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EDITORIAL COMMENT

Expanding the Roster

Developing New Inhibitors of Intravascular Thrombosis*

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It is an axiom of Major League Baseball that "all prospects are suspect." Many newly identified players seem promising initially but do not ultimately develop into stars. However, all big-league stars were prospects at one time, and new players are needed to supplement teams and replace aging athletes.

The situation is similar when it comes to cardiovascular drugs, particularly antithrombotic agents. Some have succeeded, many have failed, and others have not been widely adopted. Although mortality related to atherosclerosis has fallen impressively, clinicians must now choose from a bewildering number of therapeutic choices for nearly every clinical situation they face. When antithrombotic drugs alone are considered in the setting of ST-segment elevation myocardial infarction (MI), 96 potential combinations of antithrombotic drugs are currently available, even before dose and duration are considered. If cangrelor and low-dose rivaroxaban receive federal approval, the number may reach 384. An episode of atrial fibrillation captured on a telemetry monitor will push this figure well beyond 800.

When a new drug is proposed, one cannot help but wonder whether it is needed, how it will be evaluated, how it will fit into the current pharmacopeia, and, most critically, how clinicians will determine that prescribing it is worthwhile. Nonetheless, new "prospects" are needed in both hospital and outpatient settings. For example, although rapid reperfusion is widely practiced and door-to-balloon time has fallen considerably, 30-day mortality for patients with ST-segment elevation MI is still nearly 10% (1). Among patients who were discharged alive after acute coronary syndromes (ACS) and enrolled in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), nearly 15% experienced MI, nearly 5% had strokes, and more than 15% had died by the end of 7 years despite aggressive lipid lowering (mean low-density lipoprotein cholesterol 53 mg/dl) (2).

Virtually all clinicians recognize the central role of thrombosis in the acute manifestations of atherosclerotic vascular disease. However, clinicians are often reluctant to adopt new antithrombotic drugs, particularly when administered on top of existing regimens. The new $P2Y_{12}$ antagonists prasugrel and ticagrelor offer more potent antiaggregation than clopidogrel and are superior in preventing numerous serious cardiovascular events after ACS presentation. Prasugrel was approved in 2009, ticagrelor in 2011. Estimates of their adoption vary, but are disappointing. In the recent TOTAL (A Trial of Routine Aspiration Thrombectomy With Percutaneous Coronary Intervention [PCI] Versus PCI Alone in Patients With ST-Segment Elevation Myocardial Infarction [STEMI] Undergoing Primary PCI) trial of thrombectomy in patients with STEMI, slightly fewer than one-third of patients were discharged on either prasugrel or ticagrelor (3). The recent demonstration that ticagrelor used with aspirin was superior to aspirin alone for secondary prevention after MI raises the likelihood that more patients will be treated with aggressive dual-antiplatelet therapy (4).

Vorapaxar, a platelet protease-activated receptor (the principal thrombin receptor) antagonist, was

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approved in late 2014 for secondary prevention in peripheral artery disease or after MI. When added to a background of aspirin (97% of patients) and clopidogrel (71%), vorapaxar reduced the composite risk for death, MI, or stroke in this population from 9.5% to 7.9%, while moderate or severe bleeding (according to the GUSTO [Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries] criteria) was increased from 2.4% to 3.7% (5). How often vorapaxar will be used as a third antithrombotic drug remains to be seen.

