Rationale, Design, and Baseline Characteristics of the CURRENT AS Registry-2

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Background: There is scarce data evaluating the current practice pattern and clinical outcomes for patients with severe aortic stenosis (AS), including both those who underwent surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI) and those who were managed conservatively in the TAVI era.

Methods and Results: The Contemporary outcomes after sURgery and medical tREatmeNT in patients with severe Aortic Stenosis (CURRENT AS) Registry-2 is a prospective, physician-initiated, multicenter registry enrolling consecutive patients who were diagnosed with severe AS between April 2018 and December 2020 among 21 centers in Japan. The rationale for the prospective enrollment was to standardize the assessment of symptomatic status, echocardiographic evaluation, and other recommended diagnostic examinations such as computed tomography and measurement of B-type natriuretic peptide. Moreover, the schedule of clinical and echocardiographic follow up was prospectively defined and strongly recommended for patients who were managed conservatively. The entire study population consisted of 3,394 patients (mean age: 81.6 years and women: 60%). Etiology of AS was degenerative in 90% of patients. AS-related symptoms were present in 60% of patients; these were most often heart failure symptoms. The prevalence of high- and low-gradient AS was 58% and 42%, respectively, with classical and paradoxical low-flow low-gradient AS in 4.6% and 6.7%, respectively.

Conclusions: The CURRENT AS Registry-2 might be large and meticulous enough to determine the appropriate timing of intervention for patients with severe AS in contemporary clinical practice.

Key Words: Aortic stenosis; Surgical aortic valve replacement; Transcatheter aortic valve implantation

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Patients with severe aortic stenosis (AS) have poor prognosis unless the obstruction is not relieved by aortic valve replacement (AVR).[1] Before the introduction of transcatheter aortic valve implantation (TAVI), surgical aortic valve replacement (SAVR) was the only definitive treatment to improve clinical outcomes in patients with severe AS.[2,3] The Contemporary outcomes after sURgery and medical tREatmeNT in patients with severe Aortic Stenosis (CURRENT AS) Registry-1 was the first large-scale multicenter study enrolling consecutive patients who

were diagnosed with severe AS before the introduction of TAVI, and provided clinically relevant information on the characteristics, management and prognosis of patients with severe AS.[4,5] After the introduction of TAVI, a series of randomized controlled trials comparing TAVI with SAVR were performed for patients in various risk settings; they suggested that TAVI was associated with a comparable mortality risk compared with SAVR even in low surgical risk patients.[6–11] After publication of these low-risk trials, the number of TAVI procedure performed exponentially increased worldwide.[12] Moreover, there are many contemporary large-scale TAVI registries providing clinically important information on the management and outcomes of patients who undergo TAVI.[12–14] However, there is no large-scale registry that enrols not only patients who undergo SAVR or TAVI, but also those who are managed conservatively. Patients with severe AS usually undergo watchful waiting, if they are not symptomatic. Moreover, patients with severe AS who are of an advanced age and have multiple comorbidities often do not undergo SAVR or TAVI, even if they have symptoms, because of contra-indications and patient rejection.[5] In considering the appropriate treatment algorithm, it is essential to evaluate the current practice pattern and clinical outcomes of patients with severe AS, including both those who undergo SAVR or TAVI and those who are managed conservatively. Therefore, we designed the CURRENT AS Registry-2 that enrolls consecutive patients with severe AS, including those who are managed conservatively in the TAVI era.

Methods

Study Design and Population
The CURRENT AS Registry-2 (UMIN000034169) is a prospective, physician-initiated, non-company sponsored, multi-center registry enrolling consecutive patients who were diagnosed as having severe AS between April 2018 and December 2020 among 21 participating centers in Japan (**Supplementary Appendix 1**). Both SAVR and TAVI were available in 10 centers, only SAVR was available in 10 centers, and both SAVR and TAVI were not available in one center. Among the 21 participating centers in the CURRENT AS Registry-2, 20 centers also participated in the CURRENT AS Registry-1. The rationale for the pro-spective enrollment was to standardize the assessment of symptomatic status, echocardiographic evaluation, and other recommended diagnostic examinations such as com-puted tomography (CT) and measurement of B-type natri-uretic peptide (BNP). Moreover, the schedule of clinical and echocardiographic follow up was prospectively defined and strongly recommended in patients who were managed conservatively.

