacy outcome was adjudicated VTE, defined as a composite of asymptomatic DVT (detected by mandatory unilateral ascending venography performed after surgery, between day 8 and day 12), confirmed symptomatic VTE (symptomatic DVT of the leg or nonfatal PE), fatal PE, or unexplained death for which PE could not be ruled out. The principal safety outcome was a composite of major or clinically relevant nonmajor bleeding up to 30 days after surgery. VTE occurred in 13 of 102 patients (13%) in the 30 mg abelacimab group, 5 of 99 patients (5%) in the 75 mg abelacimab group, and 4 of 98 patients (4%) in the 150 mg abelacimab group, as compared with 22 of 101 patients (22%) in the enoxaparin group. All three abelacimab regimens met the criterion for noninferiority to enoxaparin[11]. The difference in risk (abelacimab minus enoxaparin) with the 30 mg abelacimab regimen was −9.2% (95% CI, −19.4 to 1.1; P=0.08 for superiority), whereas the difference with the 75 mg abelacimab regimen was −16.8% (95% CI,

−26.0 to −7.6; P<0.001 for superiority) and the difference with the 150 mg abelacimab regimen was −17.8% (95% CI, −26.7 to −8.8; P<0.001 for superiority). Clinically relevant bleeding through day 30 occurred in 2 of 102 patients (2%) in the 30 mg abelacimab group, in 2 of 104 patients (2%) in the 75 mg abelacimab group, in none of 99 patients in the 150 mg abelacimab group, and in none of 104 patients in the enoxaparin group.

Results of this study showed that abelacimab reduced the risk of postoperative venous thromboembolism to a greater extent than conventional anticoagulants such as enoxaparin, without increasing the risk of bleeding[11]. While the incidence of adjudicated clinically relevant bleeding was similarly low between both groups in the ANT-005 TKA trial and the FOXTROT trial, the small sample size and limited statistical power preclude reliable assessment of the hemostatic safety of the new novel anticoagulants[6,8,11].

Milvexian:

Milvexian is an exciting drug development due to its oral route of administration, considering that oral anticoagulants are a mainstay of therapy for prevention and treatment of VTE in an outpatient setting. Milvexian is a small molecule drug that binds with high affinity and is a highly selective factor XIa inhibitor. It is a first in class oral factor XIa inhibitor that is rapidly absorbed after oral administration with a half-life of approximately 12 hours[16].

One of the first studies for the oral factor XIa inhibitors was the proof-of-principle trial called the AXIOMATIC-TKR trial (Milvexian for the Prevention of Venous Thromboembolism) that was published in December of 2021[7]. The AXIOMATIC-TKR trial was a phase II, randomized, open-label, parallel-group, adaptive-design trial. The study included patients who were undergoing TKA between June 2019 to February 2021. 1242 patients were randomly assigned to receive one of seven postoperative regimens of milvexian (25 mg, 50 mg, 100 mg, or 200 mg twice daily or 25 mg, 50 mg, or 200 mg once daily) or enoxaparin (40 mg once daily). The primary efficacy outcome was VTE, which was a composite of asymptomatic DVT (detected by mandatory unilateral venography performed 10 to 14 days after surgery), confirmed symptomatic VTE (symptomatic DVT of the leg or nonfatal PE), or death from any cause. The principal safety outcome was bleeding of any severity, which was defined as the composite of major bleeding, clinically relevant nonmajor bleeding, and minimal bleeding. Among the patients receiving milvexian 25 mg, 50 mg, 100 mg or 200 mg twice daily, VTE (primary efficacy outcome) developed in 27 of 129 (21%), in 14 of 124 (11%), in 12 of 134 (9%), and in 10 of 131 (8%), respectively. These findings were consistent with a significant dose–response relationship (one-sided P<0.001)[7]. The total number of VTE developed across all twice daily milvexian regimens was 63 of 518 patients (12%), an incidence significantly lower than the prespecified benchmark of 30% (one-sided P<0.001)[7]. Among the patients receiving milvexian 25 mg, 50 mg or 200 mg once daily, VTE developed in 7 of 28 (25%), in 30 of 127 (24%), and in 8 of 123 (7%), respectively. These findings were also consistent with a significant dose–response relationship (one-sided P<0.001)[7]. In the enoxaparin group, VTE developed in 54 of 252 patients (21%). No major bleeding episodes were seen with milvexian, while one occurred with enoxaparin. The incidence of clinically relevant bleeding (the composite of major bleeding and clinically relevant nonmajor bleeding) was 1% across all dosing groups of milvexian and 2% with enoxaparin.

The results from this trial showed that milvexian is an effective antithrombotic agent. Incidence of VTE after elective TKA was significantly reduced in a dose-dependent manner in both once and twice daily milvexian regimens when the total daily dose was 100 mg or higher. Results also showed milvexian was associated with a low risk of clinically relevant bleeding that is comparable, if not lower than enoxaparin. However, larger phase III trials will need to be conducted to confirm these findings.

