Circulation Journal
Circ J 2021; **85:** 1050–1058
doi:10.1253/circj.CJ-20-0412

ORIGINAL ARTICLE
Imaging

Discrepancy of Aortic Valve Area Measurements by Doppler vs. Biplane Stroke Volume Measurements and Utility of Combining the Different Areas in Aortic Valve Stenosis
— The Asian Valve Registry —

Mai Iwataki, MD; Yong-Jin Kim, MD; Seung Woo Park, MD; Lieng Hsi Ling, MD; Cheuk-Man Yu, MD; Hiroyuki Okura, MD; Jong-Won Ha, MD; Takeshi Hozumi, MD; Hidekazu Tanaka, MD; Chisato Izumi, MD; Toshinori Yuasa, MD; Jae-Kwan Song, MD; Yutaka Otsuji, MD; Dae-Won Sohn, MD

Background: The aortic valve area index (AVAI) in aortic stenosis (AS) is measured by echocardiography with a continuity equation using the stroke volume index by Doppler ($SVI_{Doppler}$) or biplane Simpson ($SVI_{Biplane}$) method. $AVAI_{Doppler}$ and $AVAI_{Biplane}$ often show discrepancy due to differences between $SVI_{Doppler}$ and $SVI_{Biplane}$. The degree of discrepancy and utility of combined AVAIs have not been investigated in a large population of AS patients, and the characteristics of subjects with larger discrepancies are unknown.

Methods and Results: We studied 820 patients with significant AS ($AVA_{Doppler}$ <1.5 cm²) enrolled in the Asian Valve Registry, a prospective multicenter registry at 12 Asian centers. All-cause death and aortic valve replacement were defined as events. $SVI_{Doppler}$ was significantly larger than $SVI_{Biplane}$ (49±11 vs. 39±11 mL/m², P<0.01) and $AVAI_{Doppler}$ was larger than $AVAI_{Biplane}$ (0.51±0.15 vs. 0.41±0.14 cm²/m², P<0.01). An increase in ($AVAI_{Doppler}-AVAI_{Biplane}$) correlated with shorter height, lower weight, older age, smaller left ventricular (LV) diameter and increased velocity of ejection flow at the LV outflow tract. Severe AS by $AVAI_{Doppler}$ or $AVAI_{Biplane}$ enabled prediction of events, and combining these AVAIs improved the predictive value of each.

Conclusions: Discrepancy in AVAI by Doppler vs. biplane method was significantly more pronounced with increased LV outflow tract flow velocity, shorter height, lower weight, older age and smaller LV cavity dimensions. Combining the AVAIs enabled mutual and incremental value in predicting events.

Key Words: Aortic valve stenosis; Echocardiography

Aortic valve stenosis (AS) is one of the most common valvular diseases and the third most common cardiovascular disease in developed countries.[1] Aortic valve area (AVA), a standard parameter of the severity of AS, is routinely derived using the continuity equation,[2,3] for which the stroke volume (SV) is obtained either by Doppler or biplane Simpson [left ventricular end-diastolic volume (LVEDV) − LV end-systolic volume (LVESV)] method ($SV_{Doppler}$ and $SV_{Biplane}$, respectively).

$SV_{Biplane}$ can be underestimated by 2-dimensional (2D) echocardiographic LV volume measurements vs. standard magnetic resonance imaging (MRI).[4] The LV volume underestimation by echocardiography is considerable over a wide range of LV volumes, suggesting more severe underestimation in proportion to LV size in patients with smaller LVs.[4] The SV by Doppler method can be overestimated in elderly subjects whose sigmoid septal configuration narrows the LV outflow tract (LVOT).[5] Elderly subjects

Received May 1, 2020; revised manuscript received September 2, 2020; accepted September 10, 2020; J-STAGE Advance Publication released online November 19, 2020 Time for primary review: 17 days

University of Occupational and Environmental Health, School of Medicine, Kitakyushu (M.I., Y.O.), Japan; Seoul National University Hospital, Seoul (Y.-J.K., D.-W.S.); Samsung Medical Center, Sungkyunkwan University College of Medicine, Seoul (S.W.P.), South Korea; Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore (L.H.L.), Singapore; Chiu Hin Kwong Heart Centre, Hong Kong Baptist Hospital and The Chinese University of Hong Kong, Hong Kong (C.-M.Y.), China; Kawasaki Medical School, Kurashiki (H.O.), Japan; Yonsei University, Seoul (J.-W.H.), South Korea; Wakayama Medical University, Wakayama (T.H.); Kobe University Graduate School of Medicine, Kobe (H.T.); Tenri Hospital, Tenri (C.I.); Kagoshima University, Kagoshima (T.Y.), Japan; and Valvular Heart Disease Center, Asan Medical Center Heart Institute, Research Institute for Valvular Heart Disease, University of Ulsan College of Medicine, Seoul (J.-K.S.), South Korea

Mailing address: Mai Iwataki, MD, Second Department of Internal Medicine, University of Occupational and Environmental Health, School of Medicine, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu 807-8555, Japan. E-mail: mai-iwataki@med.uoeh-u.ac.jp

