

STATE-OF-THE-ART REVIEW

Transcatheter Aortic Valve Replacement in Asia

Present Status and Future Perspectives



Cheol Hyun Lee, MD, PhD,^{a,*} Taku Inohara, MD, PhD,^{b,*} Kentaro Hayashida, MD, PhD,^b Duk-Woo Park, MD, PhD^c

ABSTRACT

Over the last decade, based on evidence from multiple randomized clinical trials, transcatheter aortic valve replacement (TAVR) has become the established treatment for patients with symptomatic severe aortic stenosis. Despite the overwhelming expansion of TAVR in Western countries, the initial uptake and widespread adoption of this procedure have been relatively delayed in Asian countries, owing to the high cost of devices; limited local health and reimbursement policies; and lack of specific training/proctoring program, specialized heart team, or dedicated infrastructure. Furthermore, it has not yet been determined whether there are substantial interracial and ethnic differences in the clinical characteristics, comorbidities, and anatomic features, as well as procedural and long-term outcomes, in patients receiving TAVR. In this review, we provide not only a comprehensive look at the current status and outcomes of TAVR in Asian populations compared with those of Western populations but also a perspective on the future of TAVR in Asia. (JACC: Asia 2021;1:279–293) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Over the last 15 years, novel transcatheter therapies for valvular heart disease (VHD) have been rapidly developed and adopted worldwide (1). In Western countries, transcatheter aortic valve replacement (TAVR) was introduced earlier than it was in Asia, and since the inception of this procedure, it has been widely used for the treatment of severe aortic stenosis (AS). Among Asian countries, the first TAVR case was performed back in 2009 in Singapore (2), but the adoption of TAVR in Asia was slower than in the United States and Europe, mainly because of the lack of full reimbursement for TAVR and local regulations for new device approval (3).

Additionally, there are significant differences between Asian and Western patients in terms of physique, anatomy of the aortic complex, thrombogenicity, and hemorrhagic diathesis. In particular, reflecting the smaller body size, the aortic valvular dimension is smaller in Asian patients than in Western patients (4), which may affect the choice of device and valve size and eventually influence short- and long-term prognoses. Furthermore, compared with Western patients, Asian patients are more susceptible to bleeding events but are relatively resistant to thromboembolic events (5). Therefore, the optimal antithrombotic strategy post-TAVR for Asian patients may be different from that for Western patients.

From the ^aDivision of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Hospital, Daegu, South Korea;

^bDepartment of Cardiology, Keio University School of Medicine, Tokyo, Japan; and the ^cDepartment of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea. *Drs Lee and Inohara contributed equally to this work.

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ABBREVIATIONS AND ACRONYMS

AS	= aortic stenosis
AR	= aortic regurgitation
BAV	= bicuspid aortic valve
BSA	= body surface area
PPI	= permanent pacemaker insertion
PPM	= patient-prosthesis mismatch
PVL	= paravalvular leak
RCT	= randomized clinical trial
SAVR	= surgical aortic valve replacement
STS	= Society of Thoracic Surgeons
TAVR	= transcatheter aortic valve replacement
VHD	= valvular heart disease

Until recently, a very limited number of Asian patients were enrolled in landmark randomized controlled trials (RCTs) (6). Therefore, whether or not the clinical evidence and practical guidelines from Western countries can be unconditionally generalizable to Asian patients with different characteristics remains largely unclear. This review summarizes particular clinical or anatomic features of patients, clinical experience with available TAVR devices, specific logistic or technical considerations, and a perspective on the future of TAVR in Asia, particularly in East and Southeast Asian countries.

EPIDEMIOLOGY AND ANATOMY

RACIAL DIFFERENCES IN THE PREVALENCE AND EPIDEMIOLOGY OF AS.

AS is the most common VHD worldwide, and its prevalence increases with age. Prior studies have suggested racial/ethnic differences in AS prevalence, but these were limited by potential selection bias (7). Although East Asian ethnic groups are among the most populous (>1.5 billion people), data from Asian populations with severe AS are limited, and the diagnosis of AS was less prevalent relative to that in Western populations. Based on a prior modeling study, the prevalence rate of AS was 12.4% in elderly individuals (>75 years), and AS is estimated to affect approximately 2.7 million and 4.9 million people in North America and Europe, respectively (8). Unfortunately, the disease prevalence of AS in elderly Asian individuals is still unknown. The established risk factors for the development and progression of AS include hypertension, advanced age, congenital bicuspid aortic valve (BAV), smoking, hyperlipidemia, renal insufficiency, diabetes mellitus, atherosclerosis, and congestive heart failure (9-11). However, few studies have examined the differences in the prevalence, contributory risk factors, management, and outcomes of severe AS in racially and ethnically diverse populations, especially East Asian populations (7).

A prior study using the Healthcare Cost and Utilization Project Nationwide Inpatient Sample in the United States reported that Asian individuals might have a paradoxically lower prevalence or incidence of AS relative to White individuals, despite having a higher prevalence of traditional risk factors (12). Similarly, results from MESA (the Multiethnic Study of Atherosclerosis) reported that Chinese participants had a lower prevalence of AS or aortic valve replacement than did White participants, without a

difference in AS severity by race/ethnicity (13); however, the exact etiology and pathophysiologic mechanisms of these racial/ethnic disparities are unknown. Among the East Asian population, the most common cause of AS is degenerative calcific aortic valve disease, which shares many risk factors with atherosclerotic cardiovascular disease. AS can also be caused by congenital BAV and rheumatic VHD, which are more common in Asian countries. Although the prevalence of rheumatic VHD has steadily declined, this etiology is still substantially prevalent in Asia (4.54/1,000 in India, 1.86/1,000 in China, and 1.3/1,000 in Bangladesh) (14). However, TAVR is not usually an initial treatment because rheumatic AS progresses at a young age and is typically accompanied by mitral and tricuspid valve disease (15).

