SUPPLEMENTARY MATERIAL

Table of Contents

List of Investigators

Principal Investigators

Takeshi Kimura, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan

Ryuzo Sakata, Department of Cardiovascular Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan

List of participating centers and investigators for the CURRENT AS registry

Cardiology

Kyoto University Graduate School of Medicine: Takeshi Kimura, Tomohiko Taniguchi, Hiroki Shiomi, Naritatsu Saito, Masao Imai, Junichi Tazaki, Toshiaki Toyota, Hirooki Higami, Tetsuma Kawaji

Kokura Memorial Hospital: Kenji Ando, Shinichi Shirai, Kengo Kourai, Takeshi Arita, Shiro Miura, Kyohei Yamaji

Shimada Municipal Hospital: Takeshi Aoyama, Norio Kanamori

Shizuoka City Shizuoka Hospital: Tomoya Onodera, Koichiro Murata

Kobe City Medical Center General Hospital: Yutaka Furukawa, Takeshi Kitai, Kitae Kim

Kurashiki Central Hospital: Kazushige Kadota, Yuichi Kawase, Keiichiro Iwasaki, Hiroshi Miyawaki, Ayumi Misao, Akimune Kuwayama, Masanobu Ohya, Takenobu Shimada, Hidewo Amano

Tenri Hospital: Yoshihisa Nakagawa, Chisato Izumi, Makoto Miyake, Masashi Amano, Yusuke Takahashi, Yusuke Yoshikawa, Shunsuke Nishimura, Maiko Kuroda

Nara Hospital, Kinki University Faculty of Medicine: Manabu Shirotani, Hirokazu Mitsuoka

Mitsubishi Kyoto Hospital: Shinji Miki, Tetsu Mizoguchi, Masashi Kato, Takafumi Yokomatsu, Akihiro Kushiyama, Hidenori Yaku, Toshimitsu Watanabe

Kinki University Hospital: Shunichi Miyazaki, Yutaka Hirano

Kishiwada City Hospital: Mitsuo Matsuda, Shintaro Matsuda, Sachiko Sugioka

Osaka Red Cross Hospital: Tsukasa Inada, Kazuya Nagao, Naoki Takahashi, Kohei Fukuchi

Koto Memorial Hospital: Tomoyuki Murakami, Hiroshi Mabuchi, Teruki Takeda, Tomoko Sakaguchi, Keiko Maeda, Masayuki Yamaji, Motoyoshi Maenaka, Yutaka Tadano

Shizuoka General Hospital: Hiroki Sakamoto, Yasuyo Takeuchi, Makoto Motooka, Ryusuke Nishikawa

Nishikobe Medical Center: Hiroshi Eizawa, Keiichiro Yamane, Mitsunori Kawato, Minako Kinoshita, Kenji Aida

Japanese Red Cross Wakayama Medical Center: Takashi Tamura, Mamoru Toyofuku, Kousuke Takahashi, Euihong Ko

National Hospital Organization Kyoto Medical Center: Masaharu Akao, Mitsuru Ishii, Nobutoyo Masunaga, Hisashi Ogawa, Moritake Iguchi, Takashi Unoki, Kensuke Takabayashi, Yasuhiro

Hamatani, Yugo Yamashita
The Tazuke Kofukai Medical Research Institute, Kitano Hospital: Moriaki Inoko, Eri Minamino-Muta, Takao Kato
Hikone Municipal Hospital: Yoshihiro Himura, Tomoyuki Ikeda
Kansai Electric Power Hospital: Katsuhisa Ishii, Akihiro Komasa
Hyogo Prefectural Amagasaki General Medical Center: Yukihito Sato, Kozo Hotta, Shuhei Tsuji
Rakuwakai Otowa Hospital: Yuji Hiraoka, Nobuya Higashitani
Saiseikai Noe Hospital: Ichiro Kouchi, Yoshihiro Kato
Shiga Medical Center for Adults: Shigeru Ikeguchi, Yasutaka Inuzuka, Soji Nishio, Jyunya Seki
Hamamatsu Rosai Hospital: Eiji Shinoda, Miho Yamada, Akira Kawamoto, Chiyo Maeda
Japanese Red Cross Otsu Hospital: Takashi Konishi, Toshikazu Jinnai, Kouji Sogabe, Michiya Tachiiri, Yukiko Matsumura, Chihiro Ota
Hirakata Kohsai Hospital: Shoji Kitaguchi, Yuko Morikami

