Is Dual Antiplatelet Therapy Necessary in Transcatheter Aortic Valve Implantation?

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The use of transcatheter aortic valve implantation (TAVI) for aortic valve stenosis became possible in Japan in 2013. In the past two years, TAVI has been performed in more than 2,000 cases; gradual introduction of the practice has initially produced favorable results. According to the Japan OCEAN-TAVI registry, the 30-day mortality rate is 1.9%, which is reportedly low in comparison to the rates in the United States and Europe.¹⁾

TAVI provides a hope for cure in patients with severe aortic valve stenosis. However, patients undergoing TAVI may be at high risk for bleeding and stroke. The incidence of these 2 complications is at least 10-fold higher for TAVI than for percutaneous coronary interventions (PCI): the 30-day risk of major stroke (~3.5%) and major bleeding/vascular complications (~10%) indicate a considerable challenge for balancing the risks of embolic and bleeding events in these high-risk patients²⁻¹⁸⁾ (Table I). When TAVI is used for treating embolism, it is a common practice to use dual antiplatelet therapy (DAPT) for 3 to 6 months¹⁷⁾ (Table II). However, this practice is mainly based on experience, and no analysis has been conducted yet through a large scale RCT. In particular, since Japanese patients often develop bleeding complications, it is likely that employing DAPT across the board may not be appropriate. The occurrence of serious bleeding events negatively impacts survival after TAVI and the risk of short and mid-term mortality.¹⁹⁾

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Bleeding complications in Japanese patients are believed to occur mainly due to their higher prevalence of metabolic abnormalities and smaller physique. Watanabe, *et al* reported that one third of the patients undergoing TAVI responded well to clopidogrel.²⁰⁾ There is a high incidence of bleeding complications and good responses among Japanese patients. Japanese patients with CYP2C19-induced metabolism abnormalities can be classified into poor metabolizers (PM, 19%), intermediate metabolizers (IM, 44%), and extensive metabolizers (EM, 37%). It is reported that 56% of Japanese patients have CYP2C19-induced metabolism abnormalities.²¹⁾ Based on these findings, Watanabe, *et al* pointed out that there is a risk associated with administering DAPT to all TAVI patients. In a meta-analysis to study whether P2Y12 reactivity units (PRU) can predict the prognosis, 3059 patients undergoing PCI were analyzed in 6 studies, and a significantly high incidence of complications due to MI or stent thrombosis was reported for

patients with PRU ≥ 230 .^{20,22)} In the dual antiplatelet therapy with drug-eluting stents (ADAPT-DES) prospective study involving 8,582 PCI patients in 11 US and European hospitals, bleeding complications due to MI or ST were significantly higher in the high platelet reactivity group with PRU > 208, suggesting that personalized treatment based on PRU measurements may be effective.²³⁾ On the other hand, in the ARCTIC trial prospective study with 2,440 PCI patients, or the GRAVITAS randomized trial prospective study with 2,214 PCI patients, no significant difference in prognosis could be attributed to PRU monitoring.^{24,25)} All these are PCI-based studies, and to date, no large-scale prospective study has been undertaken with TAVI; such a study is much needed.

Compared to Americans and Europeans, Japanese have smaller physiques, and exhibit a higher tendency to calcification of the valve annulus. There is a high risk of annulus rupture, and coronary artery disorders may be likely due to calcification of the valsalva sinus. Watanabe, *et al* reported that with narrow peripheral vasculature, vascular complications and the 30-day combined safety endpoint rate were significantly higher in the small body (body surface area < 1.75 m²) group (13.0% versus 4.3%, $P < 0.01$; 27.4% versus 18.3%, $P = 0.03$, respectively).^{20,26)} In cases of vascular complications or conversion to surgical aortic valve replacement (SAVR), oral administration of DAPT increases the bleeding risk. Since Japanese people have a smaller physique, a more discreet use of antiplatelet agents is called for.

Among the TAVI patients, approximately one third had chronic atrial fibrillation (AF) and were undergoing anticoagulation therapy. AF patients often take warfarin, and there is no predetermined antiplatelet therapy for TAVI patients undergoing anticoagulant therapy. Aspirin and warfarin or warfarin alone may be the most effective and safe approach to anticoagulation in post-TAVI patients with underlying AF. In the WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting?) trial, clopidogrel with warfarin was superior to triple therapy in patients with atrial fibrillation undergoing drug-eluting stent placement (including a striking decrease in all-cause mortality associated with clopidogrel/warfarin [hazard ratio: 0.39; 95% CI: 0.16 to 0.93]).^{27,28)} Further large-scale prospective studies are required before we can confidently recommend a similar protocol for TAVI as well.

