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STATE-OF-THE-ART PAPER

Antithrombotic Treatment in Transcatheter Aortic Valve Implantation

Insights for Cerebrovascular and Bleeding Events

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Transcatheter aortic valve implantation (TAVI) has emerged as a therapeutic alternative for patients with symptomatic aortic stenosis at high or prohibitive surgical risk. However, patients undergoing TAVI are also at high risk for both bleeding and stroke complications, and specific mechanical aspects of the procedure itself can increase the risk of these complications. The mechanisms of periprocedural bleeding complications seem to relate mainly to vascular/access site complications (related to the use of large catheters in a very old and frail elderly population), whereas the pathophysiology of cerebrovascular events remains largely unknown. Further, although mechanical complications, especially the interaction between the valve prosthesis and the native aortic valve, may play a major role in events that occur during TAVI, post-procedural events might also be related to a prothrombotic environment or state generated by the implanted valve, the occurrence of atrial arrhythmias, and associated comorbidities. Antithrombotic therapy in the setting of TAVI has been empirically determined, and unfractionated heparin during the procedure followed by dual antiplatelet therapy with aspirin (indefinitely) and clopidogrel (1 to 6 months) is the most commonly recommended treatment. However, bleeding and cerebrovascular events are common; these may be modifiable with optimization of periprocedural and post-procedural pharmacology. Further, as the field of antiplatelet and anticoagulant therapy evolves, potential drug combinations will multiply, introducing variability in treatment. Randomized trials are the best path forward to determine the balance between the efficacy and risks of antithrombotic treatment in this high risk-population. (J Am Coll Cardiol 2013;62:2349–59) © 2013 by the American College of Cardiology Foundation

Stroke and bleeding are severe complications of percutaneous coronary intervention (PCI) associated with increased morbidity and mortality. In-hospital mortality for PCI complicated by stroke is 30% compared with 1% for patients without stroke (1). Similarly, bleeding is associated with a twofold increase in 1-year mortality, prolonged

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Abbreviations and Acronyms

ACCF = American College of Cardiology Foundation

AATS = American Association for Thoracic Surgery

CVE = cerebrovascular event

DAPT = dual antiplatelet therapy

PCI = percutaneous coronary intervention

SAVR = surgical aortic valve replacement

SCAI = Society for Cardiovascular Angiography and Interventions

STS = The Society of Thoracic Surgeons

TAVI = transcatheter aortic valve implantation

hospitalization, and excess costs (2). Fortunately, these complications are uncommon (1% to 2% for bleeding; 0.2% for stroke) after elective PCI.

Transcatheter aortic valve implantation (TAVI) is a life-saving procedure for patients with severe aortic stenosis who are at very high or prohibitive risk for standard surgical aortic valve replacement (SAVR) (3). However, patients undergoing TAVI may be at high risk for both bleeding and stroke. The incidence of these 2 complications is at least 10-fold higher for TAVI compared with PCI: the 30-day risks of major stroke (~3.5%) and major bleeding/vascular complications (~10%) portend a formidable challenge for balancing the risks of embolic and bleeding events in these high-risk patients (4–19). As with PCI, patients who have bleeding or stroke after TAVI have greater 30-day and 1-year mortality (4,20–25). Identifying the targets (pharmacological, mechanical) that can improve this balance requires a thorough understanding of the pathophysiology, clinical risk factors, timing, and mechanisms involved in embolic and bleeding complications of TAVI.

The Platelet Colloquium is an annual academic–industry–governmental scientific meeting devoted to identifying research challenges in platelet biology, thrombosis, and hemostasis and future areas of investigation for improving patient care. The latest meetings were held in Washington, DC, on January 20 to 21, 2012, and February 1 to 2, 2013. This review summarizes the discussions of TAVI, including the definition, risks, mechanisms, and timing of stroke and bleeding, and critically reviews periprocedural and post-procedural antithrombotic treatment and its potential influence on embolic and bleeding complications.

TAVI: Definitions of Stroke and Bleeding

The antithrombotic therapy used during and after TAVI likely contributes to the occurrence of bleeding and embolic complications. However, a lack of uniform definitions for periprocedural TAVI complications has made comparisons among studies difficult. The Valve Academic Research Consortium has proposed standardized consensus definitions for relevant clinical endpoints in TAVI (26). These definitions have recently been updated (summarized in the Online Table) (27) and provide a platform for uniformly measuring the impact of proposed antithrombotic changes.

Cerebrovascular Events and TAVI: Mechanisms, Timing, and Prognostic Value

Cerebral imaging studies have shown a very high incidence (66% to 86%) of new ischemic defects after TAVI, irrespective of the transcatheter valve type (balloon- or self-expandable) or approach (transfemoral, transapical) (28–32). These defects are usually multiple and distributed in both vascular territories and cerebral hemispheres, strongly suggesting an embolic origin. Although most defects are clinically silent, the incidence of clinically apparent stroke after TAVI averages about 3% (range 0% to 6%) (Table 1) (5–9,11,13–16,23,33). In the PARTNER (Placement of Aortic Transcatheter Valve) trials (17,18), TAVI was associated with a higher rate of cerebrovascular events (CVEs [ischemic stroke or transient ischemic attack]) compared with either medical treatment/balloon valvuloplasty or SAVR (Fig. 1) (17,18). The occurrence of periprocedural stroke has been associated with poorer outcomes at 30 days, 1 year, and 2 years after TAVI (Table 2) (4,23–25,34,35).

Although cerebral emboli can occur anytime during TAVI, they seem to occur more frequently during positioning and implantation of the valve prosthesis (36). Thus, mechanical interactions between the valve prosthesis and the calcified native valve appear to play an important role in these events. The degree of valve calcification correlates well with aortic stenosis severity (37), and patients with smaller valve areas are at higher risk of CVEs within 7 days after TAVI (24). In addition, the use of the first version of delivery catheters (22-F and 24-F, without nosecone) in the PARTNER trial might have contributed to the high rate of CVEs observed (17,18). Balloon post-dilation of the valve prosthesis for treatment of significant paravalvular leaks, repeated device implantation attempts, and valve prosthesis dislodgment/embolization have also been associated with higher rates of CVEs, mainly within 24 h after TAVI (25,35). These mechanical phenomena provide a rationale for future technology modifications, in particular embolic protection devices, to minimize cerebral embolization during valve prosthesis deployment (38–40).

Despite the recognized early risk, about half of all periprocedural CVEs occur >24 h after TAVI (Fig. 2) (25,33,35,41–43). Although later CVEs can reflect eventual embolization of atheromatous material partly mobilized by the delivery catheter, mechanisms besides or in addition to prosthesis manipulation are likely involved in a substantial number of these events. Several factors might contribute to ongoing thrombogenicity of the valve apparatus after implantation, including hemostatic activation due to vessel-wall disruption or artificial surface exposure, and flow turbulence through the valve orifice (44). Because both the balloon- and self-expandable transcatheter valve systems are stented, exposure of the stent struts to the circulation might trigger initiation of the coagulation cascade and/or platelet activation. The presence of a paravalvular space occupied by the native aortic valve might also be associated with some