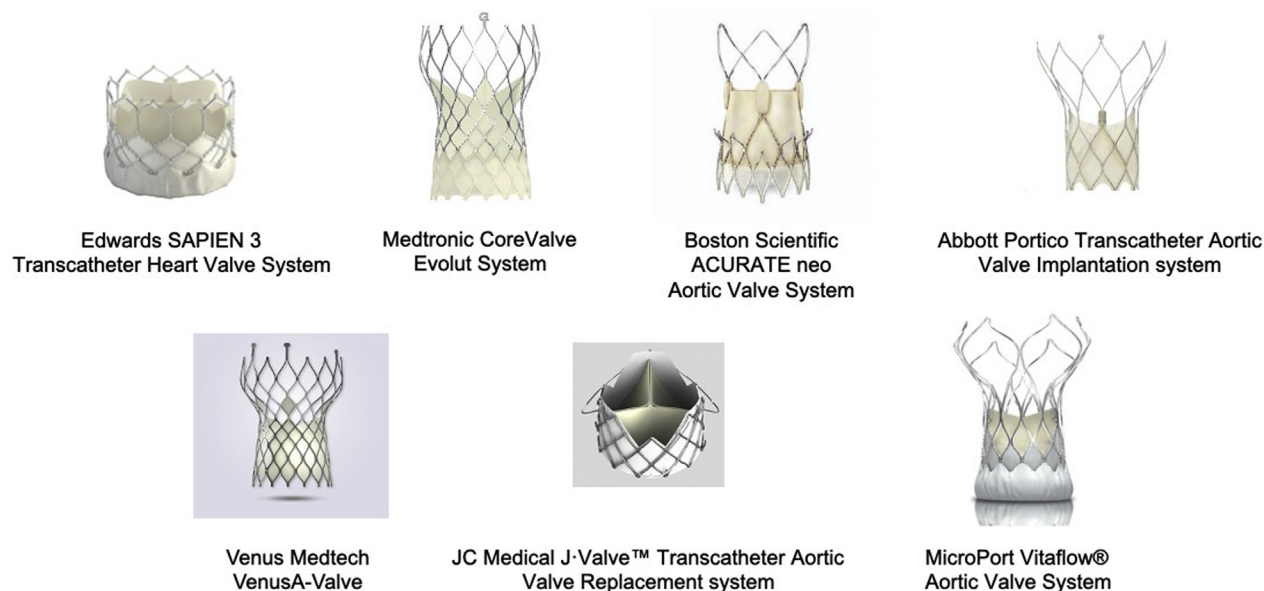
It has been widely reported that, compared to White patients, non-White patients (including Asian patients) possess higher rates of traditional AS risk factors, such as congestive heart failure, chronic kidney disease, smoking, hypertension, obesity, and diabetes mellitus (9-11,16,17). Given that comparative data on epidemiology and demographic characteristics of AS in East Asian populations and Western populations were not available, further research is required to elucidate the mechanism behind the so-called “AS paradox” in Asian populations (ie, more AS risk factors but a lower prevalence of AS) (7).

RACIAL DIFFERENCES IN PREVALENCE AND ANATOMY OF BAV.

Compared to AS in a tricuspid aortic valve, the combination of AS in BAV is frequently found in patients with younger age and involves severely calcified valves, larger dimensions of the ascending aorta, and combined aortopathy. The prevalence of BAV in Asian populations is thought to be higher than that in Western populations, although comparative clinical data are still scant. Li et al (18) reported that the incidence of BAV was 0.4% in a West China Hospital cohort, and 87% of cases were complicated by various degree of AS or aortic regurgitation (AR). In a health screening study of 23,291 Korean patients, a BAV prevalence of 0.16% was reported (19). In contrast, the prevalence of BAV was 7.9% in a community-based, cross-sectional study including 14,530 Chinese children (20). More comparative data are required to determine true racial differences in BAV incidence.

Few studies have reported potential racial differences in BAV disease between Asian and Western populations. Kong et al (21) reported BAV morphology and function using data from 2 large cohorts of European and Asian patients with BAV. Key findings were that: 1) Asians had a higher prevalence of type 1

FIGURE 1 Currently Available Transcatheter Aortic Valve Replacement Devices in Asian Countries



BAV, with more fusion of the right and noncoronary cusps, than did Europeans (Europeans vs Asians: 14% vs 20%), whereas Europeans had a higher prevalence of type 0 BAV than did Asians (15% vs 7%, respectively); 2) functionally, AS is common in both Asian and Europeans, but the prevalence of moderate and severe AR was higher in Europeans than in Asians (44% vs 27%); and 3) the indexed sizes of the annulus, sinus of Valsalva, sinotubular junction, and ascending aorta were significantly larger among Asians than among Europeans. However, in some Chinese registries, the prevalence of type 0 BAV was reported to be as high as 54.4% (22); thus, to clarify this discrepancy, further large-scale studies are needed to determine the distribution of BAV morphology types in Asian countries.

RACIAL DIFFERENCES IN THE CHARACTERISTICS OF PATIENTS RECEIVING TAVR. The management of symptomatic AS has evolved over time: from medical therapy to balloon valvuloplasty to surgical aortic valve replacement (SAVR). More recently, TAVR has been successful in reducing morbidity and mortality in high-risk patients, and eligibility is expanding to intermediate- and low-risk patients. This paradigm shift for AS management is similar to that in Asia (23), and a recent meta-analysis and stochastic simulation study suggests that the estimated number of symptomatic AS patients eligible for TAVR may be

substantial in Asian countries (24). Additionally, because the recent American College of Cardiology/American Heart Association guideline has expanded potential TAVR candidates to patients aged 65 years or older (25), a substantial number of patients would be suitable for the TAVR.

The small aortic size and peripheral vessels in Asian patients are of significant concern to physicians because of an increased risk for complications. Indeed, small body surface area (BSA), small annulus dimensions, and low coronary ostia takeoff were reported in the international Asian TAVR registry, PREVAIL JAPAN (Transfemoral and Transapical Placement of Aortic Balloon Expandable Transcatheter Valves), and OCEAN-TAVI (Optimized Transcatheter Valvular Intervention) studies (26-28). Baseline clinical, anatomic, and procedural characteristics of Asian patients compared with those of Western patients in several key TAVR registries are summarized in Supplemental Table 1. In general, the mean age and the surgical risk measured by the Society of Thoracic Surgeons (STS) scores were similar in the Asian and Western registries. With regard to anatomic features, Asian patients showed a lower left coronary artery ostial height, sinus of Valsalva height, and sinotubular junction height, as well as a smaller aortic valve annulus and sinotubular junction, than did Western patients (27,29). Low-flow AS (stroke

