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VIEWPOINT

Bleeding Risk in Asian Patients

Potential for Thrombin Amplification Pathway Blockade Using Factor XI Inhibitors

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Asian compared with non-Asian patients have a higher risk of bleeding during anticoagulant therapy and may have a lower risk of ischemic events, thereby altering the balance between benefits and risks of treatment.[1] Although differences between populations in the risk of bleeding during anticoagulant therapy are increasingly recognized, most treatment guidelines do not recommend differential dosing for Asian and non-Asian patients[2] because there is very little high-quality evidence to support dose reduction in Asian patients.

Emerging evidence suggests that a new class of drugs that target coagulation factor XI (FXI) can prevent thrombosis without compromising hemostasis.[3] The potential for FXI inhibitors to uncouple thrombosis from hemostasis appears to be explained by blockade of a thrombin amplification pathway that is important for thrombosis but largely redundant for hemostasis.[4] By preserving normal hemostasis, thrombin amplification pathway blockers (APBs) may be of particular benefit for patients at high risk of bleeding.

In this viewpoint, we review the evidence that Asians have a higher risk of bleeding than their non-Asian counterparts during treatment with anticoagulants, examine the potential for APBs to provide effective anticoagulation without increasing bleeding, and highlight the need for adequate representation of Asian populations in randomized trials of FXI inhibitors that are planned and ongoing.

ANTICOAGULATION AND BLEEDING IN ASIAN COMPARED WITH NON-ASIAN PATIENTS

Reviews and consensus documents have highlighted a higher risk of bleeding during anticoagulant therapy in Asians compared with non-Asians.[5] The evidence comes from comparisons of event rates in randomized trials and observational studies and is supported by known genetic and pharmacological differences between Asians and non-Asians. Randomized trials of anticoagulation for stroke prevention in atrial fibrillation (AF) have shown that Asians compared with non-Asians had higher rates of both major and intracranial bleeding during warfarin therapy and greater absolute reductions in bleeding with direct oral anticoagulants compared with warfarin.[1] Asians also had higher rates of intracranial bleeding during direct oral anticoagulant therapy.[1]

There are plausible biological explanations for an excess bleeding in Asians compared with non-Asians during antithrombotic therapy. Asians generally have lower body weights, a higher prevalence of hypertension, different patterns of vascular disease, and have genetic variants associated with enhanced hypercoagulability and altered drug metabolism leading to higher drug levels.[5]

The higher risk of bleeding during anticoagulant therapy in Asians compared with non-Asians suggests that outcomes may be improved by lowering the dose. Supportive evidence comes from the J-ROCKET (Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial), which demonstrated in Japanese patients with AF that a reduced dose of rivaroxaban compared with warfarin was noninferior for bleeding and did not compromise efficacy for prevention of stroke or systemic embolism.[6] However, most approved anticoagulants have

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TABLE 1 Factor XI Inhibitors in Phase 2 or 3 Clinical Trials

Category	Target	Administration Route and Frequency	Drug	Indication	Development Phase
ASO	FXI RNA	Subcutaneous, weekly to monthly	IONIS-FXI$_{Rx}$	TKA	2
				ESRD	2
			Fesomersen	ESRD	2
Monoclonal antibody	FXI or FXIa	Subcutaneous or intravenous, monthly	Abelacimab	TKA	2
				AF	3
				CAT	3
			Osocimab	TKA	2
				ESRD	2
			MK-2060	ESRD	2
			Xisomab	ESRD	2
				PICC	2
Small-molecule Inhibitor	FXIa	Intravenous or oral, once or twice daily	Asundexian	AF	3
				Stroke	3
				AMI	2
			Milvexian	ESRD	2
				TKA	2
				AF	3
				ACS	3
				Stroke	3

ACS = acute coronary syndrome; AF = atrial fibrillation; AMI = acute myocardial infarction; ASO = antisense oligonucleotide; CAT = cancer associated thrombosis; ESRD = end-stage renal disease; FXI = factor XI; PICC = peripherally inserted central catheter; SC = subcutaneous; TKA = total knee arthroplasty.

not been separately tested in Asians. An alternative approach to reduce the risk of bleeding and thereby improve clinical outcomes would be the use of safer anticoagulants. Preliminary data suggests that APBs using drugs that target coagulation FXI may fulfil this potential.

