Antithrombotic Therapy for Vascular Disease and Intervention: The Best Is Yet to Come?

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This Commentary relates to the article by S. Craige et al on pages 453–462.

The mind is not a vessel to be filled, but a fire to be kindled - Plutarch

Despite ongoing progresses, atherothrombosis continues to have a substantial morbidity and mortality burden, with platelet aggregation and the coagulation cascade activation playing a pivotal role in thrombus formation at the site of endothelial injury.[1] Indeed, endothelial barrier breakdown can be spontaneous because of the rupture or erosion of atherosclerotic plaques or iatrogenic in the course of heart and vascular procedures. In either of the cases, the unfavorable result can be the intermittent or permanent obstruction of the blood flow.[2]

In these scenarios, timely and effective platelet and coagulation cascade inhibition is of utmost importance to treat thrombotic events, prevent recurrent ischemia, and improve short-term prognosis.[3] Antithrombotic therapy, which includes both antiplatelet and anticoagulant (APAC) drugs, represents as a consequence the cornerstone of the pharmacological treatment in patients with coronary or peripheral artery disease, especially if undergoing either percutaneous or surgical revascularization.[3]

Despite the fact that the first studies on the clinical use of heparin date back to the thirties of the past century, heparin still represents the preferred anticoagulant to prevent clot formation during such procedures.[2,3] In the past years, the need to couple anticoagulant and antiplatelet effect has lead to the combination of heparin with complex antiplatelet regimens which also include new, potent, and rapid agents.[4,5] However, given the lack of locally acting drugs, the systemic exposure to aggressive antithrombotic therapies results in increased perioperative and postoperative bleeding risk. In this context, the risk–benefit ratio walks on a fine line between the thrombotic and hemorrhagic threats.[4] On this basis, the need is felt for new therapeutic approaches effective in inhibiting thrombus formation and preventing vascular occlusion with a targeted action at the site of vascular injury and a negligible effect on the systemic physiological hemostasis.[6] The perfect antithrombotic drug should be indeed comprehensively active, potent, reversible, rapid in onset/offset, and, ideally, locally impactful.

Semisynthetic APAC, an investigational medication not yet approved by the Food and Drug Administration, is a heparin proteoglycan mimic with dual APAC action tailored for vascular interventions (Fig. 1).[7] Briefly, APAC consists of mast cell-derived heparin proteoglycans in the form of a semisynthetic conjugate of unfractionated heparin and a protein core. Recent and extensive in vitro and in vivo studies have supported the promising and unique capability of APAC to produce a local antithrombotic effect by contextually inhibiting the collagen-induced aggregation and the deposition of activated platelets and reducing the fibrin formation at the site of vascular injury.[7–9] In detail, in vivo experiments suggest that APAC ability to selectively target and remain at the site of endothelial injury, also under very high flow conditions, is due to the property to colocalize with collagen, laminin, and von Willebrand factor, which are not exposed in the setting of intact endothelium.[8]

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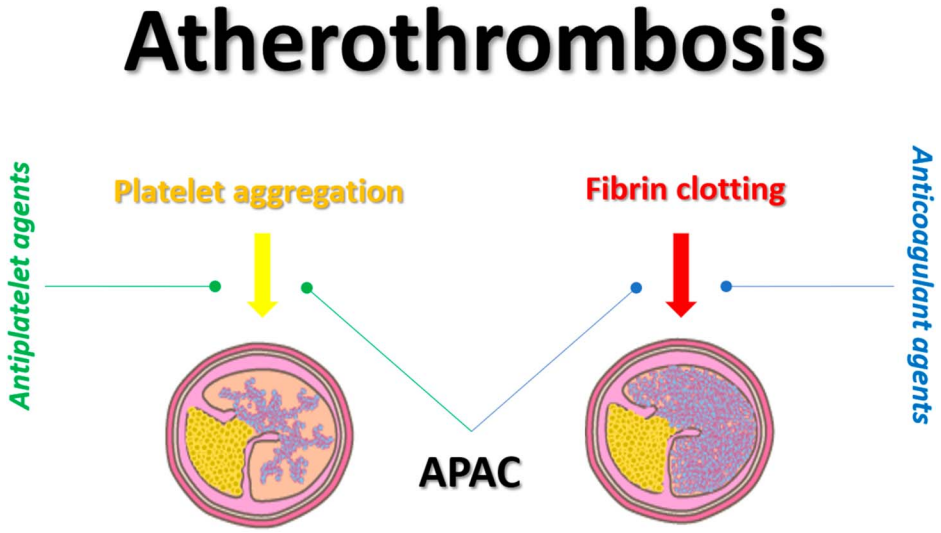

FIGURE 1. Atherothrombotic pathways include platelet activation and aggregation, and fibrin clotting. Semisynthetic APAC is an investigational heparin proteoglycan mimic with dual APAC action.

In this issue of the Journal, Craige et al[10] report the results of an interesting study on the in vivo pharmacological effects and safety features of APAC in different preclinical models. The authors investigated the toxicology profile of APAC in rat and monkey models after both single and repeated intravenous administrations and also tested the activated partial thromboplastin time (APTT) as a surrogate pharmacokinetic marker of the antithrombotic activity of APAC. This research suggests APAC to be safe because toxicological analysis has highlighted adverse effects only with high bolus dose levels, which widely exceed those expected to be used within the clinical setting (max 0.5 mg/kg). Moreover, APAC showed a rapid onset of action since its pharmacological effects were observed within 0.25 hours from administration time and to be a relatively fast reversible agent as proved by the APTT values returning to baseline by 24 hours. Remarkably, no accumulation of the drug was demonstrated after a 14-day repeated daily dosing. Of note, as underlined by the authors, APPT only represents an indirect measurement of APAC pharmacokinetics and is unable to capture its antiplatelet activity; as a consequence, efforts to identify a direct bioanalytical method to assess systemic exposure to the drug are strongly advocated. Nevertheless, it seems fair to point out that APTT is a user-friendly instrument widely used in clinical practice, and APAC carries a prevalent anticoagulant effect, over the antiplatelet one.[9] In view of these considerations, waiting for the validation of novel dedicated tools, APTT appears a reasonably reliable and sensitive, although surrogate, pharmacodynamic marker of the impact of the drug on hemostasis overall.

The growing incidence of cardiovascular diseases driven by both the insufficient control of risk factors and the population aging phenomenon,[1] along with the recent introduction of novel and progressively more complex heart and vascular procedures, makes the pursuit of the "perfect antithrombotic regimen" of paramount interest.[3] Potential strengths of APAC, in view of its future clinical use, may reside in the combined APAC action and in the targeted effect at the site of endothelium injury. The "dream antithrombotic drug" should indeed perform its pharmacological effect only where needed, gaining in this fashion the best theoretical antiischemic/hemorrhagic profile. How far from ideal we currently are is difficult to say; what is nevertheless unquestionable is that, along the lines of this research by Craige et al,[10] further investigations in the field are strongly advocated and should be in the future accordingly encouraged and sustained.

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