ISSN-1346-9843

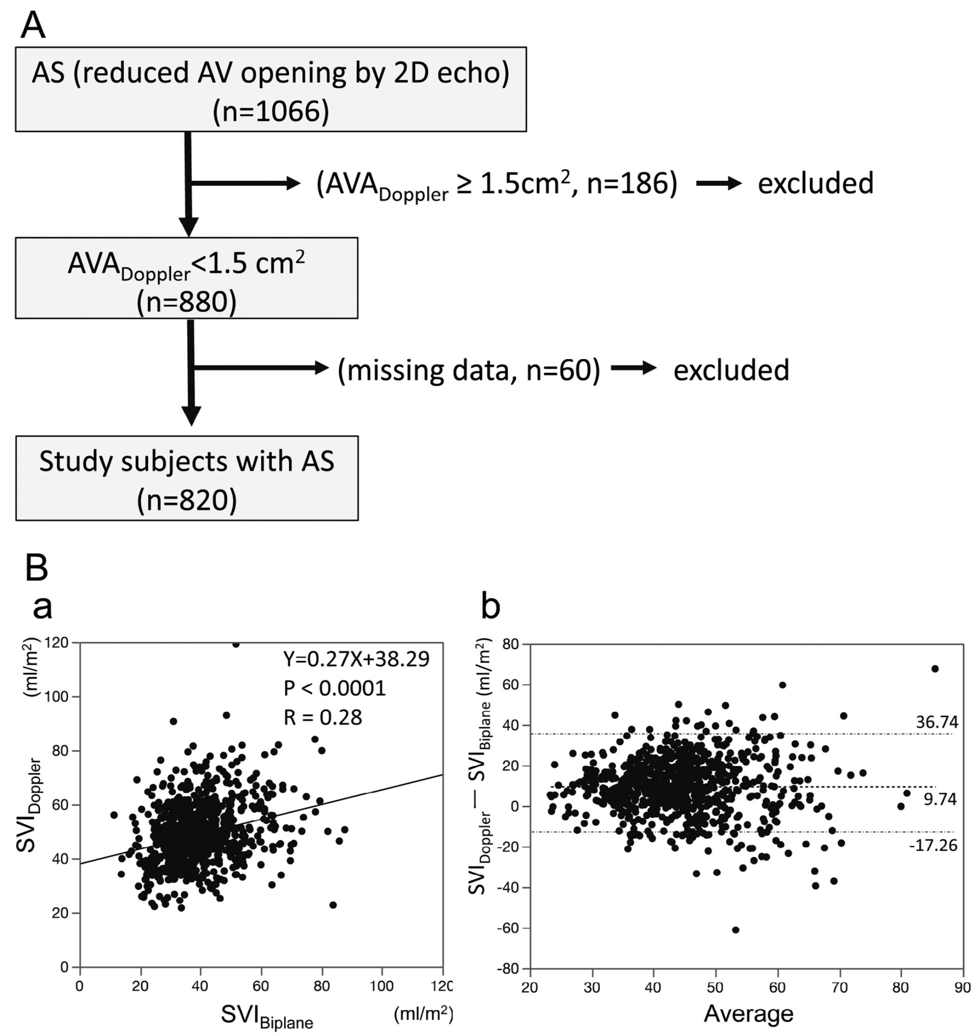

Figure 1. (**A**) Disposition of patients with aortic stenosis (AS). From the initially registered 1,066 patients with AS and reduced aortic valve opening by 2-dimensional (2D) echocardiography, 880 patients with aortic valve area (AVA) <1.5 cm^2 by continuity equation were enrolled. The 60 patients with missing data were excluded and 820 patients were finally accepted. (**B**) Significant but moderate correlation between SVI$_{Doppler}$ and SVI$_{Biplane}$ (**a**). Bland-Altman plots for the comparison between SVI$_{Doppler}$ and SVI$_{Biplane}$ (**b**) (dashed lines indicate the mean difference between methods and the limits of agreement [1.96 SD]). SVI, stroke volume index.

also have smaller LVs compared with younger subjects.[6] Therefore, it is likely that patients with a larger discrepancy between SV$_{Doppler}$ and SV$_{Biplane}$, leading to a greater discrepancy between AVA by SV$_{Doppler}$ and by SV$_{Biplane}$ (AVA$_{Doppler}$ and AVA$_{Biplane}$, respectively), have specific characteristics such as smaller LV or older age.

However, no previous studies have investigated the degree of discrepancy between SV$_{Doppler}$ and SV$_{Biplane}$ in a large AS population, nor characterized the patients in whom such discrepancies are more pronounced. As these discrepancies can result in divergent classification of AS severity and hamper clinical decision making, we aimed to evaluate the extent and source of discrepancies between AVA$_{Doppler}$ and AVA$_{Biplane}$ in the AS cohort of the Asian Valve Registry. We also evaluated the predictive value of AVA$_{Doppler}$ and AVA$_{Biplane}$ on the outcome and further evaluated mutual and incremental value by combining the 2 AVAs in the prediction of events.

Methods

Subjects

The Asian Valve Registry is a prospective multicenter registry of patients with significant AS or mitral regurgitation at 12 centers in Asian countries (Korea, Japan, Hong Kong, and Singapore).[7] From September 2010 through May 2016, a total of 1,066 patients with AS and reduced AV opening by 2D echocardiography were enrolled at the participating centers. The definition of AS severity was based on current AHA/ACC guidelines.[8] As shown in **Figure 1A**, AVA$_{Doppler}$ was <1.5 cm^2 in 880 patients, who were deemed to have significant AS. Because 60 patients had missing data, the study group comprised 820 patients with AS and AVA$_{Doppler}$ <1.5 cm^2. The protocol was approved by the institutional review board at each participating center, and written informed consent was given by all patients.

Echocardiographic Measurements

Comprehensive and standard 2D and Doppler echocardiographic examinations were performed in all patients using commercially available ultrasound machines.[9] All equipment was adequately maintained according to guidelines.[10] LVEDV and LVESV were measured from the apical 2- and 4-chamber images using the biplane Simpson method,[9] and LV ejection fraction (LVEF) was calculated. $SV_{Biplane}$ was obtained as the difference between LVEDV and LVESV.

Table 1. Clinical Characteristics, Echocardiographic Parameters and Events (n=820 Patients)

Clinical data	
Age (years)	70±11
Male (%)	434 (53)
Height (cm)	159±9
Weight (kg)	61±11
Body surface area (m²)	1.6±0.2
Heart rate (beats/min)	69±12
Systolic blood pressure (mmHg)	131±20
Diastolic blood pressure (mmHg)	71±11
Echocardiographic data	
LVEDVI (mL/m²)	64±22
LVESVI (mL/m²)	25±14
LVEF (%)	62±8
LVEDDI (mm/m²)	30±4
LVESDI (mm/m²)	18±4
RWT	0.48±0.11
Peak aortic valve pressure gradient (mmHg)	77±32
Mean aortic valve pressure gradient (mmHg)	46±21
LVOT VTI (cm)	22.9±5.0
USH	117/138 (85%)
Events	
Surgical AVR	286
Transcatheter AVR	57
All-cause death	25

AVR, aortic valve replacement; LVEDDI, left ventricular end-diastolic dimension index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESDI, left ventricular end-systolic dimension index; LVESVI, left ventricular end-systolic volume index; LVOT VTI, velocity-time integral of left ventricular outflow tract; RWT, relative wall thickness; USH, upper septal hypertrophy.