Since the bleeding risk is high for TAVI in Japanese patients because of the high prevalence of CYP2C19-induced

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Table I. Ischemic and Bleeding Outcomes at 30 Days and 1 Year in Large TAVI Registries

	European ⁸⁾ (n = 646)	Canadian ⁵⁾ (n = 339)	SOURCE ^{6,7)} (n = 1,038)	Italian ²⁴⁾ (n = 663)	FRANCE ⁹⁾ (n = 244)	Belgian ¹¹⁾ (n = 328)	FRANCE-2 ¹⁶⁾ (n = 3,195)	SOURCE XT ¹³⁾ (n = 2,706)	ADVANCE ¹⁴⁾ (n = 1,015)	ANZ ¹⁵⁾ (n = 428)
30 days										
Vascular complications	-	13.0%	12.8%	-	7.3%	-	-	-	-	12.6%
Major	-	-	7.0%	2.0%	-	-	-	6.0%	10.7%	4.0%
Minor	-	-	5.5%	-	-	-	-	-	-	8.9%
Bleeding	-	-	-	-	-	-	-	-	-	23.1%
Life-threatening/disabling	-	-	-	-	-	-	-	-	4.0%	4.7%
Major	-	-	-	-	-	-	-	7.2%	9.7%	8.9%
Minor	-	-	-	-	-	-	-	-	-	12.9%
Stroke	1.9%	2.3%	2.5%	1.2%	3.6%	5.0%	3.4%	2.2%	2.9%	3.6%
Major	-	-	-	-	-	-	1.9%	-	1.2%	-
Minor	-	-	-	-	-	-	1.5%	-	1.7%	-
1 year										
Vascular complications	-	-	-	-	-	-	-	-	-	-
Major	-	-	-	-	-	-	4.7%	-	-	-
Minor	-	-	-	-	-	-	5.0%	-	-	-
Bleeding	-	-	-	-	-	-	13.1%	-	-	-
Life-threatening/disabling	-	-	-	-	-	-	1.2%	-	-	-
Major	-	-	-	3.2%	-	-	4.5%	-	-	-
Minor	-	-	-	-	-	-	7.4%	-	-	-
Stroke	-	-	4.5%	2.5%	-	-	4.1%	-	-	5.3%

ANZ indicates Australia-New Zealand; FRANCE, French Aortic National CoreValve and Edwards Registry; SOURCE, SAPIEN Aortic Bioprosthesis European Outcome Registry; and TAVI, transcatheter aortic valve implantation. (Rodés-Cabau J, *et al.* J Am Coll Cardiol 2013; 62: 2349-59.¹⁸⁾)

Table II. Current Recommendations for Antithrombotic Agents and Strategies for TAVI

	PARTNER Trial ^{17,18)}	ACC/STS Recommendations ³⁰⁾	CCS Statement ³¹⁾
Pre-procedural	Aspirin 80 mg Clopidogrel 300 mg	-	-
Procedural	Unfractionated heparin Goal ACT: 250 s Reversal with protamine optional Bivalirudin – not allowed?	Unfractionated heparin Goal ACT: 300 s Reversal with protamine recommended Bivalirudin – not mentioned	-
Post-procedural (first 30 days)	Aspirin 81 mg/day indefinitely + Clopidogrel 75 mg/day × 90 days	Aspirin 81mg/day indefinitely + Clopidogrel 75mg/day × 3-6 months If warfarin indicated (AF), then no clopidogrel	Indefinite low-dose aspirin generally recommended + Thienopyridine × 1-3 months. If oral anticoagulant indicated (AF), avoid triple therapy unless definite indication exists

ACC indicates American College of Cardiology; ACT, activated clotting time; AF, atrial fibrillation; CCS, Canadian Cardiovascular Society; STS, The Society for Thoracic Surgeons; and TAVI, transcatheter aortic valve implantation. (Rodés-Cabau J, *et al.* J Am Coll Cardiol 2013; 62: 2349-59.¹⁸⁾)

metabolic abnormalities and their small physique, rather than blindly applying the results of Western studies, the accumulation of Japanese-specific research data is needed. In addition, since TAVI patients develop complications because approximately one third of them have AF and 60% have coronary artery disorders,²⁹⁾ studies on a case-by-case basis are required on therapy consisting of combinations of anticoagulant, aspirin, and thienopyridine, depending on varying conditions such as post-PCI, complications due to AF, and different time periods after stent placement. Instead of a standardized approach to decide the DAPT period, it is considered likely that personalized medicine that takes into account gene polymorphism based on PRU measurements from VerifyNow may be more effective.

DISCLOSURE

Conflicts of interest: The authors declare there are no conflicts of interest.

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