POTENTIAL FOR APBs THAT TARGET FXI TO PREVENT THROMBOSIS WITHOUT INCREASING BLEEDING

The potential for FXI inhibitors to prevent thrombosis without increasing bleeding was first suggested by observations from populations with congenital FXI deficiency.[7] Individuals with moderate or severe FXI deficiency have lower rates of stroke and venous thromboembolism than those with normal levels but little or no increase in spontaneous bleeding.[7,8] Some affected individuals have increased bleeding at sites of high fibrinolytic activity (eg, oropharynx, genitourinary tract) associated with trauma, surgery, childbirth, or menstruation, although bleeding cannot be predicted by factor XI levels. Animal experiments support the conclusion that FXI deficiency protects against thrombosis but is not associated with increased bleeding.[9]

The potential for APBs to prevent thrombosis without increasing bleeding appears to be explained by the role of FXI in mediating the amplification of thrombin generation. which plays a pivotal role for thrombosis but is much less important for hemostasis.[10] Thrombosis is commonly initiated by intravascular tissue factor exposure or release following plaque rupture. The resulting thrombin burst is generally insufficient to result in thrombus formation and requires amplification that is mediated by FXI. Unlike thrombosis, hemostasis is usually initiated by extravascular injury with tissue factor release resulting in a much larger thrombin burst with hemostasis that is not dependent on FXI-mediated thrombin amplification. Accordingly, by selectively blocking the thrombin amplification pathway, drugs that target FXI provide a unique potential to improve to prevent thrombosis without compromising hemostasis.

The first evidence from a randomized trial supporting the use of drugs that target FXI to prevent thrombosis without causing bleeding comes from a phase 2 study in patients undergoing elective knee arthroplasty.[3] The FXI-ASO study evaluated an FXI antisense oligonucleotide (ASO) for the prevention of venous thromboembolism in patients undergoing knee arthroplasty. Despite starting treatment 36 days before surgery, the ASO compared with enoxaparin 40 mg once daily, started the evening before or 6 to 8 hours after surgery, was associated with numerically lower rates of bleeding and was noninferior or superior for prevention of asymptomatic or symptomatic venous thromboembolism.[3] Since then, several

additional phase 2 studies involving the use of monoclonal antibodies or small-molecule agents that target FXI have demonstrated reduced bleeding compared with currently available anticoagulants, although none were powered for clinical outcomes.[10]

Table 1 summarizes FXI inhibitors that have so far been evaluated in phase II trials. In addition to ASOs that block translation of FXI mRNA and thereby lower blood levels of FXI, these include antibodies that block FXI or FXIa, and small molecule inhibitors that block FXIa. One monoclonal antibody (abelacimab) and 2 small molecule inhibitors (asundexian, milvexian) and are currently being evaluated in phase 3 trials in patients with AF (NCT05712200, NCT05757869, NCT05643573), acute coronary syndrome (NCT05754957), stroke (NCT05702034, NCT05686070), or cancer (NCT05171049, NCT05171075). Other FXI inhibitors not yet evaluated in clinical trials include aptamers and natural inhibitors.

NEED FOR ADEQUATE REPRESENTATION OF ASIANS IN FXI INHIBITOR DEVELOPMENT PROGRAMS

Concern about bleeding presents one of the greatest barriers to the use of guideline recommended anticoagulation in patients at high risk of bleeding. The evidence that Asians compared with non-Asians are at higher risk of bleeding suggests that effective antithrombotic drugs that reduce bleeding may have a particular role in Asian populations. Despite comprising one-half of the world population, Asians are consistently under-represented in registration trials of new antithrombotic drugs. FXI inhibitor development programs that are planned or ongoing provide an opportunity to address this imbalance by including substantial numbers of Asians, collecting detailed information on their baseline characteristics and cointerventions (eg, traditional medicines), and performing additional pharmacokinetic and pharmacodynamic studies to better understand optimal dosing in this population.

By also inhibiting coagulation activation induced by exposure of blood to artificial surfaces, FXI inhibitors have the additional potential to replace warfarin in patients with mechanical heart valves. This remains a critical unmet need, particularly in low- and middle-income countries where the burden of valvular heart disease is greatest and monitoring of warfarin is challenging. If currently ongoing trials of FXI in patients with acute coronary syndrome, AF, and stroke are successful, the further evaluation of these agents in patients with mechanical valves will be an important priority.

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