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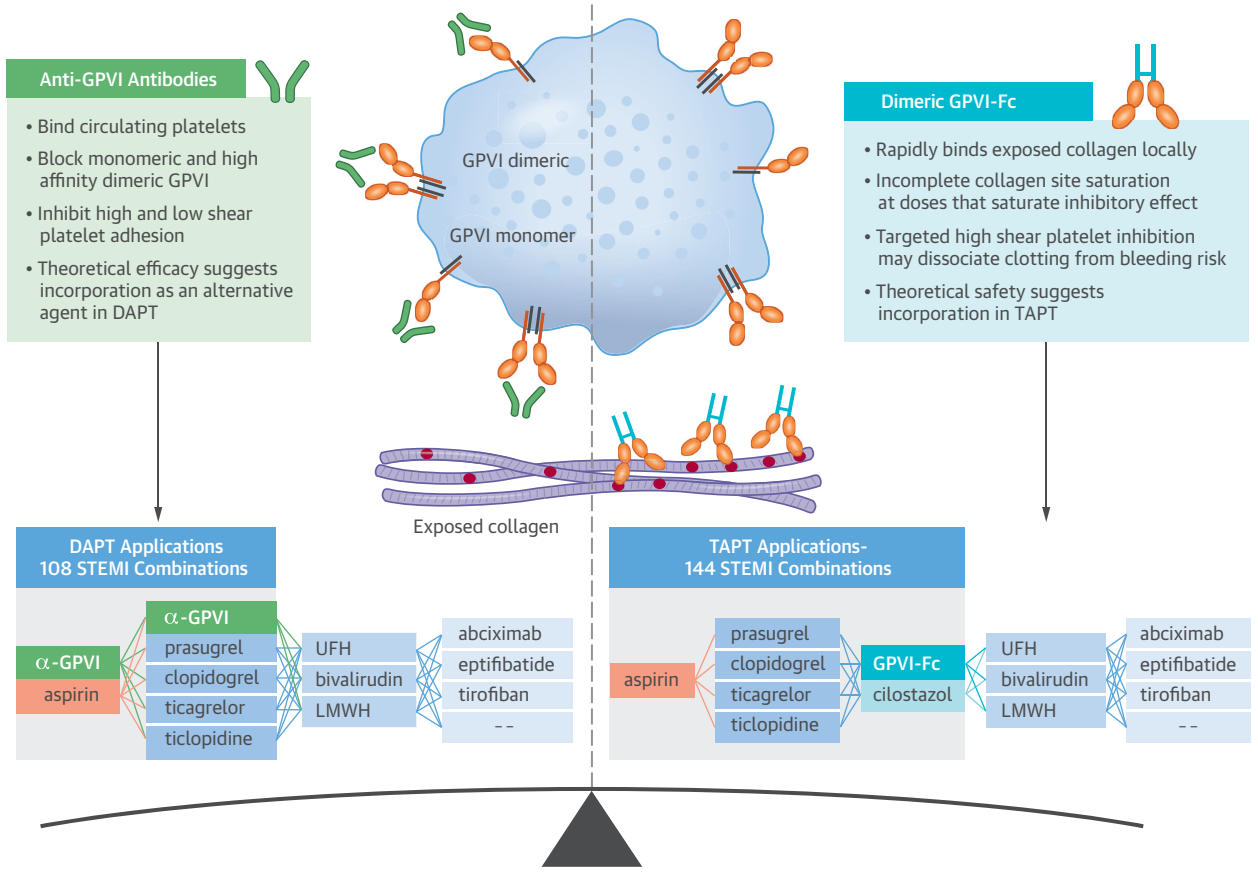
Given the reluctance to compound medications, it makes sense to search for new antithrombotic targets with the intent of perhaps replacing some older ones. In this issue of the *Journal*, Jamasbi et al. (6) report significant progress in assessing glycoprotein (GP) VI antagonists as antithrombotic candidates. The seminal role of platelet adhesion and activation in arterial thrombosis on a disrupted endothelial surface has been reviewed previously (7). GPVI, the primary platelet receptor for collagen (8), recognizes a glycine-proline-hydroxyproline motif on collagen and facilitates platelet adhesion and activation, particularly under low-shear conditions. On quiescent platelets, GPVI exists as a monomer. After platelet activation, GPVI complexes cluster on the platelet surface, and the cytoplasmic tails of adjacent GPVI molecules become linked, causing GPVI to

FIGURE 1 GPVI Mechanisms and Applications



Inhibitors of the glycoprotein VI (GPVI)–collagen axis offer an alternative to clinically approved antiplatelet agents. Although anti-GPVI antibodies that block monomeric and dimeric GPVI **(left, green)** achieve high theoretical efficacy by inhibiting low and high shear platelet deposition, soluble dimeric GPVI-Fc **(right, blue)** selectively blocks high shear adhesion, potentially dissociating clotting and bleeding risk. Yet adding dimensions to balancing antithrombotic efficacy and safety via triple-antiplatelet therapy (TAPT) or revised dual-antiplatelet therapy (DAPT) regimens may further bend (or break) the scales of clinical complexity, with 96 permutations of antithrombotic agents already in existence for ST-segment elevation myocardial infarction (STEMI) management before considering dose, duration, or other drugs on the horizon. LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.