The enrollment was conducted based on findings at the index echocardiography. We defined patients with severe AS in this study as those who met at least one of the 3 echocardiographic criteria (peak aortic jet velocity [V_{max}] >4.0 m/s, mean aortic pressure gradient [mPG] >40 mmHg, or aortic valve area [AVA] <1.0 cm^2) for the first time dur-ing the enrollment period, which was consistent with the CURRENT AS Registry-1.[4] Exclusion criteria for this study were patients who had a history of aortic valve surgery or percutaneous aortic balloon valvuloplasty.

The institutional review boards in all 21 participating centers approved the protocol. Written informed consent was obtained from each patient enrolled from 19 centers, whereas in 2 centers, the opt-out strategy waiving written informed consent was adopted with permission by the institutional review boards.

Baseline Clinical Characteristics
We evaluated comprehensive baseline clinical characteris-tics such as patient demographics, comorbidities, medical history, frailty, cognitive function, and medications at time of the index echocardiography. Frailty was assessed using the Clinical Frailty Scale. The Original Clinical Frailty Scale was advocated by the Canadian Study of Health and Aging and was modified to a 9-level scale by Geriatric Medicine Research (Dalhousie University, Halifax, NS, Canada).[15] We assessed cognitive function by conducting the Mini-Mental State Examination (MMSE) or the Mini-Cog test.[16,17] Data were collected and were directly recorded in the Electronic Data Capture system by the attending physicians or research assistants at each participating hos-pital. To ensure the quality of the data, a study manager monitored the quality of data for patients from randomly chosen participating centers.

Assessment of Symptoms
Angina, syncope, and heart failure (HF) including dyspnea were regarded as AS-related symptoms. Acute HF was defined as symptoms of HF requiring hospitalized manage-ment with intravenous drug therapy. To assess the symp-toms accurately, we also referred to the hearing with the family members of the participants. We strongly recom-mended that a treadmill exercise test and/or 6-min walk test is conducted with patients without apparent symptoms. Abnormality during exercise testing or a systolic blood pressure drop during hemodialysis was also regarded as AS-related symptoms. An abnormal exercise response dur-ing a treadmill exercise test included ventricular arrhythmia, a systolic blood pressure drop or a failure for it to rise by 20 mmHg, ST-segment depression, or development of AS-related symptoms.[18] Patients who have a negative treadmill stress test were regarded as "truly asymptomatic". Patients

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CURRENT AS Registry-2
3374 patients with severe AS screened between April 2018 and December 2020 from 21 centers in Japan
(V max >4.0 m/s, mean aortic PG >40 mmHg, or AVA <1.0 cm2)

Patients who refused the study participation: 5 patients

Entire Cohort: 3369 patients with severe AS
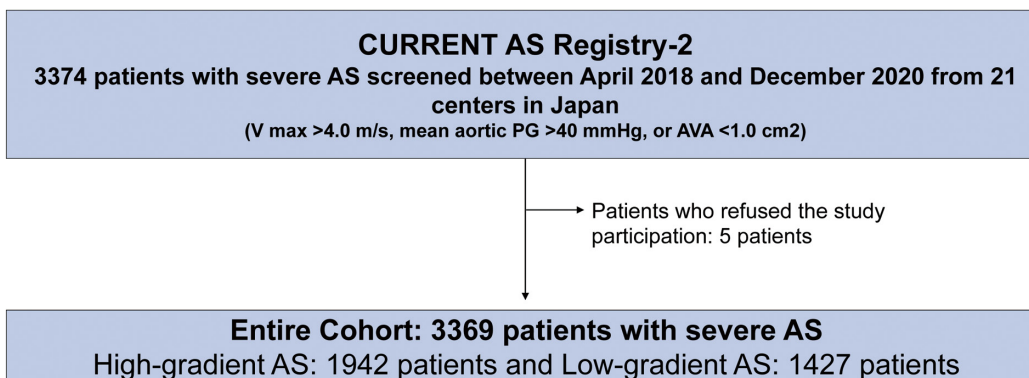High-gradient AS: 1942 patients and Low-gradient AS: 1427 patients