LVED internal diameter (LVEDD), LVED systolic diameter (LVESD), interventricular septal diastolic thickness (IVSth) and LV posterior wall diastolic thickness (LVPWth) were measured using 2D methods in the parasternal long-axis view. Relative wall thickness (RWT) was calculated as 2×LVPWth/LVEDD. In 138 patients, retrospective image analysis was performed to evaluate the presence of upper septal hypertrophy (USH), which was defined by the following criteria measured in the parasternal long-axis view: (1) the angle between the basal part of the IVS and ascending aorta <120°, (2) a ratio of the upper septal thickness to midseptal thickness ≥1.3, (3) an upper septal thickness ≥14 mm.[11] LVOT diameter was measured at the level of the aortic valve annulus in a zoomed long-axis image.[12] In the apical 3-chamber view, the pulsed-wave Doppler sample volume was placed in the center of the LVOT, and the obtained velocity-time integral (VTI_{LVOT}) was manually measured by tracing the modal velocity,[3] and its cross-sectional area (CSA) was calculated as $3.14\times(\text{LVOT diameter})^2/4$. $SV_{Doppler}$ was obtained as $CSA_{LVOT}\times VTI_{LVOT}$. Continuous-wave Doppler echocardiography was performed to obtain the velocity profile of the flow through the aortic valve in the apical 3-chamber view. Outlines of the signals were traced to obtain the peak pressure gradient (PG), mean PG, and VTI at the aortic valve level (VTI_{AV}). $AVA_{Doppler}$ was estimated by the continuity equation as follows:[2,3]

$$AVA_{Doppler}=SV_{Doppler}/VTI_{AV}=CSA_{LVOT}\times VTI_{LVOT}/VTI_{AV}$$

$AVA_{Biplane}$ was calculated as follows:

$$AVA_{Biplane}=SV_{Biplane}/VTI_{AV}=(LVEDV-LVESV)/VTI_{AV}$$

All volume, area and length measurements were normalized by body surface area (BSA) and denoted accordingly with the suffix I.

AS Severity Grading

AS severity was classified according to indexed AVA (AVAI) measured by both Doppler and biplane SV methods, being mild when AVAI was ≥0.85 cm²/m², moderate when AVAI was <0.85 and ≥0.6 cm²/m², and severe when AVAI was <0.6 cm²/m².[13–15]

Clinical Outcomes

Clinical follow-up data were available for all patients during a median follow-up period of 915 days (interquartile range, 40–1,461 days). Surgical or transcatheter aortic valve

Table 2. SV and AVA Measurements by Doppler and Biplane Methods

	Doppler	Biplane	P value
SV (mL)	79±18	64±21	<0.0001
SVI (mL/m²)	49±11	39±11	<0.0001
SVI <35 mL/m²	75/820 (9%)	321/820 (39%)	<0.0001
AVA (cm²)	0.83±0.24	0.66±0.24	<0.0001
AVAI (cm²/m²)	0.51±0.15	0.41±0.14	<0.0001
AS severity			
Mild (AVAI ≥0.85 cm²/m²)	19 (2.3%)	5 (0.6%)	<0.01
Moderate (0.85>AVAI≥0.6 cm²/m²)	222 (27.1%)	66 (8.1%)	<0.0001
Severe (AVAI <0.6 cm²/m²)	579 (70.6%)	749 (91.3%)	<0.0001

AS, aortic valve stenosis; AVA, aortic valve area; AVAI, aortic valve area index; SV, stroke volume; SVI, stroke volume index.

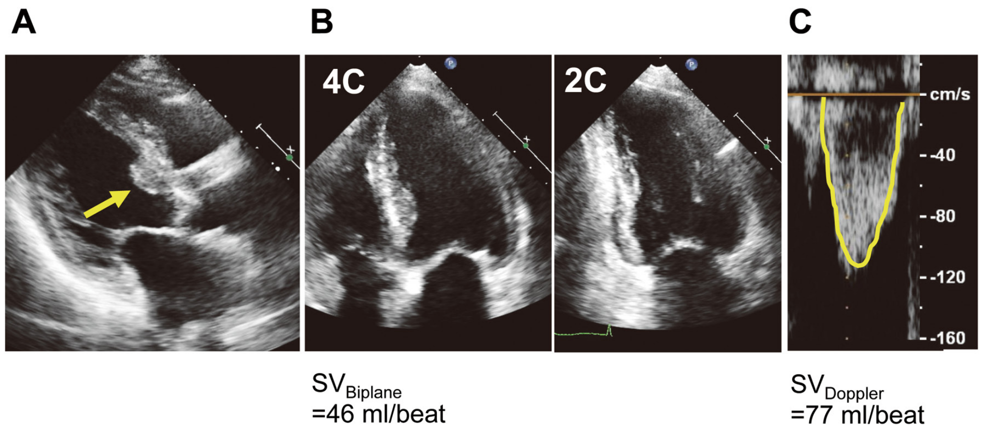

Figure 2. Representative patient with discrepant Doppler and biplane stroke volumes (SVs). This patient has upper septal hypertrophy (yellow arrow in **A**), and a small left ventricular (LV) cavity. SV by the biplane method (LV end-diastolic volume – LV end-systolic volume) is reduced at 46 mL/beat (**B**). In contrast, the Doppler echocardiography-derived SV is considerably larger at 77 mL/beat (**C**). 2C, apical 2-chamber view; 4C, apical 4-chamber view.

