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BCS Editorial

Factor XI Inhibitors: the Future of Anticoagulation in Atrial Fibrillation?

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Take Home Messages

- Many patients with atrial fibrillation experience significant bleeding complications from oral anticoagulation or are ineligible for current agents due to bleeding concerns
- Factor XI inhibition is a promising therapeutic target that may offer the opportunity to reduce thromboembolic complications whilst preserving haemostasis
- Studies so far have shown that Factor XI inhibitors effectively suppress factor XI levels in vivo and are associated with less bleeding than current agents
- Further, adequately powered phase 3 studies are required to establish efficacy in stroke prevention in atrial fibrillation

Introduction

Atrial fibrillation (AF) has been described as an 'epidemic' and affects over 35 million people worldwide (1), whilst incidence and prevalence continue to grow. Cardioembolic stroke is devastating and a major risk for patients with AF. Anticoagulation is a crucial component of AF management in those with risk factors for stroke (2). Direct oral anticoagulants (DOACs) are now used in the majority of patients on oral anticoagulants (OACs) in the UK (3,4), though many still use warfarin.

Despite the favourable safety and efficacy of DOACs, a significant bleeding risk remains (5,6). Major bleeding increases mortality (5) and concerns over bleeding may lead to discontinuation, underuse or inappropriate under-dosing of OACs (7). According to registry data, approximately 40-60% eligible for OACs are not prescribed them (7–9) though there is large variation between institutions and regions (10). Furthermore, amongst those prescribed OACs, approximately one-fifth may be inappropriately under-dosed, a strategy which fails to minimise bleeding risk but may increase mortality (11).

Factor XI (FXI) inhibitors are novel experimental agents that offer the enticing possibility of reducing thromboembolic risk in AF with minimal bleeding risk. This editorial aims to review the rationale for FXI inhibition in AF-related stroke prevention, and the results from the recent PACIFIC-AF study (12).

About the author

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Rationale for FXI Inhibition

The coagulation cascade involves the intrinsic (or contact activation) pathway and extrinsic (or tissue factor) pathway, which both lead to activation of factor X and converge to a common pathway. Current OACs both reduce pathological thrombus formation and impair haemostasis as they act either on the common pathway (DOACs) and/or both intrinsic and extrinsic pathways (warfarin) (**Figure 1**) (6).

Factor XIa (FXIa – activated form of FXI), which is procoagulant and antifibrinolytic, is only involved in the intrinsic pathway. By targeting FXI, it may be possible to uncouple the intrinsic and extrinsic pathways, thereby reducing development of pathological thrombus via intrinsic pathway inhibition with only little effect on the extrinsic pathway, therefore maintaining haemostasis.

Patients with inherited factor XI (FXI) deficiency have decreased incidence of cardiovascular events and venous thromboembolism (VTE) (14). Such individuals have a small increase in bleeding risk but this is rarely severe. Animal studies have demonstrated that treatment with an antisense oligonucleotide or monoclonal antibody targeted against FXI generates potent anti-thrombotic effects, without causing bleeding (15–17).

Early clinical studies have shown some promise (**Table 1**). FXI inhibition using monoclonal antibodies has been observed to reduce incidence of post-operative VTE in patients undergoing knee arthroplasty compared to enoxaparin, with low rates of bleeding (18,19). Whilst some early studies have been underpowered for evaluation of efficacy outcomes, such agents will be further evaluated in future larger studies for efficacy.

Monoclonal antibodies developed to inhibit FXI have rapid onset and could be given as a weekly or monthly dose, which may aid convenience and compliance (20,21). FXI inhibitors under evaluation have relatively little or no renal excretion, potentially enhancing accessibility to anticoagulation in renal disease (21). Aside from AF, they may potentially have wider applications including post-myocardial infarction (MI) and in those with increased thromboembolic risk related to cancer, renal disease, mechanical valves and indwelling cardiac devices, such as left ventricular assist devices (22).