Figure. Study flowchart. AVR included both SAVR and TAVI. High-gradient AS was defined as V_{max} >4.0 m/s or mean aortic PG >40 mmHg, whereas low-gradient AS was defined as V_{max} ≤4.0 m/s and mean aortic PG ≤40 mmHg. AVA, aortic valve area; AVR, aortic valve replacement; CURRENT AS, Contemporary outcomes after sURgery and medical tREatmeNT in patients with severe Aortic Stenosis; PG, pressure gradient; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; V_{max}, peak aortic jet velocity.

who were unable to undergo a treadmill stress test but completed a 6-min walk test to a total distance >300 m without symptoms were also regarded as "truly asymptomatic".[19,20] Asymptomatic patients who were classified as being asymptomatic by physician assessment, but were unable to perform a stress test or could not complete a 6-min walk test, were regarded as "asymptomatic by patient history".

Echocardiography and Other Diagnostic Examinations
All participants underwent a comprehensive 2-dimensional and Doppler echocardiographic evaluation at each participating center. V_{max} and mean aortic PG measurements were obtained with the use of the simplified Bernoulli equation. AVA was calculated using the standard continuity equation, and indexed to body surface area.[21,22] We made every effort to standardize the quality of echocardiography when assessing the severity of AS by holding a workshop or a hands-on seminar to provide training and targeting the echo technicians in the participating centers. In each participating center, we highly recommended the use of multiple acoustic windows (apical, high parasternal or right parasternal) to obtain the greatest peak velocity in accordance with the guidelines.[22]

We classified patients with severe AS into a high-gradient AS (V_{max} >4.0 m/s or mean aortic PG >40 mmHg) and a low-gradient AS (V_{max} ≤4.0 m/s and mean aortic PG ≤40 mmHg) group. Moreover, patients with low-gradient AS were subdivided into low-flow low-gradient AS with reduced LVEF (AVA <1 cm², mPG ≤40 mmHg, V_{max} ≤4.0 m/s, stroke volume index ≤35 mL/m², and LVEF <50%), low-flow low-gradient AS with preserved LVEF (AVA <1 cm², mPG ≤40 mmHg, V_{max} ≤4.0 m/s, stroke volume index ≤35 mL/m², and LVEF ≥50%), and normal-flow low-gradient AS (mPG ≤40 mmHg, V_{max} ≤4.0 m/s, and stroke volume index >35 mL/m²). Stroke volume was calculated by using the cross-sectional left ventricular outflow tract (LVOT) area and LVOT velocity.[21] We recommended dobutamine stress echocardiography in patients with low-flow low-gradient AS with reduced LVEF to assess whether they had true severe AS in accordance with the guidelines.[23,24] We also recommended CT to evaluate the severity of AS

by using the calcium score in patients with low-flow low-gradient AS. We also recommended to that levels of BNP or N-terminal pro-B-type natriuretic peptide (NT-proBNP) at baseline were measured to stratify the risk in accordance with guidelines.[23] Blood tests performed within 3 month before or after the day of index echocardiography were eligible for use to obtain baseline measurements.