TABLE 1 Currently Available TAVR Devices in Asian Countries

Device	FDA Approval	CE Mark	Japan	Korea	China ^a	Taiwan	Hong Kong	India ^a	Singapore	Thailand	Malaysia	Vietnam	Philippines
Edwards													
Sapien 3	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medtronic													
Evolut R	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
Evolut PRO	✓	✓	✓	✓		✓	✓	✓	✓	✓			
Evolut PRO+	✓	✓ October 2019	✓										
Melody	✓								✓	✓			
Abbott													
Portico	✓	✓				✓	✓		✓	✓			
Portico FlexNav	✓ March 2020	✓				✓				✓			
Boston Scientific													
Acurate neo	✓ 2019					✓ No cases done yet	✓			✓			✓
Acurate neo2													

The data are as of March 2021. A ✓ symbol stands for launched. ^aLocally manufactured valves are also available: in China, the Venus A-valve (Venus MedTech), J-Valve (Jie Cheng Medical Technologies), and MicroPort VitaFlow valve (MicroPort Medical) and in India, the MyVal (a balloon-expandable system from Meril Life Sciences Pvt Ltd) and Hydra (a self-expanding system from Vascular Innovations Co Ltd).
CE = Conformance Européenne; FDA = U.S. Food and Drug Administration; TAVR = transcatheter aortic valve replacement.

volume index: <35 mL/m²) is more common in Asian than in Western populations (30,31). Plausible reasons for baseline differences in TAVR recipients in Asian and Western countries are likely multifactorial based on a complex interplay of racial, genetic, socioeconomic, cultural, and patient- and provider-centric factors, as well as different health care systems. Such specific biological and anatomic features of Asian Pacific populations will be important for guiding optimal valve selection and future TAVR valve development in Asian countries, and this difference may be more suited and optimized by special device designs in the near future.

TAVR DEVICES IN ASIA

AVAILABLE TAVR DEVICES IN THE ASIA PACIFIC REGION. Currently, in most Asian countries, TAVR is widely performed as an established treatment strategy for AS. Several kinds of prosthetic valves are commercially available in Asia (Figure 1, Table 1). The Edwards Sapien (Edwards Lifesciences) family of balloon-expandable prostheses are, by far, the most common TAVR prosthesis used in Asia; one of these was the first TAVR device to be implanted in Asia in 2009. The Medtronic self-expanding prostheses (CoreValve and Evolut series) are the second most used TAVR valves in Asia. In the OCEAN-TAVI registry, 90.3% and 9.7% of all TAVR procedures in Japan were done using the Sapien and CoreValve/Evolut series, respectively (32). However, the relative proportion of the 2 most frequently used valves may vary greatly from country to country in Asia. In Singapore, Thailand, Taiwan, and Hong Kong, the Portico valve (Abbott) and Acurate valve (Boston Scientific) are

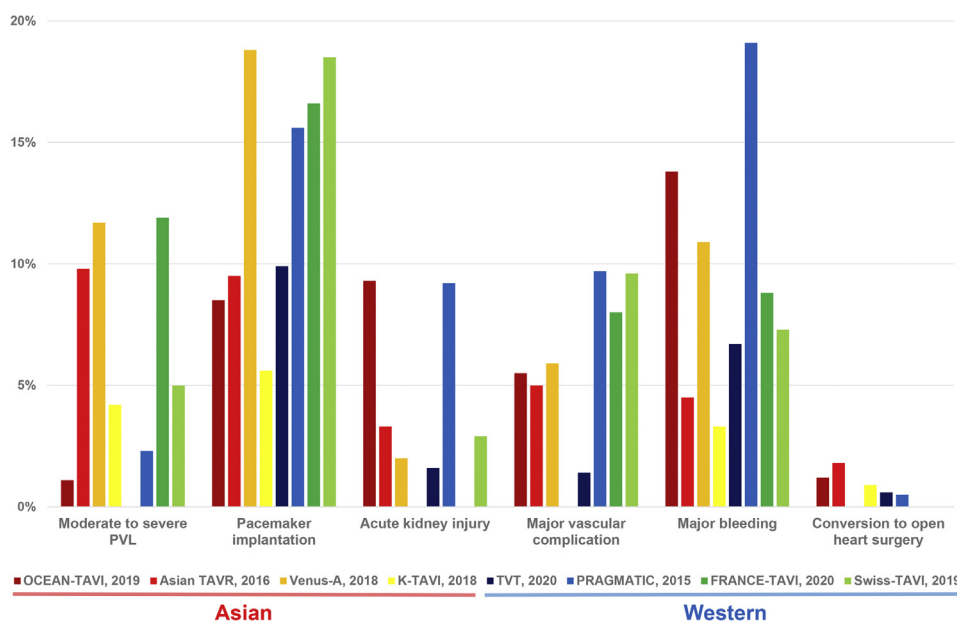
commercially available. The Lotus valve (Boston Scientific) was previously launched and had been used in several Asian countries but was recalled globally because of complexities associated with the product delivery system; it is currently no longer commercially available (33).

LOCALLY MANUFACTURED TAVR DEVICES IN THE ASIA PACIFIC REGION. In China, in addition to the Sapien 3, there are 3 locally manufactured valves that have received Chinese regulatory approval: the Venus-A valve (Venus MedTech), J-Valve (Jie Cheng Medical Technologies), and MicroPort VitaFlow valve (MicroPort Medical) (34) (Figure 1). Similarly, in India, there are 2 available indigenous valves: MyVal (a balloon-expandable system from Meril Life Sciences Pvt Ltd) and Hydra (a self-expanding system from Vascular Innovations Co Ltd), (35). The approval of these domestic valves promoted the rapid development of TAVR in both countries; however, there is scarce evidence supporting the safety and efficacy of these locally manufactured TAVR valves, and thus, high-quality comparative effectiveness studies should be encouraged.

OUTCOMES OF TAVR IN ASIA

PROCEDURAL COMPLICATIONS. The incidences of procedural complications in Asian patients and Western patients receiving TAVR are summarized in Supplemental Table 2. The rates of key procedural outcomes, such as paravalvular leakage (PVL), permanent pacemaker implantation (PPI), major vascular complications, major bleeding, and conversion to open heart surgery, were generally comparable

FIGURE 2 Key Procedural Complications in Asian Versus Western TAVR Registries



FRANCE-TAVI = French Transcatheter Aortic Valve Implantation; K-TAVI = Korean-Transcatheter Aortic Valve Implantation; OCEAN-TAVI = Optimized Transcatheter Valvular Intervention; PRAGMATIC = Pooled Rotterdam-Milan-Toulouse in Collaboration; PVL = paravalvular leak; Swiss-TAVI = Transcatheter Aortic Valve Implantation in Switzerland; TAVR = transcatheter aortic valve replacement; TVT = Transcatheter Valve Therapy.

between the 2 populations (Figure 2). Particularly, the Asian-TAVR Registry (848 patients at 11 centers in Singapore, Hong Kong, Taiwan, Japan, and Korea) showed favorable rates of procedural success (97.5%), 30-day mortality (2.5%), stroke (3.8%), and serious vascular complications (5.0%) (26). The OCEAN-TAVI registry (1,613 patients at 14 centers in Japan) (32) also showed similar procedural complication rates, which were not higher than those reported in the Western registries (36-38). Several small studies involving the Venus-A valve (39), J-valve (40), and VitaFlow (41) in China revealed that there was no significant difference in device success rate or early complication rates compared with other studies.