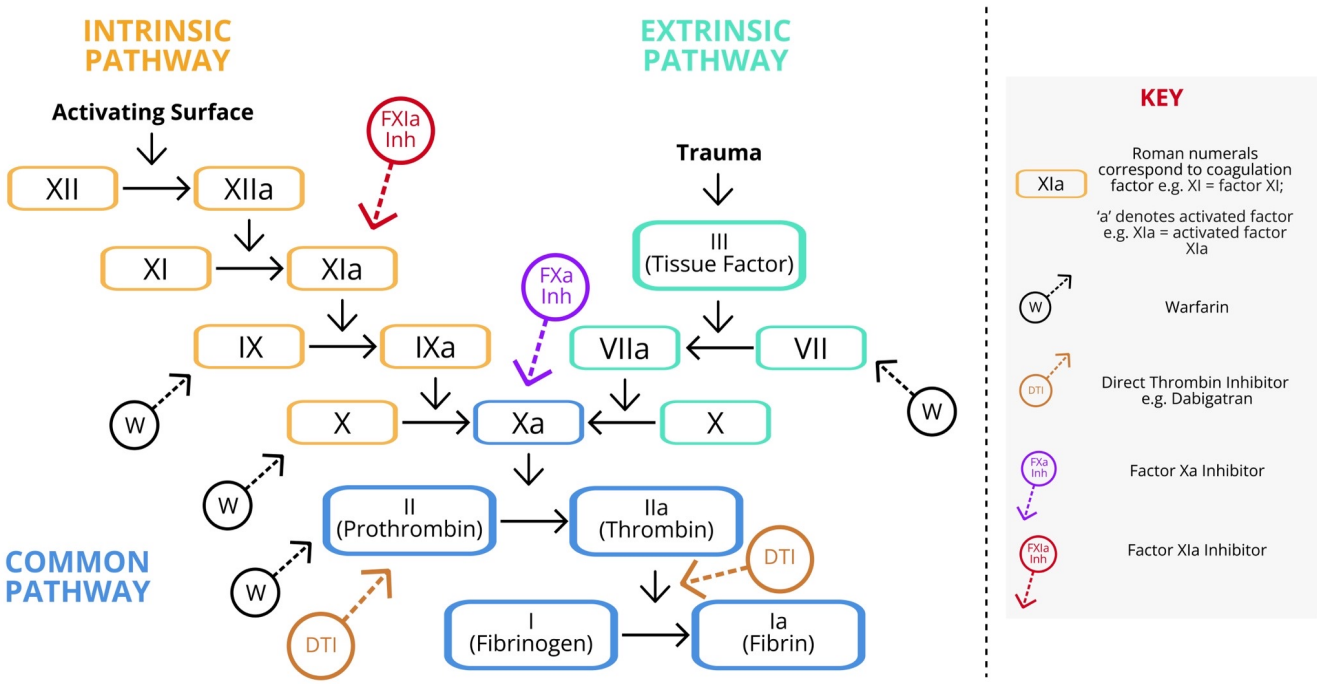

Figure 1. Mechanism of Action of Oral Anticoagulants on Coagulation Cascade (13). Image produced by N Mannakkara.

Table 1. Summary of key findings from early clinical studies of factor XI inhibitors