Initial Treatment Strategies
The study population was divided into the 2 groups according to the initial treatment strategies (initial AVR group and conservative group). The choice of an initial AVR strategy or a conservative strategy was made after a discussion between the attending physician and the patients, with occasional heart-team consultation. The choice of an initial SAVR strategy or an initial TAVI strategy was made based on the consensus by the heart-team and the preference of the patients. Patients in the conservative strategy group were further subdivided into 3 groups based on the reasons for choosing a conservative strategy (watchful waiting group, contraindication for AVR group, and patient rejection group). Patients with contraindication for AVR were defined as those who were indicated for neither SAVR nor TAVI because of advanced age and/or comorbidities based on the physicians' judgement. Patients with patient rejection were defined as those who refused both SAVR and TAVI, even though a physician recommended AVR. Patients in the watchful waiting group were defined as those who chose conservative management and were carefully followed by the outpatient department; these patients had a re-evaluation of their symptoms, underwent an echocardiography, and had their biomarkers assessed until the appropriate timing for intervention was made, in accordance with current guidelines.[23]

Follow-up Protocol
Patients in the watchful waiting group were strongly recommended to undergo regular follow up by echocardiography and have their measurements for BNP or NT-proBNP taken every 6 months in the outpatient department of the participating center, in accordance with current guide-

lines.[23] The clinical follow-up schedule of patients other than those in the watchful waiting group was left to the discretion of the attending physician. Follow-up information is to be collected by the attending physicians or research assistants at each participating center. If outpatient clinical follow up is not conducted at the participating study centers or additional follow-up information is required, we will collect data through contact with the patients, their relatives and/or referring physicians by sending mails with questions regarding clinical events, subsequent hospitalizations, and status of medical therapy.

The time zero for the clinical follow up in the present registry was the day of the index echocardiography, unless otherwise defined. In-hospital outcomes are to be assessed at the time of hospital discharge for the index AVR procedures, only among those patients in the initial AVR group

Table 1. Patient Characteristics		
	Entire cohort	Number of patients evaluated
(A) Clinical characteristics		
Age (years)	81.6±8.4	3,369
≥80	2,224 (66)	3,369
Men	1,329 (39)	3,369
Body mass index (kg/m²)	22.6±3.7	3,355
<22.0	1,561 (46)	3,369
BSA, m²	1.52±0.19	3,355
Systolic blood pressure, mmHg	132±22	2,592
Diastolic blood pressure, mmHg	69±13	2,591
Heart rate, beats/min	72±13	2,187
Hypertension	2,750 (82)	3,369
Current smoking	132 (3.9)	3,369
Dyslipidemia	1,793 (53)	3,369
Diabetes mellitus	993 (30)	3,369
On insulin therapy	167 (5.0)	3,369
Prior myocardial infarction	249 (7.4)	3,369
Prior PCI	590 (18)	3,369
Prior CABG	130 (3.9)	3,369
Prior open heart surgery	192 (5.7)	3,369
Prior symptomatic stroke	488 (15)	3,369
Atrial fibrillation or flutter	765 (23)	3,369
Aortic and/or peripheral vascular disease	257 (7.6)	3,369
eGFR	49±23	3,072
eGFR <30 not on hemodialysis	339 (10)	3,369
Serum creatinine	1.5±1.8	3,072
Creatinine level >2 mg/dL or hemodialysis	397 (12)	3,369
Hemodialysis	280 (8.3)	3,369
Anemia	1,792 (53)	3,369
Liver cirrhosis (Child B or C)	28 (0.8)	3,369
Malignancy	660 (20)	3,369
Currently under treatment	192 (5.7)	3,369
Chest wall irradiation	31 (0.9)	3,369
Immunosuppressive therapy	183 (5.4)	3,369
Chronic lung disease	764 (23)	3,369
Moderate or severe	193 (5.7)	3,369
Coronary artery disease	1,210 (36)	3,369
Clinical Frailty Scale		
1–3	1,665 (49)	3,369
4–6	1,456 (43)	3,369
7–9	248 (7.4)	3,369
STS PROM, %	4.2 (2.8–6.3)	3,369
EuroSCORE II, %	3.3 (2.0–4.9)	3,369
Logistic EuroSCORE, %	11.4 (7.5–18.3)	3,369
BNP, pg/mL	167 (67–433)	2,561
NT-proBNP, pg/mL	953 (348–3,225)	394

(**Table 1** continued the next page.)

