Novel Antithrombotic Drugs on the Horizon
The Ultimate Promise to Prevent Clotting While Avoiding Bleeding

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Diseases associated with arterial thrombosis or venous thrombosis are leading causes of mortality and morbidity globally. Since the 1930s, antithrombotic therapy has been the cornerstone of medical therapy for thrombotic diseases. However, the success of antithrombotic therapy has come at the cost of one of the most dreaded iatrogenic complications—bleeding. Recently, new evidence has emerged on potentially important differences between thrombosis and hemostasis, thereby raising the possibility of developing new antithrombotic drugs that do not cause bleeding.

Scope of Antithrombotic-Associated Bleeding
All currently used antithrombotic drugs in the clinic are associated with an inherent risk of bleeding. For example, the risk of serious major bleeding with a non–vitamin K antagonist oral anticoagulant is ≈2% to 3%, with the risk of intracranial hemorrhage of ≈0.3 to 0.5% per annum. Likewise, nonmajor bleeding with aspirin approximates 2%, and the rates of major and life-threatening bleeding rise significantly in those over 75 years of age to >2% per year. Thus, a significant proportion of patients at high risk of thrombotic disease are vulnerable to bleeding complications and often miss out on potentially beneficial antithrombotic therapy. Importantly, aside from the mortality and morbidity directly linked to the index bleeding event, there is a large body of evidence demonstrating that hemorrhagic complications are associated with adverse clinical outcomes. Despite the introduction of new anticoagulants, such as the non–vitamin K antagonist oral anticoagulants and newer antiplatelet drugs, we have reached a tipping point with regard to the achievable balance between antithrombotic potency and bleeding risk with current antithrombotic approaches. Therefore, there remains an unmet clinical need for new antithrombotic approaches that maintain efficacy while preserving hemostasis.

New Insights Into Thrombosis and Hemostasis
Recently, major progress has been achieved in our understanding of the factors that may differentially regulate pathological thrombosis from hemostasis based on the introduction of intravital microscopy, genetically engineered mouse models and the availability of diagnostic and blocking antibodies. Indeed, the ability to visualize thrombus formation in real time has highlighted that thrombus formation is a highly dynamic process and has served to identify numerous new players that may regulate pathological thrombus formation, yet be dispensable for hemostasis (Figure). Particularly, targeting factors that regulate the propagation of the thrombus, without impacting on the initial formation of the thrombus core, may hold the key to safer antithrombotic therapy.

Novel Antiplatelet Strategies
Several novel antiplatelet strategies have shown considerable promise toward inhibiting thrombosis while sparing hemostasis. These include inhibitors of the lipid kinase, phosphoinositide 3-kinase β, glycoprotein (GP) IIb/IIIa outside-in signaling, conformation-specific targeting of GP IIb/IIIa, activated platelet-targeted CD39 therapy, and a competitive inhibitor of platelet GP VI. In keeping with the concept that the differential targeting of the propagating thrombus may preserve hemostasis, all of these inhibitors do not seem to inhibit the initial adhesion of platelets in vivo and therefore presumably allow for the formation of a hemostatic core of platelets in response to vascular injury. Reassuringly, isoform-specific phosphoinositide 3-kinase β inhibitors and a competitive GP VI construct have been tested in Phase I trials where the separation of their antithrombotic effects from hemostasis was confirmed, with the GP VI function inhibitor (Revacet) currently undergoing evaluation in a Phase II trial in patients with transient ischemic attack/stroke and carotid artery stenosis.

Targeting of Cellular Components Beyond Platelets
Platelets and leukocytes are recruited to, and interact with each other, at sites of vascular inflammation and thrombus formation via platelet P-selectin and GP Ib, which bind to their cognate leukocyte counter-receptors PSGL-1 (P-selectin glycoprotein ligand-1) and Mac-1 (CD11b/CD18), respectively. Platelet–leukocyte interactions are bidirectional because activated platelets release a plethora of chemokines and cytokines, which may further enhance leukocyte recruitment and activation, whereas activated leukocytes can in turn amplify platelet activation. Recruited monocytes express tissue factor and therefore enhance coagulation, and activated leukocytes release neutrophil extracellular traps, which are highly negatively charged strands of DNA and RNA that directly activate the intrinsic coagulation.
pathway via factor (F)XII and thereby enhance thrombin generation. Activated platelets release medium chain polyphosphate, which amplifies coagulation in multiple ways, including activating the contact activation system. Likewise, protein disulfide isomerase released from activated platelets and damaged endothelial cells seems to be an essential regulator of fibrin formation and platelet accumulation in vivo, although the precise role of protein disulfide isomerase remains to be elucidated.

