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EDITORIAL COMMENT

Late Bleeding Following TAVR in Japan

An Important Cause of Mortality*

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The paper by Yamamoto et al[1] in this issue of *JACC: Asia* studies post transcatheter aortic valve replacement (TAVR) late bleeding (defined as bleeding after discharge) in a large multicenter cohort of over 2,500 patients from the Japanese OCEAN-TAVI (Optimized Transcatheter Valvular Intervention-Transcatheter Aortic Valve Implantation) registry. Importantly, 3 years after TAVR this complication was not rare, with 7.4% experiencing some form of bleeding and 5.2% experiencing major bleeding. Moreover, it conferred a more than 5-fold risk of mortality. In addition, a significant increase in mortality was found among those with minor bleeding compared with patients without bleeding events ($P = 0.002$), although it was much greater with major bleeding.

The study stands out in several respects that make its contribution to the field substantial. First, it is a large study of more than 2,500 patients. Second, several studies have studied the predictors and outcomes of early (in-hospital) bleeding but very few have the primary focus of late bleeding, up to 3 years post TAVR. Moreover, it is an important contribution because it is a study of Asian patients in the context of the predominantly Caucasian populations studied in the existing TAVR published reports.[2,3] The findings from this study confirm previously published TAVR data from Western countries, implying there are no racial or ethnic differences concerning the risk of late bleeding after TAVR.

Yamamoto et al[1] found by far the commonest source of bleeding was the gastrointestinal (GI) tract in 40.7% of patients, followed by intracranial bleeding in 25.7%. Subgroup analysis also showed a significantly increased risk of mortality in patients with GI bleeding (HR: 3.38; 95% CI: 2.26-5.05; $P < 0.001$) and hemorrhagic stroke (HR: 10.5; 95% CI: 6.85-16.0; $P < 0.001$). This is a relevant focus of future research in screening of GI and intracranial pathologies and conceivably for primary prevention. In addition, the distributions of gastric acid–suppressive agents did not differ in patients with GI bleeding and without GI bleeding ($P = 0.38$).

The coexistence of acquired von Willebrand factor deficiency secondary to aortic stenosis and angiodysplasia are known to cause Heyde's syndrome.[4] Although there has been some suggestion that TAVR may ameliorate this condition,[4] Heyde's syndrome and other incidental GI pathologies in elderly patients, exacerbated by anticoagulation and antiplatelet therapy, may be important contributors to GI bleeding that should be actively investigated in the presence of even minor degrees of pre-TAVR anemia of unknown etiology.

Intracranial bleeding was an important contributor to overall bleeding but more striking was its 10-fold risk of mortality. It is unclear whether the intracranial bleeding was spontaneous or related to falls in a typically frail population. We often observe an increase in mobility and confidence post TAVR with substantial cardiovascular symptom amelioration; it is important to have vigilance and physiotherapy support to ensure patient mobility is safe and patients are not at high risk of falls post TAVR.

The existence of atrial fibrillation (AF) was observed in approximately one-fifth of patients, whereas 19% of patients with AF were not administered oral anticoagulants (OACs) (n = 101 of 528). Notably, major bleeding was significantly higher in patients with OACs than in those without OACs ($P = 0.041$); it was also higher in patients with AF than in those without AF. However, the rates of ischemic

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stroke did not differ significantly between the OAC vs no OAC groups nor between the AF vs no AF groups. Yamamoto et al[1] emphasize that the influence on mortality was much greater with bleeding than ischemic stroke; at 3 years, 7.4% with bleeding versus 3.4% with ischemic stroke. The implication is that—in the context of TAVR—one must reconsider the paradigm of OAC even in the presence of AF, or one must consider alternatives such as left atrial appendage closure, which is the subject of ongoing studies. The findings are consistent with data from randomized studies, such as GALILEO (Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-base Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes), which demonstrated an excess of major bleeding with aspirin/rivaroxaban versus dual antiplatelet therapy following TAVR.[5]

As Yamamoto et al[1] note, although about 75% of the patients in the present study were prescribed dual antiplatelet therapy in the no OAC group, a recent randomized study[6] has demonstrated low rates of bleeding and similar rates of stroke events in patients prescribed single antiplatelet therapy versus dual antiplatelet therapy after TAVR. Single antiplatelet therapy has thus now become the evidence-based standard of care for post TAVR medical therapy in patients without AF or recent percutaneous coronary intervention. Indeed, there are individual patients in whom no antiplatelet or therapy is prescribed, particularly in the setting of bleeding or coagulopathy.

Yamamoto et al[1] rightly state that it is challenging to reduce the risk of late bleeding after TAVR. However, their work emphasizes a focus on avoidance of unnecessary antiplatelet or anticoagulation therapy and vigilance for susceptibility to falls, GI and intracranial pathologies; this is an important contribution which should further contribute to the amelioration of outcomes following TAVR in Asia.

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REFERENCES

1. Yamamoto M, Otsuka T, Shimura T, et al. Incidence, timing, and causes of late bleeding after TAVR in an Asian cohort. *JACC: Asia*. 2022;2(5):622–632.

2. Généreux P, Cohen DJ, Mack M, et al. Incidence, predictors, and prognostic impact of late bleeding complications after transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2014;64(24):2605–2615.

3. Kibler M, Marchandot B, Messas N, et al. Primary hemostatic disorders and late major bleeding after transcatheter aortic valve replacement. *J Am Coll Cardiol*. 2018;72(18):2139–2148.

4. Godino C, Lauretta L, Pavon AG, et al. Heyde's syndrome incidence and outcome in patients undergoing transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2013;61(6):687–689.

5. Dangas GD, Tijssen JGP, Wöhrle J, et al. GALILEO Investigators. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med*. 2020;382(2):120–129.

6. Brouwer J, Nijenhuis VJ, Delewi R, et al. Aspirin with or without clopidogrel after transcatheter aortic-valve implantation. *N Engl J Med*. 2020;383(15):1447–1457.

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