Asundexian:

Similar to milvexian, asundexian is a new potent oral medication that is specific for inhibiting factor XIa. It is a small molecule medication that is dosed once daily, has a mean terminal half-life of 16 to18 hours, and shows less than 15% renal elimination[17]. The studies for asundexian that are currently in process, as well as the one recently published, differ from the previous factor XIa inhibitor trials. Previous studies focused on VTE prevention in patients who had undergone TKA, where the asundexian trials will be evaluating patients who are starting on an anticoagulant due to atrial fibrillation, acute myocardial infarction or acute non-cardioembolic stroke.

One of the most recent asundexian trials published was the PACIFIC-AF trial (Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation) published in April of 2022[13]. The PACIFIC-AF trial was a multicenter, randomized, double-blind, double-dummy, dose-finding phase II trial comparing asundexian 20 mg or 50 mg once daily with apixaban 5 mg twice daily. Patients aged 45 years or older with atrial fibrillation, a CHA_2DS_2-VASc score of at least 2 if male or at least 3 if female and had conditions resulting in increased bleeding risk met the criteria for this trial. Data collection started in January 2020 and completed in June 2021. The primary endpoint was the composite of major or clinically relevant nonmajor bleeding according to International Society on Thrombosis and Hemostasis (ISTH) criteria, assessed in all patients who took at least one dose of study medication. Given the anticipated size of the phase II study, no primary or secondary thrombotic endpoints were formally analyzed. They were entirely exploratory and underpowered (including analysis of the composite of ischemic stroke, systemic embolism, myocardial infarction, or cardiovascular death, as well as the individual components)[13]. Three composite primary endpoint events occurred in the asundexian 20 mg arm, one in the asundexian 50 mg arm, and six in the apixaban arm. Overall, per the ISTH criteria, there were no episodes of major bleeding observed. There were 10 patients who experienced a nonmajor clinically relevant bleeding event and 48 who had any bleeding event. In general, bleeding rates were lower in those treated with asundexian compared with apixaban. The ratio of incidence proportions for the primary endpoint for asundexian once daily versus apixaban twice daily was 0.33 (90% CI 0.09–0.97) for pooled asundexian, 0.50 (0.14–1.68) for asundexian 20 mg, and 0.16 (0.01–0.99) for asundexian 50 mg. The ratio of incidence proportions for all bleeding events for asundexian once daily versus apixaban twice daily was 0.42 (0.26–0.67) for pooled asundexian, 0.46 (0.23–0.83) for asundexian 20 mg, and 0.38 (0.16–0.68) for asundexian 50 mg. For the exploratory thrombotic composite endpoint of cardiovascular death, myocardial infarction, ischemic stroke, or systemic embolism, two events occurred in those treated with asundexian 20 mg, four in those treated with asundexian 50 mg, and three in those treated with apixaban. Two ischemic strokes occurred in those treated with asundexian 20 mg, one in those treated with asundexian 50 mg, and none in those treated with apixaban.

Results of this trial are the first to indicate a lower bleeding incidence with a new oral anticoagulant compared to apixaban, but further efficacy trials are warranted. More studies for asundexian are currently underway including the PACIFIC-AMI and PACIFIC-STROKE trials that have yet to be published.

Conclusion:

Choosing appropriate anticoagulation therapy is an area that pharmacists have the ability to make an impact. There are many patients with comorbidities, health conditions, age, medication interactions, and/or substance abuse that place them at an increased risk of major bleeding with the current anticoagulant classes. This commonly poses the question by many healthcare providers of which class is best for these patients. Unfortunately, with the available anticoagulant classes, there isn't a clear-cut best answer that provides maximal anticoagulation efficacy without adding to or compounding the risk of major bleeding. Promising data from the published phase II trials FOXTROT, ANT-005 TKA, and AXIOMATIC-TKR have shown the novel factor XIa inhibitors could be the answer to some of the current predicaments healthcare providers face when prescribing anticoagulants to patients, especially those that have an inherently increased bleeding risk. These trials have shown that novel factor XIa inhibitors are noninferior, and in some instances superior, for preventing VTE in TKA patients with possible reductions in bleeding risk in comparison to enoxaparin and apixaban. This data provides reasonable rationale to conduct the larger phase III trials that are needed to solidify the rationale behind the development of this new anticoagulant class. The phase II trial PACIFIC-AF comparing asundexian to one of the most prescribed anticoagulants, apixaban, also brings affirmation for conducting a larger phase III trial. This phase II trial showed asundexian had significantly lower observed bleeding events compared to apixaban. This is clinically significant as apixaban exhibits one of the lowest bleeding risks amongst the currently available oral agents[13,18]. While underpowered to statistically analyze, the PACIFIC-AF trial also showed that asundexian could be just as efficacious at thrombotic prevention as apixaban. At this time, it must be kept in mind that while the idea of the novel factor XIa inhibitors for anticoagulation is appealing, that being thrombotic protection with less major bleeding risk, larger and longer studies comparing efficacy and safety to current standards of care including the conventional DOACs are still warranted. If the novel mechanism of inhibiting factor XIa can provide significant safety advantages in reducing bleeding over conventional therapies while also showing noninferior or superior efficacy in preventing thrombosis, then anticoagulation guidelines may be due for an update in the future.

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