Cardiovascular Surgery
Kyoto University Graduate School of Medicine: Ryuzo Sakata, Kenji Minakata, Kenji Minatoya
Kokura Memorial Hospital: Michiya Hanyu
Shizuoka City Shizuoka Hospital: Fumio Yamazaki
Kobe City Medical Center General Hospital: Tadaaki Koyama
Kurashiki Central Hospital: Tatsuhiko Komiya
Tenri Hospital: Kazuo Yamanaka
Nara Hospital, Kinki University Faculty of Medicine: Noboru Nishiwaki
Mitsubishi Kyoto Hospital: Hiroyuki Nakajima, Motoaki Ohnaka, Hiroaki Osada, Katsuaki Meshii
Kinki University Hospital: Toshihiko Saga
Kishiwada City Hospital: Masahiko Onoe
Osaka Red Cross Hospital: Shogo Nakayama
Shizuoka General Hospital: Genichi Sakaguchi
Japanese Red Cross Wakayama Medical Center: Atsushi Iwakura
National Hospital Organization Kyoto Medical Center: Kotaro Shiraga
The Tazuke Kofukai Medical Research Institute, Kitano Hospital: Koji Ueyama
Hyogo Prefectural Amagasaki General Medical Center: Keiichi Fujiwara
Rakuwakai Otowa Hospital: Atsushi Fukumoto
Shiga Medical Center for Adults: Masaki Park
Hamamatsu Rosai Hospital: Junichiro Nishizawa
Japanese Red Cross Otsu Hospital: Mitsuru Kitano

A clinical event committee

Hirotoshi Watanabe, MD (Kyoto University Graduate School of Medicine); Kenji Nakatsuma, MD (Kyoto University Graduate School of Medicine), Tomoki Sasa, MD (Kishiwada City Hospital)

Definitions of the clinical events

Death was regarded as cardiovascular in origin unless obvious non-cardiovascular causes could be identified. Sudden death was defined as unexplained death in previously stable patients. Any death during the hospitalization for aortic valve replacement or transcatheter aortic valve implantation was regarded as aortic valve procedure-related death. Aortic valve-related death included aortic valve procedure-related death, sudden death, and death due to heart failure related to aortic stenosis. Heart failure hospitalization was defined as hospitalization due to worsening heart failure requiring intravenous drug therapy.

Online Supplementary Table 1. Main papers from the CURRENT AS registry

First Author (Ref. #)	Year	Study objectives	Main findings	Clinical implications
Taniguchi at al. (#8)	2015	Compare clinical outcomes with initial AVR strategy versus conservative strategy in asymptomatic patients with severe AS	**[Propensity-matched cohort (N=582; 291 initial AVR, 291 conservative group)]** · The cumulative incidence of all-cause death was significantly lower in the initial AVR group than in the conservative group (15.4% versus 26.4%, p=0.009) · The cumulative incidence of heart failure hospitalization was also associated with markedly lower cumulative 5-year incidence of HF hospitalization (3.8% versus 19.9%, p<0.001). · Among 291 patients in the conservative group, AVR was performed in 118 patients (41%) during the follow-up at a median interval of 780 days from index echocardiography. **[Total cohort (N=1808; 291 initial AVR, 1517 conservative group)]** · Among 492 patients with emerging symptoms related to AS during follow-up in the conservative group, AVR was performed in 239 patients (49%). AVR was actually performed in only 74 of 201 patients (37%) presenting with NYHA III or IV HF. · The favorable effect of initial AVR strategy for the clinical outcomes was similarly seen in the adjusted analysis of the entire cohort.	· Monitoring for symptoms can be an imprecise undertaking as a guide to the timing of aortic valve intervention, and some patients will inevitably be lost to follow-up using watchful waiting strategy. Progression to required intervention within 5 years of developing severe AS is almost inevitable. One does not gain much by waiting.