Study	Population	Intervention	Results
Verhamme *et al*. 2021 (18)	412 patients undergoing total knee arthroplasty	Single-dose intravenous abelacimab (30mg, 75mg or 150mg) (a monoclonal antibody that acts as a dual inhibitor of FXI and FXIa) vs. 40mg daily enoxaparin For VTE Prophylaxis	30mg abelacimab was non-inferior to enoxaparin, and 75mg/150mg doses were superior The highest dose of abelacimab (150mg) was associated with 17.8% absolute risk reduction of VTE compared to enoxaparin, with low rate of clinically relevant bleeding
Rao *et al*. 2022 (PACIFIC-AMI) (23)	Randomised Phase 2 Trial 1601 patients with recent acute MI (within 5 days)	Patients receiving dual anti-platelet therapy randomised to OD asundexian 10mg, 20mg or 50mg vs. Placebo for dose-finding and safety evaluation	Asundexian did not increase significant bleeding (defined by BARC type 2/3/5 bleeding) – hazard ratio for pooled asundexian group vs placebo 0.98 (90% CI, 0.71-1.35) over follow-up (median 368 days) Asundexian did not reduce the composite efficacy outcome (cardiovascular death, MI, stroke or stent thrombosis) – hazard ratio for pooled asundexian 20mg and 50mg group vs placebo 1.05 (90% CI, 0.69-1.61) though was not adequately powered for this outcome
Shoamanesh *et al*. 2022 (PACIFIC-STROKE) (24)	Randomised Phase 2 Trial 1808 patients with recent non-cardioembolic stroke (within 48 hours)	Patients receiving single or dual anti-platelet therapy randomised to OD asundexian 10mg, 20mg or 50mg vs. Placebo for dose-finding and safety evaluation	Asundexian did not increase incidence of the composite bleeding outcome (defined as major or clinically significant non-major bleeding according to ISTH criteria) – 4% (pooled asundexian group) vs. 2% (hazard ratio 1.57 (90% CI, 0.91-2.71) at 26 weeks Asudexian did not reduce incidence of the primary efficacy outcome (composite of covert brain infarction on MRI or ischaemic stroke)
Piccini *et al*. 2022 (PACIFIC-AF) (12)	Randomised Phase 2 Trial 862 patients with AF (aged at least 45 and with CHA2DS2-Vasc score at least 2 (male) or 3 (female)	Asundexian 20mg OD vs. Asundexian 50mg OD vs. Apixaban BD at clinically indicated dose	Factor XIa assay at trough showed 81% and 92% inhibition of Factor XIa for asundexian 20mg and 50mg respectively. Asundexian at both 20mg and 50mg doses was associated with lower rates of the primary composite bleeding outcome and all bleeding compared to Apixaban (composite bleeding for pooled asundexian patients 0.8% vs. 2.4% for apixaban (RR 0.33 (90% CI 0.09-0.97)) (see Figure 2 for further details). The study was not powered to effectively evaluate for thromboembolic outcomes.
Sharma 2022 (not yet published) (AXIOMATIC-SSP) (25)	Randomised Phase 2 Trial 2295 patients with recent TIA or stroke (within 48 hours)	Patients on dual anti-platelet therapy for TIA or stroke randomised to milvexian (25mg OD, 25mg BD, 50mg BD, 100mg BD, 200mg BD) vs. Placebo and followed up for 90 days	Milvexian did not significantly reduce the incidence of symptomatic ischaemic stroke or TIA (4.6% (25mg OD); 3.8% (25mg BD); 7.7% in 200mg BD group; 5.5% in placebo) Milvexian did not increase bleeding (all BARC bleeding) (10.8% in lowest dose (25mg OD), 10.2% in highest dose (200mg BD) and 7.9% in placebo

AF = atrial fibrillation; BARC = bleeding academic research consortium; BD = twice daily; CI = confidence interval; MI = myocardial infarction; OD = once daily; RR = relative risk; TIA = transient ischaemic attack

PACIFIC-AF

The recently published PACIFIC-AF trial was a randomised phase 2 trial comparing asundexian 20mg or 50mg daily, to apixaban (at clinically indicated dose) for 12 weeks (12) (**Figure 2**). Asundexian is a small-molecule factor XIa inhibitor. It does not interact with CYP3A4, has approximately 15% renal clearance only and is unaffected by food or pH-altering medications (26).

Patients taking asundexian at both 20mg or 50mg dose had substantial reductions in FXIa activity, achieving 81% and 92% inhibition respectively at trough concentrations. Patients taking asundexian at either dose (n=505) had two-thirds reduction in the composite bleeding endpoint versus those taking apixaban (n=250). Though no meaningful difference in thromboembolic outcomes was observed, the study was not powered to assess for efficacy of stroke prevention.

Overall, PACIFIC-AF showed that asundexian effectively inhibited FXIa in vivo, and was associated with reduced bleeding compared to apixaban. The findings suggest that asundexian is safe and may reduce bleeding complications compared to current agents but evaluation in larger-scale studies is required to further establish whether the observed inhibition of FXIa translates to effective stroke prevention.