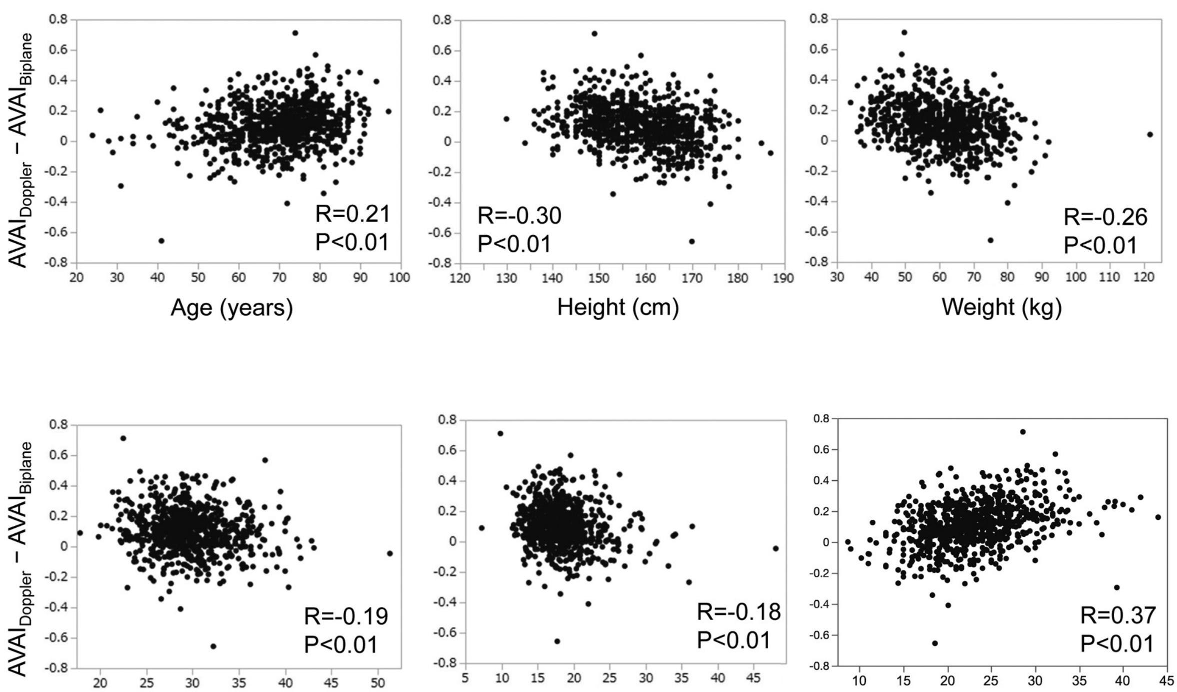

Figure 3. Correlations between discrepant aortic valve area index (AVAI) by Doppler and biplane methods against age, height, weight, left ventricular (LV) end-diastolic dimension index (LVEDDI), LV end-systolic dimension index (LVESDI) and velocity-time integral (VTI) of the LV outflow tract (LVOT). Increased LVOT VTI, shorter height, lower weight, increased age, and reduced LV dimensions were associated with increased discrepancy of AVA by the 2 methods.

replacement (AVR) and all-cause death were defined as events.

Statistical Analysis

Continuous data are expressed as mean±standard deviation, and categorical data as absolute numbers and percentages. Continuous variables between 2 groups were compared using the unpaired t-test. Proportional differences were evaluated with Fisher's exact test or chi-square as appropriate. Predictors of discrepancy between $AVAI_{Doppler}$

Table 3. (A) Factors Associated With Increased Discrepancy of AVAI by Doppler and Biplane Methods (n=820 Patients), (B) Factors Associated With Increased Discrepancy of AVAI by Doppler and Biplane Methods (Addition of Retrospective Image Analysis, n=138 Patients), (C) Factors Associated With Increased LVOT VTI (Addition of Retrospective Image Analysis, n=138 Patients)

(A) Variables	Univariable		Multivariable model 1		Multivariable model 2	
	β	P value	β	P value	β	P value
Age	0.0027	<0.0001	0.0018	<0.0001	0.0019	<0.0001
Sex, female	0.0037	<0.0001	0.0064	0.2892	0.0124	0.0484
Height	−0.0047	<0.0001	−0.0025	0.0017	−0.0010	0.2023
Weight	−0.0035	<0.0001	−0.0036	<0.0001	−0.0017	0.0011
Indexed IVSth	0.0051	0.1630				
Indexed LVPWth	0.0022	0.6106				
LVEDDI	−0.0048	0.0002	−0.0157	<0.0001		
LVESDI	−0.0070	<0.0001	0.00402	0.0649		
RWT	0.1726	0.0002			0.1372	0.0009
LVOT VTI	0.0106	<0.0001	0.01002	<0.0001	0.0009	<0.0001

(B) Variables	Univariable		Multivariable model 1		Multivariable model 2	
	β	P value	β	P value	β	P value
Age	0.0030	0.0057	0.0014	0.1648	0.0014	0.1648
Sex, female	0.0300	0.0088	0.0065	0.6148	0.0065	0.6130
Height	−0.0045	0.0003	−0.0032	0.0913	−0.0032	0.0913
Weight	−0.0034	0.0013	−0.0032	0.0117	−0.0031	0.0117
Indexed IVSth	0.0072	0.4027				
Indexed LVPWth	0.0051	0.5735				
LVEDDI	−0.0074	0.0247	−0.0176	0.0010		
LVESDI	−0.0103	0.0016	0.0009	0.8363		
USH	−0.0284	0.0418	−0.0040	0.7318	−0.0040	0.7318
RWT	0.2104	0.0510				
LVOT VTI	0.0121	<0.0001	0.0109	<0.0001	0.0110	<0.0001

(C) Variables	Univariable		Multivariable	
	β	P value	β	P value
Age	0.0030	0.0057	0.0111	0.7961
Sex, female	0.0300	0.0088	0.9751	0.0788
Height	−0.0045	0.0003	0.0817	0.3104
Weight	−0.0034	0.0013	−0.0154	0.7729
LVEDDI	−0.0074	0.0247	0.5353	0.0163
LVESDI	−0.0103	0.0016	−0.6428	0.0012
USH	−0.0284	0.0418	−1.1028	0.0257

IVSth, interventricular septal diastolic thickness; LVPWth, left ventricular posterior wall thickness. Other abbreviations as in Tables 1,2.

and $AVAI_{Biplane}$ were assessed using univariate logistic regression analysis and multivariable logistic regression modeling. Survival curves were constructed using Kaplan-Meier analysis. Survival across the 2 groups was compared by the log-rank test. A Cox proportional hazards model was used to evaluate the association of AS severity with event. Statistical significance was established at $P<0.05$. Statistical analyses were performed with JMP version 14 (SAS Institute Inc., Cary, NC, USA).