Shirai et al. (#33)	2017	Evaluate the effect of symptom status before AVR on clinical outcomes	· Initial AVR strategy in asymptomatic patients with severe AS was associated with better survival and less HF hospitalization compared with symptomatic patients.	· This study could provide additional support for the early AVR strategy in asymptomatic severe AS.
Taniguchi et al. (#53)	2017	Characterize the demographics and evaluate clinical outcomes of patients with HG-AS and LG-AS	· LG-AS patients had worse crude clinical outcomes than HG-AS patients, although the higher gradient was associated with poorer outcomes after adjusting the baseline characteristics and the initial AVR strategy. · The initial AVR strategy was associated with better long-term clinical outcomes than the conservative strategy in HG-AS and LG-AS patients, although AVR was less frequently performed in LG-AS patients than in HG-AS patients (28% versus 60%). · The favorable effect of initial AVR strategy was also seen in patients with LG-AS with preserved LVEF.	· The poorer crude clinical outcomes in LG-AS patients might be partly because of the comorbidities and partly because of the lower prevalence of the initial AVR strategy.
Nakatsuma et al. (#41)	2017	Evaluate the prognostic valve of Vmax in conservatively managed severe AS patients with preserved LVEF	·The cumulative 5-year incidence of the AS-related events remained very high in asymptomatic patients with less greater Vmax, and increasing Vmax was associated with incrementally higher risk for AS-related events in conservatively managed severe AS patients with preserved left ventricular ejection fraction.	· The effect size of Vmax ≥5.0 m/s relative to Vmax 4.0 to 4.5 m/s for aortic valve–related death or HF hospitalization in asymptomatic patients was similar to that in symptomatic patients, supporting the guidelines recommendation of AVR in asymptomatic patients with very severe AS (Vmax ≥5.0 m/s). · Patients with Vmax ≥4.5 m/s were also at higher risk for adverse AS-related events.
Minamino-Muta et al.	2017	Evaluate the factors	· The factors associated with high LV mass index were female,	· Considering the different effects of high LV

(#44)		associated with high LV mass index (LV mass index >115 g/m^2 for males and >95 g/m^2 for females) and the impact of LV mass index on clinical outcomes in severe AS	BMI ≥22, absence of dyslipidemia, LVEF <50%, Vmax ≥4m/s, regurgitant valvular disease, hypertension, anaemia, and end-stage renal disease. · The deleterious impact of high LV mass index on the outcomes found in patients with conservative treatment had in contrast no effect on the outcomes in patients who were managed surgically.	mass index on outcomes between treatment strategies, ventricular response is important for the risk stratification and the timing of surgical or transcatheter intervention in patients with severe AS.
Taniguchi et al. (#35)	2018	Investigate the impact of LVEF on clinical outcomes stratified by initial treatment strategy (conservative or initial AVR) in patients with severe AS.	· LVEF 50% to 59% and <50%, but not LVEF 60% to 69%, were independently associated with poorer long-term outcomes compared with LVEF >70% with the conservative strategy. In the initial AVR strategy, the adjusted risk of low LVEF for the primary outcome measure (a composite of aortic valve–related death or HF hospitalization) was markedly attenuated across the 4 LVEF groups.	· Survival in patients with severe AS is impaired when LVEF is <60%, and LVEF <60% predicts deterioration of LVEF and appears to represent abnormal LVEF in severe AS.
Taniguchi et al. (#10)	2018	Examine the incidence of sudden death and the risk factors associated with sudden death in patients with severe aortic stenosis.	· The incidence of sudden death in asymptomatic patients with severe aortic stenosis might be higher than that reported in previous studies. The cumulative 5-year incidence of sudden death censored at AVR, accounting for the competing risk, was 7.2% (1.4%/year) in asymptomatic patients. · Several clinical and echocardiographic characteristics were found to be significantly associated with the risk of sudden death, particularly hemodialysis, prior MI, BMI <22, Vmax ≥5 m/s, and LVEF <60%.	· Identification of characteristics associated with an increased risk for sudden death might improve the understanding of potential mechanisms. · Baseline clinical factors can help inform sudden death risk stratification. We should take these risk factors for sudden death into account when we decide the appropriate timing for surgical or transcatheter intervention.
Nagao et al. (#25)	2018	Clarify the characteristics of severe AS patients who	• Risk factors for developing AHF included age, female sex, lower BMI, untreated coronary artery stenosis, anemia, history of HF,	· AHF complicating severe AS was associated with an extremely dismal prognosis, which