	Entire cohort	Number of patients evaluated
(B) Presentation		
Etiology		
Degenerative	3,103 (92)	3,369
Congenital (unicuspid, bicuspid, or quadricuspid)	226 (6.7)	3,369
Rheumatic	37 (1.1)	3,369
Infective endocarditis	2 (0.1)	3,369
Other	1 (0.03)	3,369
Symptoms		
Any symptoms probably related to AS	2,010 (60)	3,369
Chest pain	312 (9.2)	3,369
Syncope	193 (5.7)	3,369
Heart failure	1,760 (52)	3,369
NYHA class		
II	1,106 (33)	3,369
III	459 (14)	3,369
IV	195 (5.8)	3,369
(C) Medication at index echocardiography		
Antiplatelet therapy		
Aspirin	911 (27)	3,366
Thienopyridine		
Clopidogrel	396 (12)	3,366
Prasugrel	40 (1.2)	3,366
Ticlopidine	9 (0.3)	3,366
Statins	1,563 (46)	3,366
β-blockers	946 (28)	3,366
ACE inhibitors/ARB	1,657 (49)	3,366
Calcium channel blockers	1,792 (53)	3,366
Warfarin	277 (8.2)	3,366
DOAC	453 (14)	3,366
Proton pump inhibitors	1,454 (43)	3,366
H2 blocker	249 (7.4)	3,366
OHA	736 (22)	3,366

Data are presented as mean±SD, median (interquartile range) or n (%), unless otherwise stated. Anemia was defined as serum hemoglobin <12.0 g/dL for women or <13.0 g/dL for men. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AS, aortic stenosis; AVR, aortic valve replacement; BNP, B-type natriuretic peptide; BSA, body surface area; CABG, coronary artery bypass grafting; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; H2, histamine H2-receptor; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OHA, oral hypoglycemic agent; PCI, percutaneous coronary intervention; PROM, predicted risk of mortality; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.

who actually underwent SAVR or TAVI. Follow-up data from all enrolled patients are to be collected at 1, 3, and 10 years after the last patient was enrolled.

Clinical Outcomes
The clinical outcome measures included all-cause death, cardiovascular death, non-cardiovascular death, aortic valve-related death, sudden death, HF hospitalization, stroke, myocardial infarction, major bleeding, emerging symptoms related to AS, and AVR. We also assessed a composite of aortic valve-related death and HF hospitalization. Aortic valve-related death included aortic valve procedure-related death, sudden death, and death due to HF, which was possibly related to the aortic valve. Clinical events such as death, stroke and major bleeding are defined according to the Valve Academic Research Consortium (VARC)-3, but if the events are not able to be adjudicated according to VARC-3, we will adopt VARC-2 definitions.[25,26] Details of

clinical outcomes and definitions are presented in the **Supplementary Appendix 2**. Death, stroke, myocardial infarction and major bleeding are to be adjudicated by the clinical event committee (**Supplementary Appendix 3**).

Analytical Plan
One of the main objectives of this study is to explore the appropriate timing of intervention in asymptomatic patients with severe AS by comparing the long-term clinical outcomes between patients in the watchful waiting strategy group and those in the initial AVR strategy group. Owing to the pre-defined follow-up schedule of patients in the watchful waiting strategy group, we might assess the role of serial measurement of echocardiographic parameters and BNP. Another objective of this study is to assess the practice patterns and clinical outcomes in the pre-specified subgroup of patients. In particular, we are focusing on those patients with low-flow low-gradient severe AS in