Results

Patients' Characteristics and Events

The clinical and echocardiographic characteristics of the patients are shown in **Table 1**. Just over half were men, BSA was 1.6±0.2 m², LVEF was 62±8%, and mean and peak aortic valve PGs were 46±21 and 77±32 mmHg, respectively. In the 138 patients with retrospective image analysis, the incidence of USH was 117 (85%). During the follow-up, 368 events occurred (286 surgical AVRs, 57 transcatheter AVRs and 25 deaths).

Comparison of SV and AVA Measurements Between Methods

Table 2 shows the SV and AVA measurements by Doppler and biplane methods. $SVI_{Doppler}$ was significantly larger than $SVI_{Biplane}$ (49±11 vs. 39±11 mL/m², $P<0.0001$), resulting in a significant difference in the incidence of reduced SVI (<35 mL/m²) by the 2 methods. $SVI_{Doppler}$ showed moderate correlation with $SVI_{Biplane}$ (**Figure 1B-a**). The Bland-Altman plot showed a fixed bias but no proportional bias ($P<0.0001$, $r=0.28$) in $SVI_{Doppler}$ compared with $SVI_{Biplane}$ (**Figure 1B-b**). $AVAI_{Doppler}$ was also significantly larger than $AVAI_{Biplane}$ (0.51±0.15 vs. 0.41±0.14 cm²/m², $P<0.0001$). **Figure 2** shows a representative patient with discrepant SVIs with the 2 methods. This patient had USH (yellow arrow in **Figure 2A**),

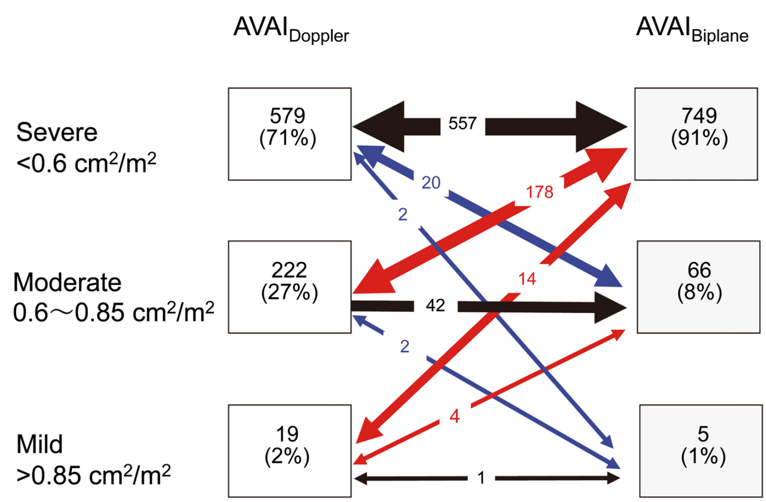

Figure 4. Change in severity or reclassification of aortic stenosis between the Doppler and biplane methods. From Doppler to biplane evaluation, a considerable number of patients were reclassified to a more severe class. From biplane to Doppler evaluation, multiple patients were reclassified to a milder class.

a small LV cavity and the SV by biplane method was reduced (**Figure 2B**) while the SV by Doppler was considerably larger (**Figure 2C**).

Figure 3 shows scatter plots and correlations between ($AVAI_{Doppler} - AVAI_{Biplane}$) and age, height, weight, LVEDDI, LVESDI and VTI_{LVOT}. Increased discrepancy of AVAI by the 2 methods was significantly correlated with increased VTI_{LVOT} (r=0.37, P<0.01), shorter height (r=−0.30, P<0.01), lower weight (r=−0.26, P<0.01), older age (r=0.21, P<0.01), smaller LVEDDI (r=−0.19, P<0.01), smaller LVESDI (r=−0.18, P<0.01), and increased RWT (r=0.13, P<0.01). Multivariate analysis revealed that increased VTI_{LVOT}, shorter height, lower weight, older age, smaller LVEDDI, and increased RWT were all independently associated with increased discrepancy of AVAI by Doppler and biplane methods (**Table 3A**). We further evaluated factors associated with discrepant AVAIs in 138 USH patients with retrospective image analysis. Multivariate analysis revealed that increased LVOT VTI, lower weight and reduced LVEDDI were independently associated with discrepant AVAIs (**Table 3B**). Further analysis demonstrated smaller LV dimensions and USH as independent factors associated with increased LVOT VTI (**Table 3C**).

Consequently, changing the method either from Doppler to biplane or from biplane to Doppler resulted in significant reclassification of AS (P<0.01). **Figure 4** shows an example of striking reclassification of AS. Mild AS by Doppler changed to moderate by biplane in 4 of 19 (21%), from mild to severe in 14 of 19 (74%), and from moderate to severe in 178 of 222 (80%) patients. In the opposite direction, severe AS by biplane was changed to moderate by Doppler in 178 of 749 (23%) and to mild in 14 (1.9%) patients.

Predictive Value of AS Severity by the 2 Methods and Utility of Combining the 2 AVAIs

Event-free survival of all patients with severe and not severe AS by Doppler was compared. Cox proportional hazards model analysis demonstrated higher probability of events in patients with $AVAI_{Doppler}$ <0.6 cm²/m² compared with those with $AVAI_{Doppler}$ >0.6 cm²/m² [hazard ratio (HR) 2.7, 95% confidence interval (CI) 2.05–3.56, P<0.0001] (**Figure 5A-a**). Similarly, there was a higher probability of events in patients with $AVAI_{Biplane}$ <0.6 cm²/m² compared with those with $AVAI_{Biplane}$ >0.6 cm²/m² (HR 2.12, 95% CI 1.35–3.34, P<0.005] (**Figure 5A-b**).