With regard to specific procedural complications, PVL was not a small occurrence in the early days of TAVR, was a powerful independent predictor of mortality, was an important evaluation index after post-TAVR (42). However, with the continuous advancement of TAVR devices and implant or sizing techniques, the prevalence of PVL has dramatically decreased over time. Nevertheless, the overall incidence of moderate or severe PVL is now reported in approximately 3% or more in recent studies, which is also related to higher mortality rates (6,43,44). In

Asian populations, the incidence of moderate to severe PVL was reported as 1.1% in the OCEAN-TAVI registry and 9.8% in the Asian-TAVR Registry, but the rate of PVL was substantially reduced with newer-generation TAVR devices (45,46). Atrioventricular block requiring PPI is mainly caused by mechanical or inflammatory trauma to the conduction system by a TAVR device, and the reported rates were 5% to 20% in several previous reports (26,32,47-50), which were similar to those in the Asian registries. Known risk factors for PPI include older age, baseline right bundle branch block or left bundle branch block, hypertension, diabetes, prior myocardial infarction, and use of self-expanding valves, rather than racial factors (51). The incidences of other serious complications, including coronary obstruction, annular rupture, device embolization, serious bleeding, and disabling strokes, were quite low, and these complications were not specific for Asian patients.

SHORT- AND LONG-TERM OUTCOMES. The incidences of death or stroke at 30 days and 1 year and key findings of the Asian and Western registries are summarized in Table 2. The incidences of mortality and stroke during long-term follow-up in Asian populations were similar to those in Western populations

(Figure 3). Several studies have proposed that racial and ethnic disparities exist in the performance and outcomes of TAVR (26,52,53). In a recent report from the (transcatheter valve therapy (TVT) registry including 70,221 patients (91.3% White, 3.8% Black, 3.4% Hispanic, and 1.5% Asian/Native American/Pacific Islander), the adjusted 1-year mortality rate was significantly lower among patients of Asian/Native American/Pacific Islander descent than in White patients (53). However, the proportion of Asian patients was very small in this registry (<2%). It has been reported that the clinical outcomes of TAVR in Asian populations were comparable with those of Western populations from RCTs and clinical registries (7,26). In the Asian Registries, despite the presence of anatomic features of concern, the long-term clinical outcomes post-TAVR were similar to reports from previously published trials and observational studies (Central Illustration). Unfortunately, there have been no large-scale studies directly comparing patient characteristics and outcome differences in TAVR recipients between Asian and Western populations. Further comparative studies will provide clinical insights to understand race-based differences in TAVR outcomes.

SPECIAL CONSIDERATIONS FOR TAVR IN ASIA

REIMBURSEMENT POLICIES AND LOGISTIC ISSUES.

The adoption of TAVR in Asia has been relatively delayed compared to that in Western countries (3), which is mainly attributed to the high cost of devices and the lack of full reimbursement for TAVR in most parts of Asia. In South Korea, the government decided on a policy of 20% reimbursement for medical expenditures related to TAVR by the national medical insurance program, at least until the mandatory 3-year monitoring period was over (June 2018) (54). Similarly, in India, a patient needs to pay approximately 80% of the treatment cost related to TAVR (35). Several studies demonstrated that TAVR is economically dominant by providing both greater quality-adjusted life expectancy and lower long-term treatment costs than SAVR (55,56). However, the high cost of TAVR devices still represents a major obstacle to the liberal adoption of TAVR, and thus, low-income patients might have to choose the lower-cost cardiac surgical option. Japan is the only exception in Asia, where public health insurance covers all treatment costs, even of TAVR. The self-pay burden is determined by a patient's age and annual income and ranges from 10% to 30%. Most patients undergoing TAVR pay <10% of medical expenditures because

the “high-cost medical expense benefit” is also applied, which means that a ceiling amount is predetermined (57). Given the coverage of public health insurance, Japan has had the largest number of TAVR implants to date in Asia (6,810 cases in 2018) (58). Currently, the local Asian companies manufacturing devices are trying to increase the potential market of TAVR by lowering prices, which may increase market competition and eventually contribute to device cost reduction.

Each country has its own regulatory pathway. In Singapore, medical devices are regulated by the Health Sciences Authority, and its process time is significantly reduced by prior approval in a reference market, including the United States (U.S. Food and Drug Administration) and Europe (Conformite Europeenne mark). Given that, the approval of a new medical device in Singapore is usually takes less time than it does in other Asian countries. The review process in Japan is relatively slow because a domestic clinical trial is mandatory in addition to internationally performed trials, according to the regulatory authority (Pharmaceuticals and Medical Devices Agency). However, recently, through the U.S.-Japan Medical Device Harmonization by Doing initiative, the regulatory bodies of both countries have agreed on standards for global clinical trials related to cardiovascular devices, which has facilitated device approvals in both countries (59). Furthermore, participation in global trials is key for boosting the approval process. A total of 3 and 8 Japanese institutes participated and enrolled Asian patients in the RCTs of PARTNER-3 (Placement of Aortic Transcatheter Valves-3) and the Evolut Low-Risk Trial, respectively, which facilitated the review process regarding the expansion of TAVR indications in patients with low surgical risk (6,44). These efforts may further bridge the present gap of clinical evidence and several logistic issues between Western and Asian countries.