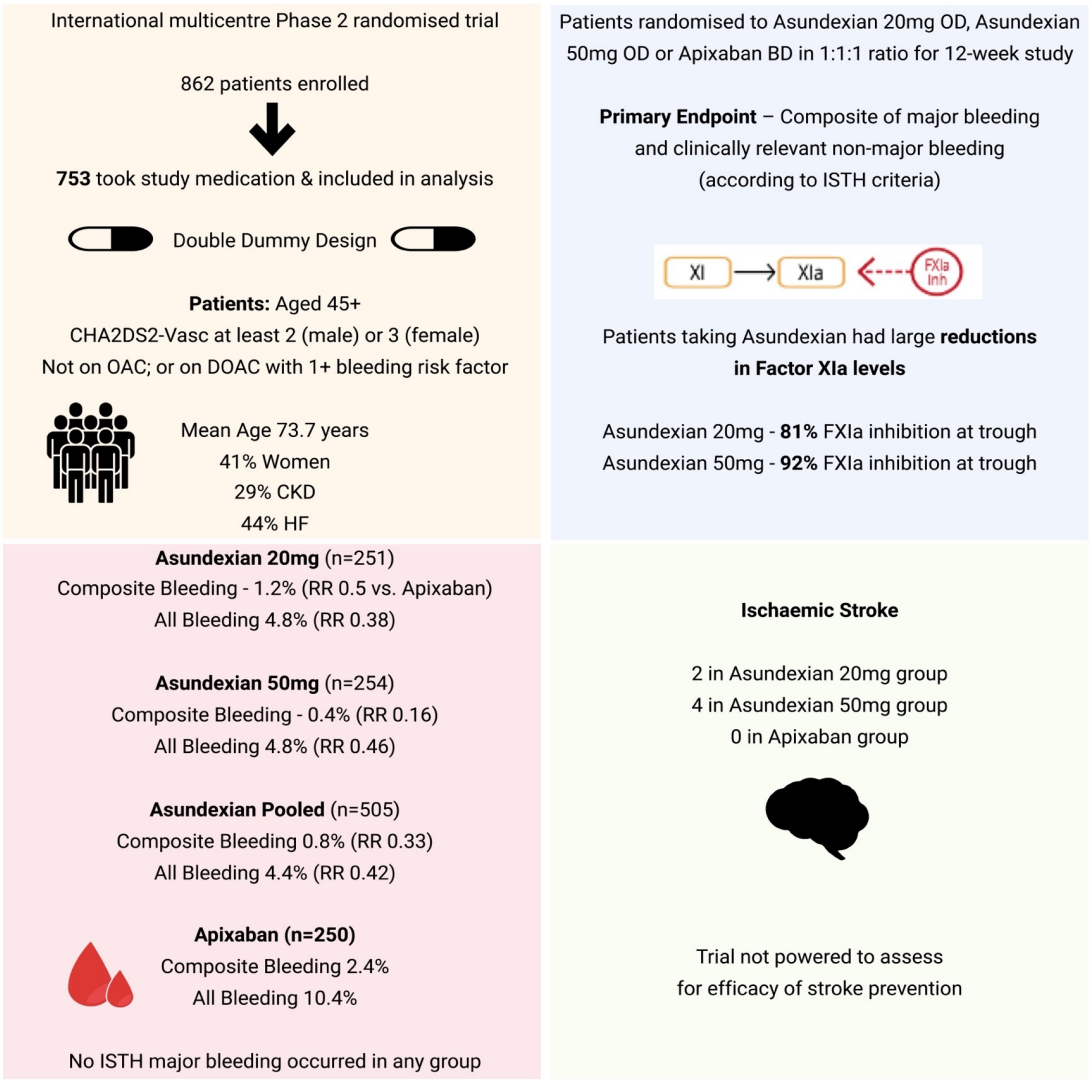

Figure 2. Key points from the PACIFIC-AF study (12). Image produced by N Mannakkara.
BD = twice daily; CKD = chronic kidney disease; DOAC = direct oral anticoagulant; HF = heart failure; ISTH = International Society on Thrombosis and Haemostasis; OAC = oral anticoagulation; OD = once daily; RR = risk ratio

Future Studies

OCEANIC-AF, starting in late 2022, will be a phase 3 randomised controlled trial following on from PACIFIC-AF. It will compare asundexian to apixaban in a larger cohort of AF patients over a prolonged period, assessing efficacy of stroke prevention, systemic embolism, and major bleeding (27). LIBREXIA-AF, similarly, will be a phase 3 randomised trial comparing milvexian to apixaban for stroke prevention in AF (28). Further trials of other agents, including monoclonal antibodies, are also underway (29,30). Such studies should answer whether FXI inhibitors are ready for use in clinical practice.

Conclusions

FXI inhibition may offer the opportunity to reduce thromboembolic complications in AF with minimal effect on bleeding risk. They may offer the opportunity to reduce bleeding complications and therefore improve access to anticoagulation for those with bleeding risk or currently ineligible. Early and recent studies have been promising and showed that agents can effectively suppress FXI, however further studies are needed to establish efficacy and long-term safety before they can be considered for use in clinical practice.

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