Table 2. Echocardiographic Characteristics

	Entire cohort	Number of patients evaluated
V_{max}, m/s	4.1±0.8	3,369
>4	1,900 (56)	3,369
>4.5	972 (29)	3,369
>5	469 (14)	3,369
Mean aortic PG, mmHg	41.3±17.6	3,199
>40	1,488 (47)	3,199
AVA (equation of continuity), cm²	0.75±0.19	3,362
<1.0	3,237 (96)	3,362
AVA index, cm²/m²	0.49±0.13	3,348
LVEF, %	60.7±11.2	3,368
<40	219 (6.5)	3,369
<50	492 (15)	3,369
<60	1,108 (33)	3,369
Stroke volume index, mL/m²	46±12	3,346
≤35	621 (19)	3,346
Eligibility for severe AS		
High-gradient AS	1,942 (58)	3,369
Low-gradient AS	1,427 (42)	3,369
Low-flow low-gradient AS with reduced LVEF	154 (4.6)	3,369
Low-flow low-gradient AS with preserved LVEF	227 (6.7)	3,369
Normal-flow low-gradient AS with preserved LVEF	898 (27)	3,369
Normal-flow low-gradient AS with reduced LVEF	138 (4.1)	3,369
Unknown flow or unknown EF	10 (0.3)	3,369
LV end-diastolic diameter, mm	45±6	3,367
LV end-systolic diameter, mm	30±7	3,344
IVST in diastole, mm	11±2	3,342
PWT in diastole, mm	10±2	3,342
LVMI, g/m²	Men: 113±30 Women: 106±30	3,342
High LVMI (Men: >115, and Women: >95)	Men: 553 (42) Women: 1,187 (59)	3,369
Any combined valvular disease (moderate or severe)	882 (26)	3,369
AR	349 (10)	3,369
MS	100 (3.0)	3,369
MR	384 (11)	3,369
TR	340 (10)	3,369
TR pressure gradient ≥40 mmHg	350 (10)	3,369

Data are presented as mean±SD or n (%), unless otherwise stated. High-gradient AS was defined as V_{max} >4.0 m/s or mean aortic PG >40 mmHg, whereas low-gradient AS was defined as V_{max} ≤4.0 m/s and mean aortic PG ≤40 mmHg. Low-flow low-gradient AS with reduced LVEF was defined as patients who met all the following criteria: AVA <1 cm², mPG ≤40 mmHg, V_{max} ≤4.0 m/s, stroke volume index ≤35 mL/m², and LVEF <50%. Low-flow low-gradient AS with preserved LVEF was defined as patients who met all the following criteria: AVA <1 cm², mPG ≤40 mmHg, V_{max} ≤4.0 m/s, stroke volume index ≤35 mL/m², and LVEF ≥50%. Normal-flow low-gradient AS was defined as patients who met all the following criteria: AVA <1 cm², mPG ≤40 mmHg, V_{max} ≤4.0 m/s, and stroke volume index >35 mL/m². Five patients were enrolled with V_{max}=4.0, mPG ≤40 mmHg, and AVA >1.0 (protocol violation). These patients were regarded as having high-gradient AS. AR, aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; EF, ejection fraction; IVST, interventricular septum thickness; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MS, mitral stenosis; MR, mitral regurgitation; PG, pressure gradient; PWT, posterior wall thickness; TR, tricuspid regurgitation; V_{max}, peak aortic jet velocity.

whom long-term clinical outcomes will be compared between watchful waiting and AVR. We plan to make risk stratification for patients with severe AS by assessing the effects of patients characteristics and echocardiographic data on long-term clinical outcomes. Moreover, in an attempt to explore the appropriate choice of SAVR or TAVI, we plan to compare the in-hospital and long-term outcomes for up to 10 years between SAVR and TAVI.

We also plan to assess the incidence of structural valve deterioration during long-term follow up after SAVR and TAVI, and evaluate whether either TAVI or SAVR is more appropriate for re-AVR.

Other analytic plans are to evaluate the role of the exercise test or the 6-min walk test in assessing the symptoms of AS and in predicting clinical outcomes, and to evaluate the relationship of echocardiographic data or CT data

assessed at core laboratories with clinical outcomes. Finally, we plan to make a historical comparison of the practice patterns and clinical outcomes between CURRENT AS Registry-1 and -2 to realize the impact of therapeutic improvement, particularly the introduction of TAVI, on long-term clinical outcomes of patients with severe AS.