The number of centers performing TAVR in Asia is increasing rapidly (23). In the early days, TAVR procedures started centered on high-volume tertiary referral hospitals, but recently, TAVR procedures are spreading to medium-volume secondary hospitals as well. Multidisciplinary heart team discussions involving cardiac surgeons, imaging specialists, and anesthesiologists as well as interventionists are an essential part of TAVR. Among them, cooperation with cardiac surgeons is particularly important, and the trend of active participation in all TAVR steps from valve positioning to deployment, as well as patient selection, access site approach, and hemodynamic support, will be important not only in the United States

TABLE 2 Short- and Long-Term Clinical Outcomes of TAVR in Asian and Western Registries

Study, Year (Ref. #)	Design	Device Type	Asian, n	Western, n	Duration, mo	Endpoint/Definition			Summary of Key Findings
						Primary Endpoint/ Definition	Death	Stroke	
Asian TAVR registries									
OCAEN-TAVI, 2019 (32)	Multicenter registry	BE, SE	1,613	—	12	All-cause death at 30 d and 1 y/VARC-2	30 d All-cause death: 1.7% Cardiac death: 1.4% 1 y All-cause death: 11.3% Cardiac death: 4.5%	Procedural Disabling stroke: 1.7%	Excellent early and midterm outcomes have been achieved to overcome the learning curve.
Asian-TAVR, 2016 (26)	Multicenter registry	BE (n = 549), SE (n = 299)	848	—	24	All-cause death at 30 d and 1 y/VARC-2	30 d All-cause death: 2.5% Cardiac death: 1.7% 1 y All-cause death: 10.8% Cardiac death: 4.6% 2 y All-cause death: 16.7% Cardiac death: 8.0%	Procedural Any stroke: 3.8% Disabling stroke: 2.2%	Despite the presence of anatomic features of concern, the clinical outcomes of TAVR in Asian populations were favorable.
Venus-A, 2018 (39)	Multicenter registry	SE	101	—	12	All-cause death at 1 y/VARC-2	30 d All-cause death: 5.3% 1 y All-cause death: 6.9%	Procedural Any stroke: 1.0%	The AS population in China presenting for TAVR has a high prevalence of BAV. The Chinese TAVR devices are favorable and similar to those in TAV.
K-TAVI, 2018 (74)	Multicenter registry	BE, SE	576	—	12	All-cause death at 1 y/VARC-2	30 d All-cause death: 2.6% Cardiac death: 1.2% 1 y All-cause death: 8.9% Cardiac death: 3.3%	30 d Any stroke: 1.6% Disabling stroke: 1.2% 1 y Any stroke: 3.2% Disabling stroke: 2.2%	The K-TAVI registry showed favorable 1-y outcomes with decreasing complication rates over time in real-world Korean patients.
Western TAVR registries									
TVT, 2020 (50)	Web-based multicenter registry	BE, SE	11,006	265,310	12	All-cause death at 30 d and 1 y/DCF version 1.3	30 d All-cause death: 7.1% → 3.8% (2011 → 2019) 1 y All-cause death: 24.3% → 16.6% (2011 → 2019)	30 d Stroke: 2.1% → 1.6% (2011 → 2019) —	Since 2011, the 30-d mortality rate has decreased (from 7.2% to 2.5%) and the stroke rate has started to decrease (from 2.75% to 2.3%), but pacemaker need is unchanged (from 10.9% to 10.8%). Outcomes up to 1 y have steadily improved.
PRAGMATIC, 2015 (49)	Multicenter registry	BE, SE	—	1,062	24	All-cause death at 30 d and 1 y/VARC-2	30 d All-cause death: 5.9% Cardiac death: 5.3% 1 y All-cause death: 18.5% Cardiac death: 11.2%	30 d Any stroke: 4.0% Disabling stroke: 2.4% —	The prevalence of MAS in this real-world, all-comer TAVI population was relatively high (39.5%). MAS was associated with lower device success and higher incidence of PVL.
FRANCE-TAVI, 2020 (47)	Multicenter registry	BE, SE (PS matching)	—	BE (n = 3,910) SE (n = 3,910)	24	Moderate to severe PVL at discharge or in-hospital all-cause death/VARC-2	2 y BE: 26.6% 2 years SE: 29.8%; P = 0.002	—	The present study suggests that use of SE was associated with a higher risk of paravalvular regurgitation and higher in-hospital and 2-y mortality rates compared with use of BE.
Swiss-TAVI, 2019 (48)	Multicenter registry	BE, SE	—	TAVR (n = 4,599) VIV (n = 157)	12	All-cause death at 1 y/VARC-2	1 y, TAVR: All-cause death: 13.0% Cardiac death: 9.0% 1 y, VIV All-cause death: 6.8% Cardiac death: 4.8%	1 y, TAVR Any stroke: 4.8% 1 y, VIV Any stroke: 2.2%	VIV procedures showed favorable 30-d and 1-y clinical outcomes compared with TAVI procedures for the native aortic valve disease.

AS = aortic valve stenosis; BAV = bicuspid aortic valve; BE = balloon expandable; DCF = data collection form; FRANCE-TAVI = French Transcatheter Aortic Valve Implantation; K-TAVI = Korean-Transcatheter Aortic Valve Implantation; MAS = mixed aortic stenosis; OCAEN-TAVI = Optimized Transcatheter Aortic Valve Intervention; PRAGMATIC = Pooled Rotterdam-Milan-Toulouse in Collaboration; PS = propensity score; PVL = paravalvular leak; SE = self-expanding; Swiss-TAVI = Transcatheter Aortic Valve Implantation in Switzerland; TAV = tricuspid aortic valve; TAVI = Transcatheter Aortic Valve Implantation; TAVR = transcatheter aortic valve replacement; TVT = transcatheter valve therapy; VARC = Valve Academic Research Consortium; VIV = valve-in-valve.

