Few therapies in contemporary medicine have been as transformative as transcatheter aortic valve replacement (TAVR). Not only does the procedure reduce mortality compared with medical therapy in patients who are not operative candidates (1), but it is also superior to surgery in high-risk patients (2). The primary endpoint for the pivotal trials of TAVR (1,2) has been all-cause mortality, but other events reflecting the safety of the procedure, such as vascular complications and bleeding, have also been assessed.

As with other endovascular procedures, these events after TAVR are associated with a significant increase in adverse outcomes such as renal failure and mortality (3). The early iterations of TAVR devices used very large bore sheaths (up to 24 F), which likely influenced the risk of bleeding and vascular complications in the elderly and frail patients included in the trials. Moreover, the anticoagulant agent used in the procedures was 7,000 to 10,000 units of unfractionated heparin (UFH). In this context, hemorrhagic complications in the pivotal TAVR trials occurred with a relatively high frequency. Strategies to mitigate the risk of these complications are a priority in the TAVR space.

Currently available lower profile aortic valve delivery sheaths reduce arterial trauma and likely lower the incidence of bleeding. Another approach, however, is to manage procedural antithrombotic therapy in a way that makes the procedure safer. An obvious choice in this regard is bivalirudin, a direct thrombin inhibitor with a short half-life, which has been associated with reduced bleeding complications in certain clinical situations. In this issue of the Journal, Dangas et al. (4) present the results of the BRAVO-3 (Effect of bivalirudin on Aortic Valve Intervention Outcomes 3) trial that explores the role of bivalirudin in TAVR. The trial randomized 802 patients undergoing TAVR to receive either bivalirudin or UFH. Somewhat surprisingly, the primary endpoints of bleeding at 48 h post-procedure and net adverse clinical events at 30 days were not significantly different between the 2 arms. These results raise several important issues about approaches to reduce bleeding complications in a procedural arena that is rapidly evolving.

In general, the goals of antithrombin therapy in cardiovascular procedures are to reduce the risk for ischemic events and to reduce the risk for thrombus formation on intravascular equipment. From a clinical standpoint, optimal anticoagulation therapy should meet these goals while not increasing the risk of bleeding. Although several agents have been studied for use during percutaneous coronary intervention (PCI), UFH and bivalirudin are the most commonly used. UFH is the traditional choice; it is inexpensive, titrable, and reversible. However, UFH also has several well-known limitations, such as unpredictable levels of anticoagulation, platelet activation, and potential for heparin-induced thrombocytopenia. Bivalirudin overcomes many of these limitations, and its short half-life allows for a rapid offset, theoretically reducing bleeding risk post-procedure. Some randomized trials have supported this putative benefit, particularly when bivalirudin was compared against a combination of UFH and a glycoprotein IIb/IIIa inhibitor (GPI) (5). Later trials have not been as definitive. A pooled analysis of 16 randomized trials, including >33,000 patients undergoing PCI, found that bivalirudin does significantly reduce bleeding compared with a strategy of

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UFH plus GPI; however, compared with UFH alone or GPI added to bivalirudin, this safety advantage is no longer present (6). What accounts for these differences, and how does it relate to procedural strategies for TAVR?

It is important to recognize that procedural medicine rarely stagnates. Devices and techniques continue to iterate, and adjuvant medical therapy also evolves, often rapidly. An example of this evolution is the adoption of a radial approach to PCI. Both randomized and observational data definitively indicate that using radial access significantly reduces bleeding risk compared with femoral access (7). In high-risk patients such as those with ST-segment elevation myocardial infarction undergoing primary PCI, the radial approach is also associated with a reduction in mortality (8). Because the majority of bleeding complications after PCI are access site related, the value of an antithrombotic strategy aimed at reducing bleeding may have less relevance in the setting of transradial PCI. Of course, nonaccess site bleeding (e.g., gastrointestinal hemorrhage) may also be an issue, but these bleeding events are likely more closely related to prolonged post-procedure infusions of GPI rather than the antithrombin therapy itself. With the advent of more potent oral antiplatelet agents, the use of GPI has dramatically decreased over time. Therefore, contemporary PCI involves radial access, low-profile arterial access introducer sheaths (5- or 6-F), loading of oral antiplatelet agents, and selective use of GPI, all of which reduce ischemic and bleeding complications. A trial specifically testing this strategy in patients with ST-segment elevation myocardial infarction demonstrated no benefit of bivalirudin on major adverse cardiovascular events or on bleeding outcomes (9).