In 222 patients with moderate AS by Doppler, $AVAI_{Biplane}$ > or <0.6 cm²/m² did not show different event rates (**Figure 5B-a**). Therefore, this reclassification was not useful for predicting events. However, in 579 patients with severe AS by Doppler, $AVAI_{Biplane}$ <0.41 cm²/m² (mean value in this group) showed higher probability of events (HR 1.37, 95% CI 1.07–1.76, P<0.05) (**Figure 5B-b**), expressing the utility of subdividing this group into "very severe" and "severe" AS. Further, in 749 patients with severe AS by the biplane method, $AVAI_{Doppler}$ <0.6 cm²/m² showed higher probability of events (HR 2.83, 95% CI 2.08–3.85, P<0.0001) (**Figure 5B-c**), indicating that reclassification of severe AS by the biplane method to moderate/mild AS by Doppler may be useful to evaluate the relatively benign population in this patient group.

Discussion

We have highlighted the considerable difference between $SV_{Doppler}$ and $SV_{Biplane}$ (mean values averaging 20–25%), leading to non-negligible differences between $AVAI_{Doppler}$ and $AVAI_{Biplane}$, and indeed highly disparate grading of AS severity by the 2 methods. This inconsistency of echocardiographic evaluation of AS severity according to the methodology for deriving SV in a large number of prospectively studied patients in multiple experienced centers deserves attention. In addition, the combination of $AVAI_{Doppler}$ and $AVAI_{Biplane}$ was clinically relevant. In patients with severe AS by the biplane method, reclassification to either severe or to moderate/mild AS by $AVAI_{Doppler}$ enabled separation of patients with worse or better outcome. In addition, in patients with severe AS by the Doppler method, subdividing this group by better or worse $AVAI_{Biplane}$ enabled separation of patients with "severe" and "very severe" outcomes.

The present study also identified the clinical and echocardiographic characteristics of patients with larger discrep-

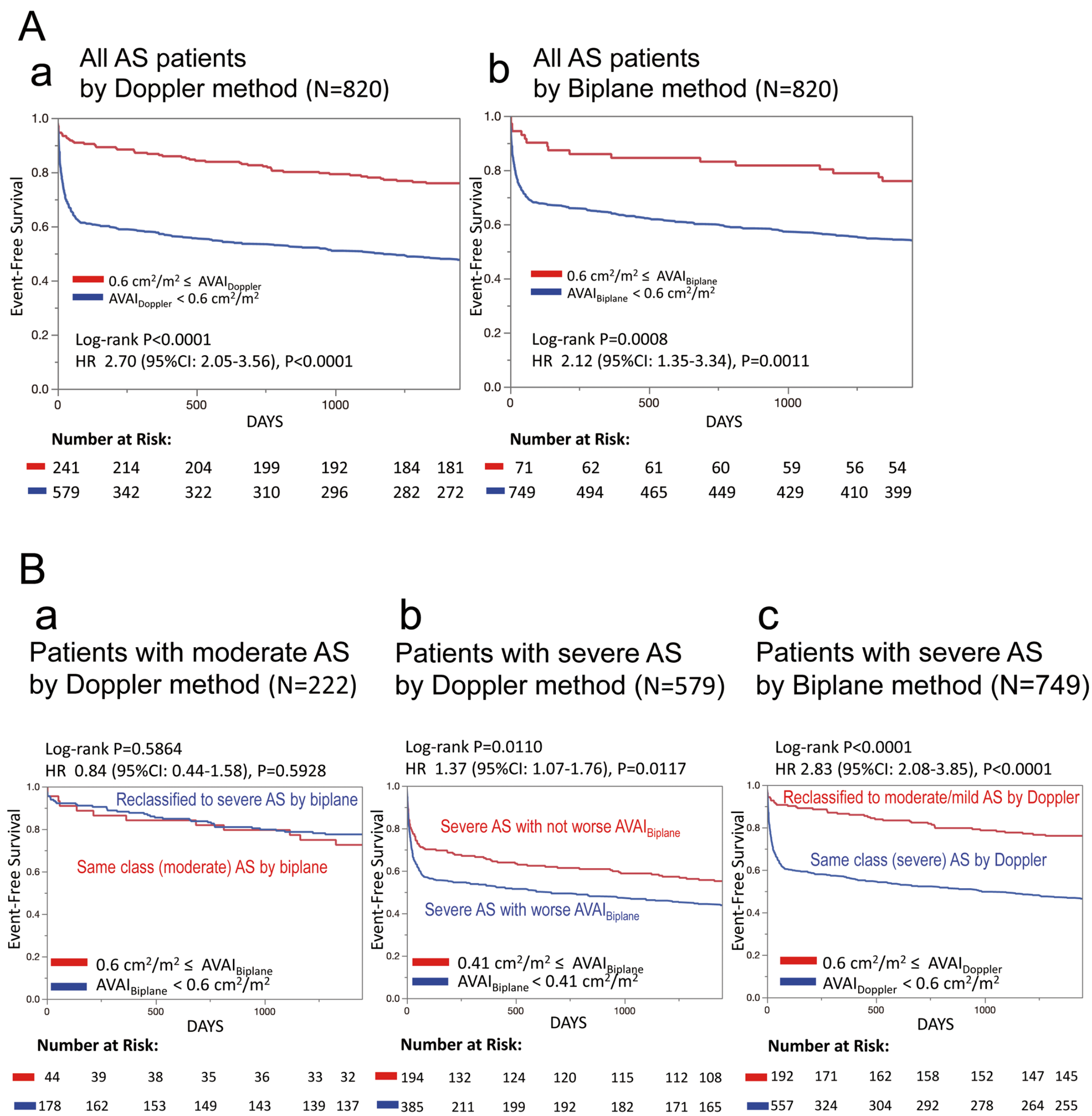

Figure 5. (**A**) Clinical outcomes of patients diagnosed as having severe or not severe aortic stenosis (AS) by aortic valve area (AVA) by Doppler evaluation ($AVAI_{Doppler}$) < or >0.6 cm²/m² (**a**) and those of patients diagnosed as severe or not severe AS by AVA by biplane evaluation ($AVAI_{Biplane}$) < or >0.6 cm²/m² (**b**). The are significant differences in patients' outcome according to the criteria used. (**B**) Presence or absence of a difference in the incidence of subsequent events between subdivided groups by combining the AVA by Doppler evaluation ($AVAI_{Doppler}$) and that by biplane evaluation ($AVAI_{Biplane}$). In patients with moderate AS by $AVAI_{Doppler}$, subdivision by $AVAI_{Biplane}$ <0.6 cm² or not failed to show different outcomes (**a**). However, in patients with severe AS by $AVAI_{Doppler}$, subdivision by $AVAI_{Biplane}$ <0.41 cm² (mean value in this group) or not showed significantly different outcomes (**b**). In patients with severe AS by $AVAI_{Biplane}$, subdivision by $AVAI_{Doppler}$ <0.6 cm² or not showed significantly different outcomes (**c**).