		develop acute HF (AHF) defined as hospitalized HF at enrolment, and evaluate the effect of AHF on clinical outcomes of severe AS patients according to the initial treatment strategies	LVEF <50%, presence of any combined valvular disease, Vmax ≥5 m/s and TRPG ≥40 mmHg, and negative risk factors included dyslipidemia, history of PCI and hemodialysis. • The prognosis of patients with severe AS complicated by AHF was poor, with extremely high rates of all-cause death and HF hospitalization. • AHF patients as compared with chronic HF patients less frequently underwent AVR, and had higher long-term mortality rates even after AVR.	could not be fully resolved by AVR. Careful management to avoid the development of AHF is crucial.
Minamino-Muta et al. (#49)	2019	Develop a clinical scoring system to predict AS-related adverse events within 1-year after diagnosis in asymptomatic patients with severe AS.	• The risk score comprised independent risk predictors including LVEF <60%, hemoglobin ≤11.0g/dl, chronic lung disease (2 points), diabetes mellitus, HD, and any concomitant valve disease (1 point). The predictive accuracy of the model was good with the area under the curve of 0.79 and 0.77 in the derivation and validation sets.	· The clinical scoring system might be helpful for decision making for AVR in the periodic follow-up of asymptomatic patients with severe AS.
Ishii et al. (#23)	2019	Investigate the baseline characteristics and clinical outcome in symptomatic patients who denied AVR in comparison with those conservatively managed patients based on physician judgment in patients with severe AS	• Patient rejection was the reason for non-referral to AVR in nearly one-quarter of the symptomatic patients with severe AS who were managed conservatively. • Despite less comorbidities and lower surgical risk, the dismal outcome in patients who refused AVR was similar to that in patients who were not referred to AVR based on physician judgment.	· This study highlight the profound risk of patient rejection for AVR as well as the risk of delaying AVR, which should be adequately informed to the patients and the family members.
Kanamori et al. (#42)	2019	Evaluate the prognostic impact of AVA in asymptomatic patients	• AVA ≤0.60 and 0.8 cm^2 ≥AVA >0.6 cm^2 as compared with AVA >0.80 cm^2 were associated with higher risk for the composite of aortic valve–related death or HF	· AVA ≤0.6 cm^2 would be a useful marker to identify high-risk subsets of patients with asymptomatic severe AS.

		with severe AS	hospitalization. • The excess risk of AVA ≤0.60 cm^2 relative to AVA >0.80 cm^2 remained significant even in patients without very severe AS.	
Nakatsuma et al. (#45)	2019	Evaluate the prognostic impact of BNP levels in patients with asymptomatic severe AS, who were not referred for AVR	· Patients with asymptomatic severe AS with elevated BNP levels were associated with a higher risk of AS-related adverse events. · Asymptomatic patients with BNP levels of <100 pg/mL had relatively low event rate.	· Patients with asymptomatic severe AS with BNP levels of <100 pg/mL might be safely followed with watchful waiting strategy.
Minamino-Muta et al. (#40)	2019	Investigate the prognostic impact of the decline in LVEF at 1-year follow-up in patients with severe AS managed conservatively	· There were 10.8% patients with >10% declines in LVEF. · LVEF and the prevalence of valve regurgitation and atrial fibrillation significantly increased in the group with declines in LVEF. · The cumulative 3-year incidence of AS-related adverse events was significantly higher in the group with declines in LVEF than in the group with no decline.	· Monitoring declines in LVEF at 1-year follow-up would be clinically useful in patients with severe AS under conservative management.
Kushiyama et al. (#34)	2019	Evaluate the initial AVR relative to conservative strategy on long-term outcomes stratified by age (age ≥ and <75 years) in asymptomatic patients with severe AS	• The rate of HF hospitalization was very low once they underwent AVR. • The favorable effect of the initial AVR relative to conservative strategy for HF hospitalization was seen regardless of the age strata. However, the lower mortality risk of the initial AVR relative to conservative strategy was significant in patients with age ≥ 75 years, but not in patients with age <75 years with significant interaction.	• The benefit of the initial AVR in reducing HF hospitalization in asymptomatic patients with severe AS was consistently seen regardless of age. The magnitude of mortality benefit of initial AVR was greater in super-elder patients than in non-super-elder patients.

AHF=acute heart failure; AS=aortic stenosis; AVR=aortic valve replacement; BMI=body mass index; BNP= B-type natriuretic peptide; HF=heart failure; HG-AS=high gradient severe aortic stenosis; LG-AS=low gradient severe aortic stenosis; LV=left ventricular; LVEF=left ventricular ejection fraction; PCI=percutaneous coronary intervention; TRPG=tricuspid regurgitation pressure gradient; Vmax=peak aortic jet velocity;