**Novel Anticoagulant Strategies**

The clinical observation that patients with FXII or FXI deficiency have no or mild bleeding phenotypes, combined with the demonstration that FXI- and FXII-deficient mice are protected from thrombosis, has spurred great interest in developing strategies to inhibit the contact activation system. Indeed, an antisense oligonucleotide that inhibits FXI production has shown promise in a Phase II trial for venous thrombosis prophylaxis postknee arthroscopy—importantly this approach was not associated with any bleeding side effects. A highly specific antibody, which inhibits activated FXII (FXIIa), has also been developed and shows potent antithrombotic effects in preclinical animal models. In addition, disruption of neutrophil extracellular trap formation or inhibition of polyphosphate also demonstrate considerable antithrombotic effects in animal models, while sparing hemostasis. Last, protein disulfide isomerase inhibitors, which have been demonstrated to inhibit fibrin formation in vivo, are currently in Phase II/III clinical trials in the context of cancer-related venous thrombosis.

**Challenges to Translation**

The translation of these findings, with the promise of differentiating thrombosis from hemostasis, into the clinic faces numerous challenges. First, the animal models demonstrating these new regulators are not physiological and do not fully recapitulate human pathology. Further, in the context of murine thrombosis models, thrombosis is often triggered in different vascular beds than encountered clinically, mouse platelets do not share the same repertoire of receptors as human platelets, and variation exists in the thrombosis models used and the outcomes measured. Second, the use of new inhibitors in animal
models often relies on the administration of antithrombotic drugs before the development of a thrombus; therefore, the efficacy of these new approaches in the setting of an established thrombosis remains to be tested. Last, the potential clinical indications for any of these new therapies will need to be defined. For example, it is likely that inhibition of the contact activation will demonstrate efficacy in preventing thrombosis on artificial surfaces such as central venous catheters or extracorporeal circuits, where it is known that contact factor activation plays a prominent role in triggering thrombosis. However, whether these approaches display benefit in the context of atrial fibrillation or an established arterial thrombosis remains to be proven. Likewise, an important aspect of new antiplatelet agents will be whether they display efficacy in preventing stent thrombosis given the important differences in the biological trigger of a thrombus in the context of an atherosclerotic plaque when compared with stent thrombosis. These questions highlight the potential shortcomings of current models of thrombosis, where the inciting events initiating thrombus formation are distinct from those encountered in the clinic.

Fundamental to the translation of any new antithrombotic drug is the demonstration that hemostasis is minimally affected. However, the commonly used readout of bleeding in animal studies—the tail bleeding time—may not always predict clinical bleeding. There are many reasons as to why the tail bleeding time may not accurately detect hemostatic defects. There remains a relative lack of standardization of this model, introducing variables such as the anesthetic drugs used, the type of tail injury applied, and the outcome measured. In addition, the nature of the injury in the tail bleeding model means that vasospasm, even in the presence of an unstable thrombus, may be sufficient to temporarily halt bleeding. Indeed, salient lessons from previously developed antithrombotic drugs, such as the PAR (protease-activated receptor) antagonists, have highlighted that effects on hemostasis may not always be detected in preclinical models. This is especially the case in an era where many patients are on combinations of antithrombotic drugs—a situation rarely tested in preclinical studies. As such, the development of new bleeding models that are more predictive of clinically relevant hemostatic responses may be an important step forward for antithrombotic drug development. Furthermore, another challenge in translating any new antithrombotic drug are the often large and expensive clinical trials required to demonstrate efficacy in comparison to standard therapies.

**Conclusions**

Despite the challenges of translating promising animal data into the clinic, the emergence of novel antithrombotic targets holds the promise to improve cardiovascular outcomes, minimize iatrogenic bleeding complications, and significantly increase the number of patients who are afforded protection by antithrombotic drugs.

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**References**


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