ancies in derived SV and AVA. Increased VTI_{LVOT} in relation to USH, shorter height, lower weight, older age, smaller LV dimensions, and increased RWT were predictors, even with BSA adjustment. Healthcare providers should be aware of these characteristics when evaluating patients with AS, and if necessary revisit the grading of AS severity in candidates at risk of greater discrepancy.

Relation to Previous Studies

LV volume measured by biplane 2D echocardiography is reported to be underestimated compared with that by MRI, leading to underestimation of SV by the echocardiographic technique.[9,16] SV measured by the LVOT Doppler method can be overestimated, especially in patients in whom the basal IVS bulges toward the LVOT, causing flow velocity acceleration.[11] Dumont and Arsenault compared AVA measured by the LVOT Doppler and biplane Simpson methods, and found excellent correlation between these.[17] They further demonstrated better correlation of $AVA_{Biplane}$ to invasively measured AVA by Gorlin equation in patients with LVOT flow acceleration, suggesting overestimation of SV and AVA by Doppler technique in these patients. Although not a specific focus of their study, data from Mistry et al suggest relatively greater underestimation of LV volume by echocardiography (compared with MRI) in patients with smaller LV cavity.[4] Our findings are consistent with but also extend these reports by more comprehensive identification of other clinical and imaging characteristics that may confound the assessment of AS severity.

Sato et al[11] have done an important study in which they measured $AVAI_{Doppler}$, $AVAI_{Biplane}$ and $AVAI_{3DE}$ in 265 patients with AS. $AVAI_{3DE}$ utilized 3D echocardiography to obtain LVEDV and LVESV to derive SV and AVA. They found considerable difference between $AVAI_{Doppler}$ vs. $AVAI_{Biplane}$ or $AVAI_{3DE}$. Presence of USH was the main factor in the discrepancy. They further analyzed the optimal cutoff point of each AVAI to diagnose peak aortic flow velocity >4 m/s, considered as severe AS in the present study. This resulted in a change of the severity criteria. For instance, the criterion of severe AS by $AVAI_{3DE}$ changed from $<0.6\,cm^2/m^2$ to $<0.41\,cm^2/m^2$, which resulted in reclassification of moderate AS by $AVAI_{Doppler}$ to severe AS by the new 3D echocardiographic criterion in 22 patients. In the patients initially diagnosed as moderate AS by Doppler, they found a prognostic difference between those reclassified as severe AS by $AVAI_{3DE}$ $<0.41\,cm^2/m^2$ and those remaining in the same moderate class by $AVAI_{3DE}$ $>0.41\,cm^2/m^2$. Therefore, Sato et al reported the important clinical utility of using multiple AVAIs. The present study mostly reconfirmed their findings in a large number of patients. We further evaluated the utility of combining $AVAI_{Doppler}$ and $AVAI_{Biplane}$. For instance, patients with severe AS by $AVAI_{Biplane}$ were subdivided to those with reclassified moderate/mild AS by $AVAI_{Doppler}$ $>0.6\,cm^2/m^2$ and those remaining in the same severe class by $AVAI_{Doppler}$ $<0.6\,cm^2/m^2$, and the former group had better outcomes (**Figure 5B-c**). Patients with severe AS by $AVAI_{Doppler}$ were subdivided by $AVAI_{Biplane}$ > or $<0.41\,cm^2/m^2$ and they showed "severe" and "very severe" outcomes, respectively (**Figure 5B-b**). In addition, the present study demonstrated the characteristics of patients with discrepant $AVAI_{Doppler}$ and $AVAI_{Biplane}$, such as increased VTI_{LVOT} with relation to USH, older age, shorter height, lower weight, and smaller LV.

Study Limitations

A major limitation of this study is the lack of a "gold standard" measure of SV and AVA. Chuang et al have reported that $SV_{Doppler}$ is overestimated while $SV_{Biplane}$ is underestimated compared with SV obtained by MRI.[15] Poh et al found that SV was more accurately determined by real-time 3D as compared with 2D echocardiographic methods, especially in elderly AS patients with USH.[18] It is likely that the "true" SV and AVA values are intermediate between the Doppler and biplane derived values.

Data on IVS shape, which may cause LVOT flow acceleration, were evaluated in 138 patients with possible retrospective image analysis. The importance of USH has been reported many times.[5,19,20] The present study also demonstrated the important role of USH in causing increased LVOT VTI, contributing to discrepant AVAIs, and reconfirming the results of the previous study.[11] However, our data were obtained from a smaller number of patients being retrospectively analyzed.

Conclusions and Clinical Implications

Doppler echocardiography is the primary imaging modality used to determine AVA, a standard index of AS severity.[21] The current study has demonstrated, in a large cohort of Asian patients with AS, the considerable differences in SV and AVA measurements by the Doppler and biplane methods, both of which are part of the standard repertoire of echocardiographic laboratories. SV and AVA measured by the Doppler method were significantly larger than those obtained by the biplane method. These discrepancies were more pronounced with increased VTI_{LVOT}, shorter height, lower weight, older age, smaller LV dimensions, and increased RWT, even after BSA adjustment. However, combining $AVAI_{Doppler}$ and $AVAI_{Biplane}$ mutually improved their predictive abilities, which could be a practical option when physicians hesitate to make a clinical decision because of the discrepant AVAIs.