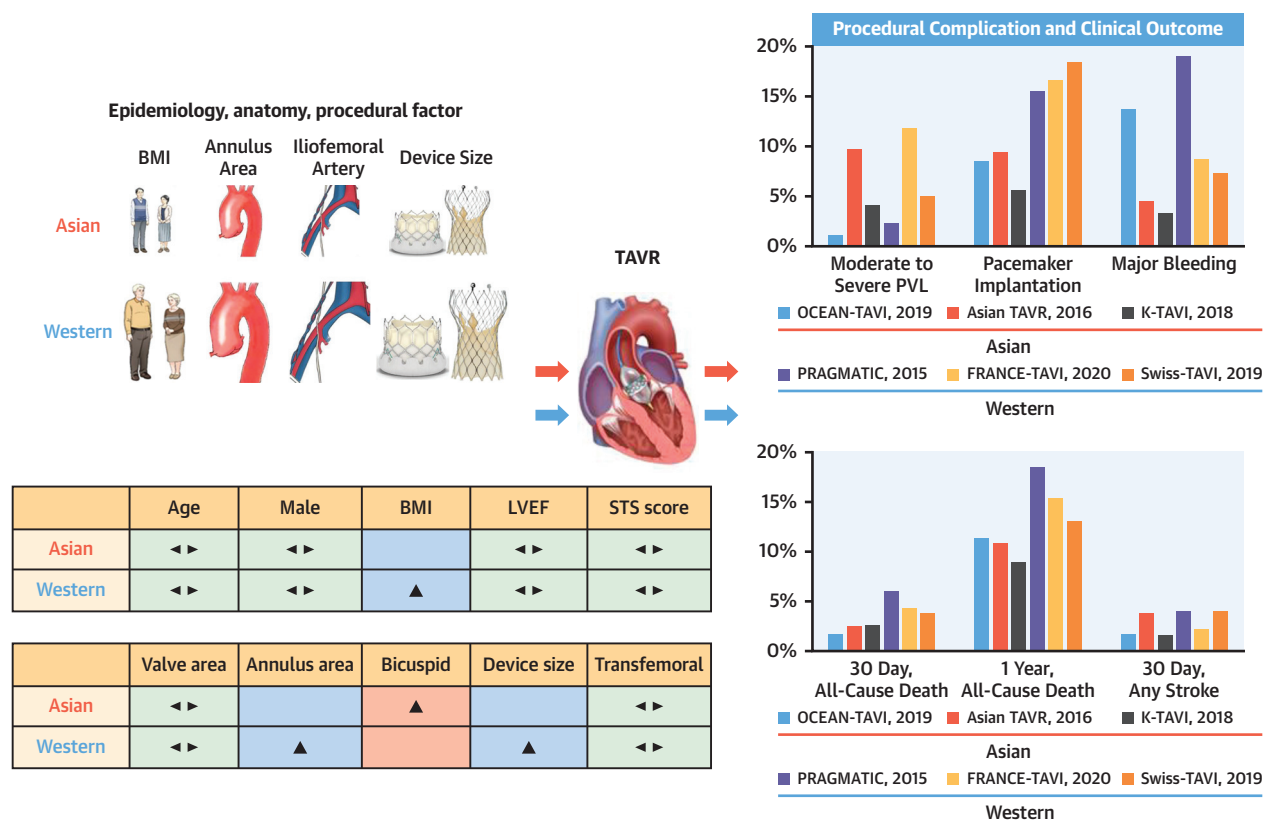


(60) but also in many Asian countries. In addition, in low-volume centers as well as low-income and developing countries, the ability of experts in each field of the heart team may be insufficient. Therefore, it may be possible to raise ability through regular expert training or the supervision of procedures through proctorship and international scientific meetings.

SUGGESTED SIZING ALGORITHM AND CHOICE OF TAVR VALVES. Preprocedure computed tomography imaging is instrumental for determining the optimal size of transcatheter heart valves. It is well known that the aortic annulus is smaller in Asian populations than in Western populations. In line with this, in the OCEAN-TAVI registry, about two-thirds of patients were treated with 20-mm or 23-mm Sapien 3 valves and the 26-mm CoreValve series (32). Additionally, the sizes of the sinotubular junction and sinus of Valsalva need to be taken into account; the sinus of Valsalva is also smaller in Asian populations than in Western populations, which may result in coronary obstruction (4). To avoid coronary obstruction for patients with a small sinus of Valsalva, smaller sizes of self-expanding valves than expected by perimeter-based sizing may be an option (61). Otherwise, the sizing process is the same as that performed in Western countries; therefore, the previously established sizing algorithm can be

applied to Asian populations. The choice of valve type (balloon-expandable vs self-expanding) is dependent on the operator's experience and preference, the availability of device, and clinical and anatomic situations. Calcification of the left ventricular outflow tract is known to be a potential risk factor for annulus rupture, especially when a balloon-expandable valve is deployed. Thus, in this situation, a self-expanding valve is preferred. Furthermore, coronary access is a bit challenging when a self-expanding valve is deployed; therefore, for patients with pre-existing coronary artery disease, a balloon-expandable valve may be beneficial in terms of future coronary access. Importantly, data regarding coronary access after TAVR in Asian patients is scarce. Other factors that need to be considered include high-risk features of atrioventricular block (pre-existing right bundle branch block and/or short membranous septum), small access diameter, and severe patient-prosthesis mismatch. Given the higher incidence of pacemaker implantation after TAVR with a self-expanding valve, it may be better to choose balloon-expandable valve for patients with the high-risk feature of atrioventricular block. However, a recent report demonstrated that the cusp overlap technique—valve deployment using a right/left cusp overlap view, allowing operators to identify the correct implantation plane for

CENTRAL ILLUSTRATION Specific Clinical and Anatomic Features and Outcomes of Transcatheter Aortic Valve Replacement in Asian Populations



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BMI = body mass index; FRANCE-TAVI = French Transcatheter Aortic Valve Implantation; K-TAVI = Korean Transcatheter Aortic Valve Implantation; LVEF = left ventricular ejection fraction; OCEAN-TAVI = Optimized Transcatheter Aortic Valve Intervention; PRAGMATIC = Pooled Rotterdam-Milan-Toulouse in Collaboration; Swiss-TAVI = Transcatheter Aortic Valve Implantation in Switzerland; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

assessment of the valve deployment depth at the level of the noncoronary cusp—can reduce the incidence of pacemaker implantation after the deployment of self-expanding valve (62).

TAVR IN BAV. The prevalence of BAV in patients undergoing TAVR was 2.7% in the OCEAN-TAVI registry (63); 5.8% in the Asian-TAVR Registry (26); and 3% to 3.5% in the TVT registry (64,65). BAV is reported to be very common in Chinese patients, with a prevalence near 50% in patients with severe AS undergoing TAVR (22). The high prevalence of BAV in the Asian-TAVR Registry may be due to a truly high incidence or the enrollment of low-risk or young patients (22,26,63). In some cases, TAVR in BAV can be challenging. Calcium distribution throughout the aortoannular complex is frequently asymmetric, along with a raphe resistant to predilatation and

aortic root dilatation. These variations may interfere with valve expansion and, thus, have an adverse impact on valve hemodynamics and durability, which, in turn, can result in high transvalvular gradients, PVL, device malpositioning, and high PPI rates post-TAVR (66).

