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EDITORIAL COMMENT

Going Polymer Free and Dual Antiplatelet Free Earlier

The Coevolution of Stent and Pharmacotherapy*

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The evolution of intracoronary stent design has been mirrored by a coevolution in anticoagulant and antiplatelet therapy. Devices and drugs have coevolved to simultaneously minimize the risk of the 2 competing and opposing evolutionary driving forces: thrombosis and bleeding. Pharmacologic strategies have adapted to improvements in stent design and stent designs have adapted to improvements in and limitations of pharmacologic strategies. The LEADERS FREE (A Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug Coated Stent Versus the Gazelle Bare Metal Stent in Patients With High Risk of Bleeding) trial represents 1 of the latest chapters in this coevolution (1).

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THE COEVOLUTION OF STENT DESIGN AND PHARMACOLOGIC STRATEGIES

Bare-metal stents evolved to reduce the restenosis and abrupt closure associated with conventional balloon angioplasty (**Figure 1**). The selection pressure imposed by stent thrombosis was met by dextran, high-dose aspirin, dipyridamole, and warfarin. The high risk of bleeding associated with this potent antithrombotic cocktail was the evolutionary impetus for soon replacing warfarin with ticlopidine, which combined with aspirin constituted dual antiplatelet therapy (DAPT). Ticlopidine's hematologic complications were the evolutionary pressure that drove the replacement of ticlopidine with the safer alternative, clopidogrel.

On the stent side, BMS restenosis served as the selection pressure to develop drug-eluting stents (DES). DES overcame restenosis, but concerns arose regarding an increased risk of late stent thrombosis, particularly with discontinuation of DAPT (2). Stent thrombosis served as the selection pressure for prolonged DAPT—a strategy that would serve as a "Band-Aid" while even newer generations of DES that optimized the magnitude and speed of intimal stent strut coverage were developed.

The "Band-Aid" of prolonged DAPT reduced late and very late DES thrombosis but increased bleeding. Second-generation stents that eluted newer drugs from durable polymers further optimized the magnitude of re-endothelialization to simultaneously minimize the risk of both thrombosis and restenosis (3). Further alternative advances have now been made in vascular healing (more rapid and complete stent strut coverage) through the use of bioresorbable polymers that minimize the duration of exposure to polymers that may injure the vessel wall (4). By improving re-endothelialization and speeding vascular healing, advances in stent design as well as the drugs and polymers used for elution have now potentially reduced the need for prolonged DAPT, thereby reducing the risk of bleeding.

In managing the patient at high risk of bleeding, rather than going back to an older stent design and using a BMS as has been recommended by some (5), polymer-free metallic drug-coated stents such as that studied in the LEADERS FREE trial offer an alternative strategy (1). This drug-coated stent transfers the drug into the wall of the artery early and quickly over

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a month and speeds vessel healing as opposed to a traditional polymer-coated DES that transfers antirestenotic drugs over several months.

MANAGEMENT OF THE PATIENT AT HIGH RISK OF BLEEDING

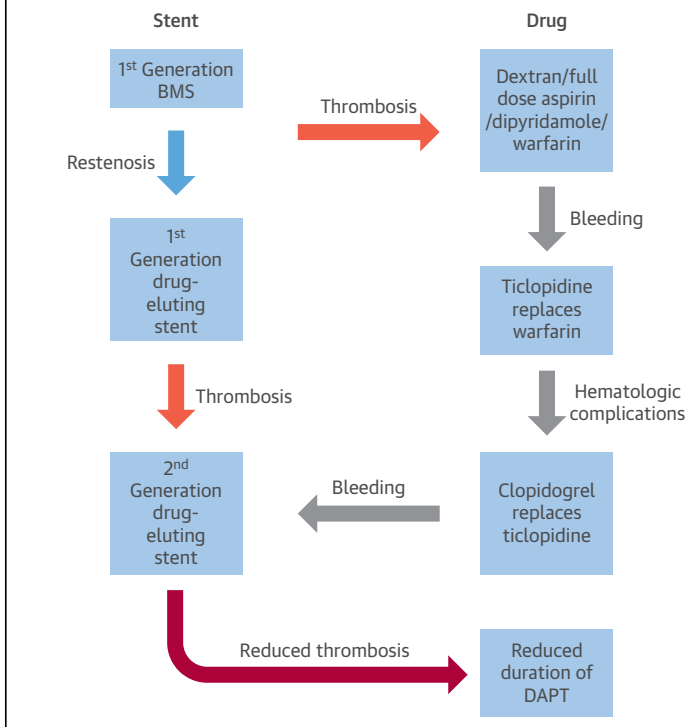
Optimizing a patient's overall clinical outcome hinges on balancing the risk of bleeding and thrombosis. There is a complex interplay among bleeding, thrombosis, and clinical outcomes. Most investigators agree that minor bleeding is not associated with mortality, but the published reports are divided as to whether major bleeding is associated with long-term mortality. There are patients with major bleeds who die either at the time of or soon after the event; examples include patients with intracranial hemorrhage, gastrointestinal bleeding, and retroperitoneal bleeding. Some studies indicate that bleeding is not, however, associated with longer-term mortality, say 40 days after the event (6). Other studies, including the LEADERS FREE trial, as well as other observational data indicate that major bleeding is associated with long-term mortality (7). Many studies claim that bleeding is independently associated with mortality in multivariate models adjusting for confounders.

Despite the attempts of all studies to adjust for known confounders, the impact of unidentified and poorly characterized or measured confounders, such as frailty, may play a role: frail "little old ladies" with renal impairment tend to die, but they also tend to bleed, and it is hard to disentangle these confounders. Transfusion may temporarily save the patient's life, but it may be associated with short-term adverse consequences due to the introduction of old, nondeformable red blood cells with poor oxygen carrying capacity, the viscosity of which may reduce cardiac output, as well as long-term adverse outcomes as a consequence of microchimerism (8). In this latter scenario, the transfused blood contains stem cells that may take up residence in the patient's marrow that may in turn cause an autoimmune response. Another explanation is that those people who bleed tend to discontinue not just antiplatelets and anticoagulants, but other guideline-based therapies, and that causes the patient to veer off the track of evidence-based medicine and thereby suffer poor clinical outcomes.

The magnitude of the association of stent thrombosis and bleeding with mortality may vary depending on the time that has elapsed since the index event. Early stent thrombosis carries a high mortality rate, whereas late stent thrombosis is associated with a lower mortality (7). In contrast, bleeding early after the index event has been associated with a lower mortality than bleeding late after the index event (7). Debate regarding the optimal duration of DAPT hinges on these competing risks. In a meta-analysis, a shorter duration of DAPT was associated with lower rates of bleeding but higher rates of stent thrombosis (9). This higher rate of stent thrombosis with short duration DAPT was diminished, however, with the use of second-generation DES. It is also notable that all-cause mortality was numerically greater for long-term DAPT than short-term DAPT (odds ratio: 0.87; 95% confidence interval: 0.74 to 1.01; $p = 0.073$).

The benefit of long-term versus short-term DAPT has been debated. With respect to the patients at high risk of bleeding studied here, current American College of Cardiology/American Heart Association guidelines state "In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months may be reasonable" (5). A growing

FIGURE 1 Coevolution of Intracoronary Stents and Pharmacotherapy



Shown here is the complex interrelationship between evolution in stent design and evolution in pharmacotherapy to minimize ischemic and bleeding complications. BMS = bare-metal stent(s); DAPT = dual antiplatelet therapy.