Our study highlighted the importance of attentiveness to methodology and the need for cautious interpretation of AS severity in real-world settings. Discrepancies in calculated AVA pose clinical dilemmas, especially when there is discordance between the AVA and the PG or symptoms. In such circumstances, the clinical and echocardiographic features that characterize subjects at higher risk of such discrepancies should be considered. Additionally, the specific technique relied upon to adjudicate AVA should be carefully evaluated for feasibility and reliability, with a focus on image quality and LVOT geometry, among other considerations. Where doubt remains, recourse to planimetry of the AVA (which may be challenging in the setting of highly calcified valves) or alternative radiologic imaging techniques may be required.

Acknowledgments

We are grateful for the support of the entire staff of the Asian Valve Registry. M.I. was supported by the Japan Society of the Promotion of Science KAKENHI, Tokyo, Japan, grant no. 19K20721.

Disclosures

Y.O. is a member of *Circulation Journal*'s Editorial Team.

IRB Information

University of Occupational and Environmental Health Ethics Committee, Reference no. H24-146

References

1. Saikrishnan N, Kumar G, Sawaya FJ, Lerakis S, Yoganathan AP. Accurate assessment of aortic stenosis: A review of diagnostic modalities and hemodynamics. *Circulation* 2014; **129:** 244–253.
2. Ishii M, Taniguchi T, Morimoto T, Ogawa H, Masunaga N, Abe M, et al. Reasons for choosing conservative management in symptomatic patients with severe aortic stenosis: Observations from the CURRENT AS registry. *Circ J* 2019; **83:** 1944–1953.
3. Alskaf E, Kardos A. The mystery of defining aortic valve area: What have we learnt from three-dimensional imaging modalities? *J Echocardiogr* 2018; **16:** 130–138.
4. Mistry N, Halvorsen S, Hoffmann P, Muller C, Bohmer E, Kjeldsen SE, et al. Assessment of left ventricular function with magnetic resonance imaging vs. echocardiography, contrast echocardiography, and single-photon emission computed tomography in patients with recent ST-elevation myocardial

infarction. *Eur J Echocardiogr* 2010; **11:** 793–800.
5. Swinne CJ, Shapiro EP, Jamart J, Fleg JL. Age-associated changes in left ventricular outflow tract geometry in normal subjects. *Am J Cardiol* 1996; **78:** 1070–1073.
6. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; **28:** 1–39.
7. Heo R, Jin X, Oh JK, Kim YJ, Park SJ, Park SW, et al. Clinical usefulness of pressure recovery adjustment in patients with predominantly severe aortic stenosis: Asian Valve Registry data. *J Am Soc Echocardiogr* 2019; **33:** 332–341.
8. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation* 2014; **129:** e521–e643.
9. Iso T, Takahashi K, Yazaki K, Ifuku M, Nii M, Fukae T, et al. In-depth insight into the mechanisms of cardiac dysfunction in patients with type 1 diabetes mellitus using layer-specific strain analysis. *Circ J* 2019; **83:** 1330–1337.
10. Daimon M, Akaishi M, Asanuma T, Hashimoto S, Izumi C, Iwanaga S, et al. Guideline from Japanese Society of Echocardiography: 2018 focused update incorporated into guidance for the management and maintenance of echocardiography equipment. *J Echocardiogr* 2018; **16:** 1–5.
11. Sato K, Seo Y, Ishizu T, Nakajima H, Takeuchi M, Izumo M, et al. Reliability of aortic stenosis severity classified by 3-dimensional echocardiography in the prediction of cardiovascular events. *Am J Cardiol* 2016; **118:** 410–417.
12. Otto CM, Pearlman AS, Comess KA, Reamer RP, Janko CL, Huntsman LL. Determination of the stenotic aortic valve area in adults using Doppler echocardiography. *J Am Coll Cardiol* 1986; **7:** 509–517.
13. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BO, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr* 2009; **22:** 1–23.
14. Bavishi C, Balasundaram K, Argulian E. Integration of flow-gradient patterns into clinical decision making for patients with suspected severe aortic stenosis and preserved LVEF: A systematic review of evidence and meta-analysis. *JACC Cardiovasc Imaging* 2016; **9:** 1255–1263.
15. Oh JK, Taliercio CP, Holmes DR Jr, Reeder GS, Bailey KR, Seward JB, et al. Prediction of the severity of aortic stenosis by Doppler aortic valve area determination: Prospective Doppler-catheterization correlation in 100 patients. *J Am Coll Cardiol* 1988; **11:** 1227–1234.
16. Chuang ML, Hibberd MG, Salton CJ, Beaudin RA, Riley MF, Parker RA, et al. Importance of imaging method over imaging modality in noninvasive determination of left ventricular volumes and ejection fraction. *J Am Coll Cardiol* 2000; **35:** 477–484.
17. Dumont Y, Arsenault M. An alternative to standard continuity equation for the calculation of aortic valve area by echocardiography. *J Am Soc Echocardiogr* 2003; **16:** 1309–1315.
18. Poh KK, Levine RA, Solis J, Shen L, Flaherty M, Kang YJ, et al. Assessing aortic valve area in aortic stenosis by continuity equation: A novel approach using real-time three-dimensional echocardiography. *Eur Heart J* 2008; **29:** 1296–1306.
19. Diaz T, Pencina MJ, Benjamin EJ, Aragam J, Fuller DL, Pencina KM, et al. Prevalence, clinical correlates, and prognosis of discreate upper septal thickening on echocardiography: The Framingham heart study. *Echocardiograhy* 2009; **26:** 247–253.
20. Yoshitani H, Isotani A, Song JK, Shirai S, Umeda H, Jang JY, et al. Surgical as opposed to transcatheter aortic valve replacement improves basal interventricular septal hypertrophy. *Circ J* 2018; **82:** 2887–2895.
21. Pibarot P, Clavel MA. Doppler echocardiographic quantitation of aortic valve stenosis: A science in constant evolution. *J Am Soc Echocardiogr* 2016; **29:** 1019–1022.