The pivotal trials of TAVR demonstrated 30-day major vascular complication rates of 5.9% to 17.0% and major bleeding rates of 9.3% to 28.0% with transcatheter procedures. These rates are several-fold higher than any seen in studies of PCI. If bivalirudin does positively affect bleeding outcomes, TAVR is the ideal setting in which that should be evident, but the results of the BRAVO-3 trial suggest otherwise (4). There are 3 potential reasons for this lack of effect: 1) bivalirudin is not effective at reducing bleeding complications; 2) other factors influence bleeding and negate the effect of bivalirudin; and 3) the trial is subject to type II error and was not adequately powered. The data from the published reports of PCI summarized earlier indicate that bivalirudin may be safer than UFH but only in the setting of a femoral approach and when UFH is used in combination with GPI. Thus, the issue of whether bivalirudin truly reduces bleeding risk is highly dependent on other procedural factors. For example, in the BRAVO-3 trial, the majority of patients in both groups underwent the procedure using an introducer sheath size of ≤8-F (smaller than those used in the earlier TAVR trials), which likely lowered the overall risk for bleeding. Moreover, >90% of patients had the femoral arteriotomy successfully closed with a closure device. With respect to antithrombin dosing, which is critical to reducing bleeding risk (10), the trial recommended titration of UFH dosing to achieve an activated clotting time (ACT) of 250 s. Although the ACT values are not reported, the overall rate of bleeding complications was lower than those reported in the pivotal trials of TAVR, suggesting that sheath size, method of hemostasis, and UFH dosing all negated the effect of bivalirudin. The lower rate of bleeding also subjects the trial to type II error. The sample size of BRAVO-3 was based on an assumed major bleeding rate of 19% in the control (UFH) group and a 47% relative risk reduction with bivalirudin. The actual rate of bleeding complications in the UFH arm was 9.0%, much less than what was expected. With this event rate, the trial would have needed at least 1,700 patients (i.e., more than double the number actually enrolled) to have 80% power to show a 40% reduction in bleeding complications with bivalirudin. It thus seems that all 3 elements may have influenced the results of BRAVO-3.

These negative results call into question the role of bivalirudin in TAVR. Because the BRAVO-3 trial showed that bivalirudin was noninferior to UFH with respect to 30-day net adverse cardiovascular events (a composite of all-cause mortality, myocardial infarction, or stroke; and major bleeding) and the rates of all endpoints were numerically lower in the bivalirudin-treated group (4), bivalirudin seems to be a reasonable alternative to UFH for TAVR. However, the cost difference between the 2 agents begs the question of when bivalirudin should be considered. An obvious situation is when the patient has heparin-induced thrombocytopenia. Another clinical scenario in which bivalirudin can be considered is when very large doses or repeated doses of UFH may be necessary to maintain therapeutic ACT values, such as in patients who are overweight or obese. The predictable anticoagulant effect of bivalirudin could provide an advantage in this context. Other than these specific conditions, there is no question that until further data are available, UFH is the preferred agent for TAVR.

The findings of the BRAVO-3 trial (4) are an important reminder that cardiovascular procedures are multifaceted, comprising devices, techniques,
and adjuvant medical therapy. All 3 dimensions can evolve and often do, with a change in 1 affecting the others. A constant re-evaluation of each is necessary to determine the optimal combination to balance efficacy and safety.

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