EDITORIAL

How Un-POPular Is Bleeding in Patients with TAVI?

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For years, bleeding complications in patients undergoing transcatheter procedures, predominantly percutaneous coronary interventions (PCIs), were not included in the primary outcome of clinical trials. It was not until the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events 2) trial, which assessed two anticoagulant strategies for PCI, that bleeding became a component of the primary outcome and was found to be a predictor of death at 1 year that was as powerful as myocardial infarction.[1]

As the population ages, increasing numbers of patients have indications for oral anticoagulants, either a vitamin K antagonist or direct-acting oral anticoagulants. Not infrequently, these patients undergo PCI and require dual antiplatelet therapy. In 2009, a comprehensive review indicated that among patients receiving vitamin K antagonists, dual antiplatelet therapy resulted in a high incidence of bleeding, often accompanied by a paradoxical increase in ischemic events.[2] Subsequently, the WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial confirmed that among patients undergoing PCI who were receiving vitamin K antagonists, treatment with clopidogrel alone was associated with a lower incidence of bleeding and fewer ischemic outcomes than was dual antiplatelet therapy.[3] Bleeding often results in hypotension or cessation of antithrombotic therapy, both of which promote ischemic events.[3] In a recent, larger trial involving patients receiving oral anticoagulants who had undergone PCI or had an acute coronary syndrome, apixaban, as compared with vitamin K antagonists, reduced the incidence of bleeding without an increase in ischemic events.[4] The addition of aspirin to a $P2Y_{12}$ inhibitor increased the incidence of bleeding without reducing ischemic events.[4]

Bleeding risk is particularly relevant in patients undergoing transcatheter aortic-valve implantation (TAVI), especially those receiving oral anticoagulants, given the typical age of the patients undergoing TAVI, the frequent presence of coexisting conditions, and the use of large-bore access catheters. Expert opinion suggests that administration of clopidogrel may attenuate the risk of stroke and other embolic complications that are due in part to thrombus on the bioprosthetic valve.[5] Nijenhuis et al. now report in the *Journal* the results in cohort B of the POPular TAVI trial,[6] testing the hypothesis that in patients receiving anticoagulation, the use of oral anticoagulants alone would be safer than oral anticoagulants plus 3 months of clopidogrel. They assessed two coprimary end points: all bleeding and non–procedure-related bleeding within 12 months after TAVI. Secondary end points were a composite of death from cardiovascular causes, non–procedure-related bleeding, stroke, or myocardial infarction and a composite of death from cardiovascular causes, ischemic stroke, or myocardial infarction.

Although the trial confirmed a higher incidence of all bleeding among patients receiving oral anticoagulation plus clopidogrel than among those receiving oral anticoagulation alone (34.6% vs. 21.7%), there are concerns regarding the classification of bleeding and the reliability of secondary outcome analyses. Bleeding occurring during TAVI or the index hospitalization was unadvisedly defined as non–procedure-related,

even if it occurred at the access site. Details regarding baseline and procedural characteristics, including aspirin use, the specific direct-acting oral anticoagulants used by some patients, and how often oral anticoagulants were withheld periprocedurally, are lacking. Despite improved techniques for TAVI, continued use of oral anticoagulants around the time of the procedure could have increased bleeding risk. Although there was no clear signal that withholding clopidogrel resulted in an increased risk of stroke, myocardial infarction, or death from cardiovascular causes, given the size of the trial and the wide noninferiority margins for estimates of differences between groups in these outcomes, that possibility has not been ruled out. Furthermore, the assumption of proportional hazards for the two primary outcomes was not met, which possibly compromises statistical methods, and the lack of a clopidogrel placebo could have allowed ascertainment bias.

Another recent trial of clopidogrel plus 3 months of aspirin as compared with rivaroxaban plus 3 months of aspirin in patients undergoing TAVI without an indication for oral anticoagulation was stopped prematurely because of excess mortality in the rivaroxaban group, although the latter regimen reduced the incidence of bioprosthesis leaflet-motion abnormalities and leaflet thickening.[7,8] Given that apixaban has an apparently favorable risk–benefit profile and that less than a quarter of the patients in the POPular TAVI trial received direct-acting oral anticoagulants, we await the completion of the ongoing ATLANTIS (Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis) trial comparing apixaban with antiplatelet therapy in patients undergoing TAVI without an indication for oral anticoagulants and comparing apixaban with vitamin K antagonists in those receiving oral anticoagulants.[9,10]

TAVI is a breakthrough technique, providing a less invasive alternative to surgery for most patients with aortic stenosis, with similar benefit in terms of survival and quality of life. The development of safe and effective procedural and long-term antithrombotic regimens, especially for patients receiving oral anticoagulants, is warranted. In the current trial, the selection of bleeding as the primary outcome and its high frequency in the trial emphasize the importance of this event.[6] The ideal would be an anticoagulant regimen that minimizes the risk of death, stroke, myocardial infarction, or permanent disability, whether resulting from thrombosis or bleeding. These are the events that matter most to patients. Future trials assessing antithrombotic regimens for patients undergoing TAVI should be powered to evaluate these adverse outcomes.

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