Liao et al (67) evaluated 157 consecutive TAVR patients and compared clinical outcomes between those with BAV (n = 87) and those with tricuspid aortic valve (n = 70) in a Chinese single center. The rates of second valve implantation (bicuspid vs tricuspid: 14.9% vs 12.9%), more than mild PVL (40.2% vs 31.9%), and PPI (24.1% vs 28.6%) were not different between patients with BAVs and tricuspid aortic valves. A large-sized TAVR registry for BAV, which included Asian populations, demonstrated that rates of surgical conversion, second valve implantation, PVL, and absence of device success were higher in BAV patients than in

tricuspid aortic valve patients when early-generation devices were used (68). However, when new-generation devices were used, there were no significant differences in these adverse procedural events between BAV and tricuspid aortic valve. Interestingly, the rates of these adverse procedural events were not different between type 0 (2 symmetric leaflet/cusps and 1 commissure without evidence of a raphe) and type 1 (a single raphe due to fusion of the left coronary cusp with either the right or noncoronary cusp) BAV cases. Similarly, a recent report from the TVT registry showed that there was no significant difference in 30-day or 1-year mortality between BAV and tricuspid AS cases post-TAVR (69). Also, there were no significant between-group differences in valve hemodynamics, PVL, and improvement in functional and health status post-TAVR. Yoon et al (70) demonstrated that, among patients undergoing TAVR in BAV, calcified raphe and excess leaflet calcification were associated with increased risk of procedural complications and midterm mortality. These cumulative data from Asian and Western populations may demonstrate the feasibility of TAVR for BAV with contemporary devices, which is a product of the evolution of device technology, operator experience, improved imaging, and procedural advancements.

VALVE-IN-VALVE TAVR. TAVR within failed bioprosthetic surgical aortic valves is a feasible therapeutic option with acceptable midterm results. The PARTNER 2 Valve-in-Valve Registry (N = 365; mean STS score: $9.1\% \pm 4.7\%$) demonstrated that the 1-year all-cause mortality was 12.4%, mean gradient was 17.6 mm Hg, and effective orifice area was 1.16 cm^2 , with greater than mild paravalvular regurgitation of 1.9% (71). The study also showed a significant improvement in quality-of-life outcome and functional capacity (6-m walk test distance) at 1 year. In Asian countries, data regarding TAVR within failed bioprosthetic surgical aortic valves are scarce. Given that smaller surgical valves are generally implanted in Asian patients, there is a concern about whether valve-in-valve TAVR with smaller TAVR valves can provide a sufficient outcome. Furthermore, redo TAVR for failed TAVR valves have been increasing in the United States, with acceptable 30-day and 1-year mortality rates in this high-risk population (72). In Asian countries, redo TAVR is not allowed in the current health care system; however, given that the indication of TAVR is expanding to younger patients, further discussion is needed about whether to accept redo TAVR as an alternative approach with surgical explantation after TAVR.

VASCULAR ACCESS. A previous imaging study showed that the mean iliac minimal luminal diameter of Asian patients appeared to be 1 to 2 mm smaller and that the mean common femoral artery minimal luminal diameter was 0.5 to 1.5 mm smaller than those of Western patients (73). Such anatomic differences may raise concerns for increased vascular complications and point to the need for devices smaller than those currently manufactured by most Western brands. Nevertheless, with newer-generation low-profile TAVR devices, more than 90% of Asian patients are now receiving TAVR procedures via the transfemoral approach (74,75), which was similar to the contemporary trend of the STS-American College of Cardiology TVT registry (50). From a practical viewpoint, it is important to make device and valve selections based on detailed preprocedure computed tomographic measurements for vascular access, especially in high-risk patients. Then, a real-time ultrasound-guided puncture with a micropuncture kit (Cook Medical) can minimize vessel trauma. Additionally, the “road-map” system via contralateral access sites can be useful in patients with high femoral artery bifurcations. Also, as the profile of devices has become smaller, vascular closure with a single ProGlide (Abbott) in the transfemoral approach could achieve rates of technical success and procedural complications similar to those of the double ProGlide technique (76,77), and this strategy is more preferred in Asian patients with small vessel sizes.

PATIENT-PROSTHESIS MISMATCH. Patient-prosthesis mismatch (PPM) is a condition in which the effective orifice area of a normally functioning implanted valve prosthesis is small relative to the patient’s body size (78). The incidence and pattern of PPM may be more prevalent in Asian patients, who have specific anatomic and procedural characteristics (ie, smaller body size, smaller aortic valve dimension size, and frequent use of smaller TAVR prostheses), than in Western patients (26,29,79). However, it is still undetermined whether there are interracial differences in the incidence and prognostic value of PPM post-TAVR. Prior studies revealed conflicting results regarding the prognostic impact of PPM post-TAVR (80-85). In the TVT registry, moderate to severe PPM was present following TAVR in 36.7% of patients (moderate: 24.6%; severe: 12.1%). Independent predictors for severe PPM were small (≤ 23 -mm diameter) valve prosthesis, valve-in-valve procedure, large BSA, female sex, young age, low ejection fraction, atrial fibrillation, severe mitral or tricuspid regurgitation, and non-White/Hispanic race (84). The presence of severe PPM was associated with high mortality and heart failure

rehospitalization rates at 1 year. In contrast, a recent report on the OCEAN-TAVI registry revealed that the incidence of moderate to severe PPM was 9.6% (moderate: 8.9%; severe: 0.7%), but the presence of PPM was not associated with an increased risk of mortality (85). In this Japanese cohort, independent predictors for PPM were young age, large BSA, small aortic valve area, small annulus area, no balloon postdilatation, and use of the Edwards Sapien 3.

With regard to the race-specific differential incidence of PPM, the annular area on preprocedure computed tomography is small in Asians, but BSA is substantially smaller in Asian than in White individuals (84-86). Thus, the incidence of PPM was not higher and even was lower in Asian populations (presumably because of fewer obese patients) than in Western populations. Regarding the clinical impact of PPM, the prognostic relevance of PPM on mortality or hard clinical endpoints has been highly debated in a series of TAVR studies (80-85). Some studies reported that PPM post-TAVR was associated with an increased risk of mortality and adverse cardiac events (81-84), whereas other studies revealed that PPM was not associated with an increased risk of adverse clinical outcomes (80,85). Differential prognostic values of PPM post-TAVR among studies might in part be explained by the varying sizes of the study samples, different demographic characteristics of patients, practice patterns, or types and sizes of TAVR devices, as well as unmeasured clinical or anatomic confounders. Further large-scale clinical studies with longer-term follow-up are required to determine the true prognostic value of PPM post-TAVR. In addition, TAVR was reported to increase the effective orifice area and reduce PPM risk compared to SAVR (81), but if severe PPM is expected even with TAVR, SAVR with the technique of aortic root enlargement may be an alternative option (87).