Patient and Public Involvement
In this study, patients were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results
Patient Characteristics of the Entire Cohort
Among 3,374 patients who were enrolled in this study, 5 patients were excluded because they refused study participation after enrollment. Therefore, the current study population consisted of 3,369 patients with severe AS (**Figure**). In the entire cohort, the mean age was 81.6 years and 60% of patients were women (**Table 1**). The etiology of AS was degenerative in 90% of patients. AS-related symptoms were present in 60% of patients, which were most often heart failure symptoms. Regarding echocardiographic variables, mean V_{max} was 4.1 m/s, mean mPG was 41.3 mmHg and mean AVA was 0.75 cm². The prevalence of high-gradient AS and low-gradient AS was 58% and 42%, respectively. The prevalence of classical low-flow low-gradient AS was 4.6% and paradoxical low-flow low-gradient AS was 6.7% (**Table 2**).

Discussion
The CURRENT AS Registry-2 is the first large-scale study enrolling consecutive patients with severe AS after introduction of TAVI, which enables us to evaluate the current clinical practice patterns and long-term clinical outcomes in patients with severe AS.

The strength of the CURRENT AS Registry-2 was as follows. First, this study included not only patients who were referred for AVR, but also those who were managed conservatively. It will give us the opportunity to assess the appropriate timing of intervention for severe AS in the TAVI era. It should be noted that we did make every effort to detect mild symptoms related to AS, which might facilitate early AVR in patients who were "asymptomatic according to the patient history". Second, in this study, we divided the patients treated by conservative management into three categories (watchful waiting group, contraindication for AVR group, and patient rejection group). In our prior study, we compared the long-term outcomes in asymptomatic patients with severe AS who were treated with a conservative vs. initial AVR strategies; we we found improved clinical outcomes with the initial AVR strategy than with the conservative strategy.[4] However, we included those patients with rejection and contraindication for AVR in the conservative group, which undoubtedly overestimated the clinical event rate for those patients treated with conservative management. To assess the true impact of AVR compared with conservative therapy in asymptomatic patients with severe AS, patients who were managed under the watchful waiting strategy would be the appropriate comparator group to patients who were managed with the initial AVR strategy. Recently, a meta-analysis suggested early intervention for asymptomatic patients with severe AS was associated with significant reduction in long-term

mortality as compared with conservative management.[27] However, there was still a scarcity of data comparing the watchful waiting strategy with the initial AVR strategy, including TAVI in asymptomatic patients with severe AS. Guidelines recommended AVR for patients with asymptomatic severe AS who had reduced EF, very severe AS, rapid progression of AS, and elevated neurohormones, as well as in those scheduled for other cardiac sugery.[23,24] In this study, we will have opportunities to compare the watchful waiting strategy with AVR in asymptomatic patients with severe AS. Third, in this study, we collected echocardiographic data in detail. In particular, we obtained stroke volume data for almost all patients. These data will enable us to assess clinical outcomes in some clinically important sub-groups such as low-flow low-gradient AS with and without preserved LVEF. A prospective cohort study suggested that early AVR might provide better clinical outcomes compared to conservative management in patients with low-flow low-gradient AS, irrespective of left ventricular ejection fraction (LVEF);[28] however, there was not enough data guiding the optimal treatment of these patients with low-flow low-gradient AS with preserved LVEF, although a randomized controlled trial is currently being conducted.[29] We might have opportunity to assess clinical outcomes and confirm the optimal treatment strategy for patients with low-flow low-gradient AS with preserved LVEF. The current study population included a large proportion of patients with normal-flow low-gradient AS, which might be regarded as moderate AS. One of the aims of this registry is to clearly distinguish between patients with high-gradient severe AS, classical low-flow low-gradient AS, paradoxical low-flow low-gradient AS, and normal-flow low-gradient AS by assessing the long-term outcomes of these groups.

Conclusions
The CURRENT AS Registry-2 is a large, prospective, multi-center registry enrolling consecutive patients who were diagnosed as having severe AS. This study included not only those patients who underwent AVR, but also those patients who were managed conservatively. This study might be large and meticulous enough to provide important information on the appropriate timing of intervention for patients with severe AS in the contemporary clinical practice setting.

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Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-21-1062