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EDITORIAL COMMENT

Bleeding Versus Clotting? Both Are Equally Bad After Percutaneous Coronary Intervention*

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Since the early days of coronary stenting, interventional cardiologists have learned to fear stent thrombosis. It was not difficult for us to understand that acute occlusion of a coronary stent and the resulting myocardial infarction could cause morbidity and death. We pass this fear along to our patients and tell them never to stop taking their dual-antiplatelet therapy (DAPT) without our approval, or else they could suffer the consequences of a massive heart attack and may not survive. We are not overdramatizing this risk. Although the published 1-year mortality after stent thrombosis ranges from 10% to 30% (1), there is no doubt that this event will shorten a patient's life. Over the years, we have identified the important patient, lesion, and procedural factors that lead to stent thrombosis (1) and enthusiastically embrace methods and therapies that might reduce the chance of stent thrombosis and hopefully improve outcomes after percutaneous coronary intervention (PCI).

Of course, we also fear bleeding, but for many interventional cardiologists, it is considered a lesser evil. I have heard colleagues refer to bleeding as the "cost of doing business," an unfortunate but perhaps necessary price to pay to prevent the much more dreaded stent thrombosis. It is only relatively recently that we learned that post-PCI bleeding is not just an annoyance; procedure-related and in-hospital bleeding after PCI is associated with increased long-term mortality (2-4). These observations focused our attention on "bleeding-avoidance strategies" with great emphasis on reducing access-related bleeding both by fine-tuning our decisions regarding intraprocedural anticoagulation and by shifting from femoral to radial access (5). It is important to note, however, that bleeding is not just access site or intraprocedure related. In an analysis of pooled data involving 17,393 patients undergoing primarily femoral-access PCI, bleeding within 30 days of PCI occurred in 5.3% of patients, access-site bleeding in 2.1% and non-access-site bleeding in 3.3% (6). In this study, bleeding was associated with an increased risk for death at 1 year (hazard ratio: 3.17), and there was actually a higher risk for mortality for patients with non-access-site bleeding (hazard ratio: 3.91) compared with those with access-site bleeding (hazard ratio: 1.82) (6).

We know that early bleeding is associated with increased mortality in the long term, but what about bleeding months after PCI, during the period of prolonged DAPT? The significance of late bleeding on mortality is less clear. Additional knowledge regarding the impact of later bleeding would be crucial to our understanding of this problem and would inform our decisions regarding the duration of DAPT, a currently unresolved and controversial issue.

In the DAPT trial, about 10,000 patients undergoing PCI were randomized to a shorter duration (12 months) versus a prolonged duration (30 months) of DAPT (7). Prolonged DAPT reduced stent thrombosis compared with shorter DAPT (0.4% vs. 1.4%) and reduced major adverse cardiovascular and cerebrovascular events (4.3% vs. 5.9%) but at the cost of increased bleeding (2.5% vs. 1.6%) (7). There was a statistically insignificant but somewhat concerning trend of increased mortality with prolonged DAPT (2.0% vs. 1.5%; $p = 0.052$). A meta-analysis of

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short-duration versus long-duration DAPT including 10 randomized trials also found less thrombosis with long-duration DAPT but more bleeding and a trend toward higher all-cause mortality compared with short-duration DAPT (8).

SEE PAGE 1349

And so for every patient in whom we perform PCI, we must choose: bleeding or clotting? And which is worse? The interesting analysis by Baber et al. (9) published in this issue of *JACC: Cardiovascular Interventions* provides valuable insight into this question. The investigators analyzed outcomes over 2 years in more than 5,000 contemporary-era patients in the PARIS (Patterns of Non-Adherence to Dual Antiplatelet Therapy in Stented Patients) registry undergoing stent implantation (about 70% with second-generation drug-eluting stents). Over 2 years, all-cause mortality was 4.7%. Coronary thrombotic events occurred in 5.9% of patients and significant bleeding in 8.1%, with only about 8% of these due to periprocedural bleeding. Both thrombosis and bleeding were independently associated with a nearly equivalent and more than 3-fold risk for death; the hazard ratio for mortality was 3.3 for a thrombotic event and 3.5 for a bleeding event. Interestingly, most of the thrombotic events occurred while on DAPT and with a higher mortality risk compared with those off DAPT. Also of interest and a very important contribution of this study was the observation that out-of-hospital serious bleeding events were associated with the greatest mortality risk (hazard ratio: 5.1). We can conclude that bleeding is bad and an expensive "cost of doing business."

There are a few important limitations of this study. As the investigators acknowledge, only clopidogrel was studied; the rates of bleeding and thrombosis and the mortality impact of these events in the face of potent agents such as ticagrelor or prasugrel are not known. Furthermore, there are no data regarding clopidogrel or aspirin responsiveness in this population; this might explain the higher hazard associated with thrombotic events occurring on DAPT.

Currently, our decisions regarding the choice of antiplatelet agents and the duration of DAPT are entirely empirical. Personally, I am more inclined to use prolonged DAPT in patients I perceive to have no obvious increase risk for bleeding but a higher likelihood of stent thrombosis or those in whom I greatly worry about the consequences of stent thrombosis. For example, I often prescribe long-term DAPT in patients undergoing PCI for left main stem, proximal left anterior descending coronary artery bifurcation lesions, and long, small-caliber vessels, even if there is some concern about increased bleeding. I do not know if this is correct or if I am putting them at greater harm from bleeding. Clearly, we need additional tools to help us with this decision. Clinical models to predict the risk for bleeding have been proposed, but they tend to focus on early bleeding (within 30 days of PCI) (10). Low platelet reactivity has been associated with higher risk for bleeding with clopidogrel and high platelet reactivity with an increased risk for stent thrombosis over 8.5 months (11). We need these models to include the newer agents as well. Ideally, a model would predict both early and late bleeding after PCI and could lead to strategies to reduce that risk. Perhaps more important would be the creation of a model that incorporates both the risk for stent thrombosis, taking into consideration the important patient, lesion, and procedural variables, and the consequences of stent thrombosis. For example, a greater "stent thrombosis hazard score" would be assigned to a patient with a left-dominant, large-caliber distal left main stem lesion treated with bifurcation stents and a lower score assigned to a patient treated with a short, fat stent to the distal right coronary artery supplying a small posterior descending artery. Clearly the consequence of stent thrombosis would be very different in these 2 patients, and we might be more willing to accept greater bleeding risk in the first patient compared with the second. Only with such tools can we make truly informed decisions balancing the risk for bleeding against the consequences of thrombosis.

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