ANTITHROMBOTIC STRATEGY FOLLOWING TAVR.

Patients with AS undergoing TAVR are often at high risk for clinically relevant bleeding and ischemic cardiovascular events. Therefore, balancing ischemic and bleeding risks in patients undergoing TAVR remains a concern. Several clinical guidelines, based on expert consensus, recommend empirical dual antiplatelet therapy (ie, aspirin plus clopidogrel) for 3 to 6 months for TAVR recipients without indication for oral anticoagulation (88,89). However, the optimal antithrombotic strategies and duration post-TAVR are still unknown.

Several randomized studies have been conducted recently to investigate this important issue. The

ARTE (Aspirin Versus Aspirin Plus Clopidogrel Following Transcatheter Aortic Valve Implantation) trial and the Popular TAVI Trial Cohort A (without oral anticoagulant indications) showed that single antiplatelet therapy was significantly associated with lower risk of bleeding without differences in thromboembolic events versus dual antiplatelet therapy (90,91). In addition, GALILEO (Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) and ATLANTIS (Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis) demonstrated that low-dose (10 mg) rivaroxaban or apixaban is not superior to antiplatelet therapy or conventional antithrombotic strategy (92,93). Valve leaflet thrombosis occurrence was lower with rivaroxaban or apixaban than with antiplatelet therapy or conventional antithrombotic therapy, but this did not translate into an improvement in clinical outcomes. Especially in patients without an indication for oral anticoagulants, higher noncardiovascular mortality was seen with rivaroxaban or apixaban than with conventional antiplatelet therapy.

Most of these RCTs have been performed in Western populations, and thus, clinical evidence on Asian populations is still scarce. It is well-known that compared with Western patients, East Asian patients are more susceptible to bleeding events but are relatively resistant to thromboembolic events (the so-called “East Asian paradox”) (94). A recent report from the OCEAN-TAVI registry found that clopidogrel monotherapy was associated with a lower incidence of cardiovascular death than was aspirin monotherapy, regardless of concomitant oral anticoagulant use (95). However, it is still questionable whether the “less-is-more” concept of antithrombotic strategy is always better in TAVR patients (96). Additionally, given that RCTs performed in Asian populations are limited and that the causal relationship of leaflet thrombosis with cerebral embolic events post-TAVR is still uncertain, the results from the ADAPT-TAVR (Anticoagulation Versus Dual Antiplatelet Therapy for Prevention of Leaflet Thrombosis and Cerebral Embolization After Transcatheter Aortic Valve Replacement; [NCT03284827](#)) trial will provide important insight into mechanisms underlying the association of leaflet thrombosis and cerebrovascular thromboembolic events and the

treatment effect of edoxaban in East Asian populations (94).

FUTURE DIRECTIONS OF TAVR IN ASIA

The field of transcatheter valve interventions in the Asia Pacific is now rapidly expanding. The improvement of health and socioeconomic status has translated into incremented life expectancy, and the increasing number of elderly patients with VHD can benefit from these interventions. To address this health issue, Asia Pacific countries are tackling specific challenges, such as population- and public health care system-related issues, which will be crucial to overcome for the widespread and successful clinical implementation of transcatheter valve interventions. To make access to TAVR easier in Asian countries, several key players (ie, physicians, patients, device and pharmaceutical industries, governments, and regulatory authorities) need to collaborate and facilitate the approval process of novel devices and the coverage of expensive TAVR costs by health insurance.

Given the differences between Asian and Western patients in terms of the size of the aortic complex and susceptibility to bleeding events, large-scale data need to be derived from Asian countries to evaluate whether compelling evidence from Western countries is applicable. To accomplish this, every country needs to have its own nationwide database with uniform definitions, which will enable the integration of information, interaction between key players, and use of collective clinical insights from different countries. A well-defined database with a sufficient number of patients from various Asian countries will be a powerful tool to create evidence. The Japanese TVT Registry is a nationwide TAVR registry, established by 4 academic societies (Japanese Circulation Society, The Society of Japanese Cardiovascular Surgery, Japanese Association for Thoracic Surgery, and Japanese Association of Cardiovascular Intervention and Therapeutics), in collaboration with the Pharmaceuticals and Medical Devices Agency and industry, and enrolling all patients who underwent TAVR in Japan (97). As registration in the Japanese TVT Registry is mandatory for the application for institutional certification and renewal, consecutive TAVR patients are enrolled. However, because of the limited budget and insufficient research support system, physicians are required to enter the data by themselves; therefore, data quality and sustainability are significant issues. Furthermore, participation in a pivotal clinical trial is important to close the device lag between Western and Asian countries and facilitate the approval process of novel devices.

HIGHLIGHTS

- Given increased life expectancy in the Asia Pacific, the field of TAVR is rapidly expanding.
- There were substantial interracial differences in clinical, anatomic, and procedural characteristics in TAVR patients.
- There were specific population- and health care system-related challenges to TAVR use in Asia.
- Future research into racial/ethnic disparities can help optimize TAVR procedures in Asia Pacific countries.

CONCLUSIONS

Until recently, few comparative studies existed regarding differential clinical, anatomic, and procedural characteristics and outcomes of TAVR between Asian and Western populations. Although the association between racial disparities and adverse clinical events among TAVR patients has been a major topic of study, the contributing factors are still poorly understood. Given that the elderly population is rapidly increasing in Asian countries, a substantial number of potential candidates for TAVR is expected, with more affordable device prices and, thus, broader TAVR use. Further racial and ethnic-based comparative studies will provide a better understanding of the observed racial differences in the clinical and anatomic characteristics and outcomes of TAVR recipients between Asian and Western populations, which may facilitate risk stratification and the development of race-based novel approaches for TAVR procedures.

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ADDRESSES FOR CORRESPONDENCE: Dr Kentaro Hayashida, Department of Cardiology, Keio University School of Medicine, Shinanomachi 35, Shinjuku-ku, Tokyo 160-8582, Japan. E-mail: khayashidamd@gmail.com. OR Dr Duk-Woo Park, Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, South Korea. E-mail: dwpark@amc.seoul.kr. Twitter: [@dukwoo_park](https://twitter.com/dukwoo_park), [@taku_inohara](https://twitter.com/taku_inohara).

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KEY WORDS aortic stenosis, outcomes, race and ethnicity, valvular disease

APPENDIX For supplemental tables, please see the online version of this paper.



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