Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis Hospitalized With Acute Heart Failure

Danon Kaewkes, MD[a,b], Tomoki Ochiai, MD[a,c], Nir Flint, MD[a,d], Vivek Patel, MS[a], Jigar Patel, MD[a], Isic Kim, MD[a,e], Yusuke Enta, MD[a], Jubin Joseph, MD[a], Sung-Han Yoon, MD[a], Tarun Chakravarty, MD[a], Mamoo Nakamura, MD[a], Wen Cheng, MD[a], and Raj Makkar, MD[a,*]

Optimal timing and outcomes of transcatheter aortic valve implantation (TAVI) in patients presenting with acute heart failure (AHF) remain unclear. In this consecutive cohort of 1,547 patients with severe aortic stenosis undergoing TAVI, the AHF status at admission was collected, and patients were classified into AHF and elective TAVI groups. In the AHF group, early TAVI was defined as TAVI performed ≤60 hours after emergency room arrival. The primary outcome was all-cause mortality at 30-day and 2-year after TAVI. There were 139 (9%) patients who underwent TAVI while hospitalized with AHF. At baseline, this group had higher rates of chronic kidney disease, higher Society of Thoracic Surgeons score, and lower left ventricular ejection fraction. After adjusting for baseline differences, the AHF group had significantly higher all-cause mortality at 30-day and 2-year than the elective TAVI group (8% vs 2%; p = 0.002, and 33% vs 18%; p = 0.002, respectively). In the AHF group, 43 (31%) patients underwent early treatment with TAVI. No significant difference in all-cause mortality at 30-day was observed between early and non-early TAVI groups (5% vs 10%; p = 0.617). All-cause mortality at 2-year was lower in the early TAVI groups (16% vs 40%, log-rank p = 0.022); however, after multivariable adjustment, the difference was barely statistically significant (p = 0.053). In conclusion, TAVI in patients with AHF was associated with worse short and long-term outcomes. In AHF setting, early TAVI did not significantly reduce all-cause mortality at 30-day; however, it showed a strong trend for lower all-cause mortality at 2-year. **(Am J Cardiol 2021;144:100−110)**

Aortic stenosis (AS) is a progressive disease that can remain asymptomatic for decades, but once symptoms occur, survival is severely compromised.[1] Heart failure (HF) developing as a consequence of left ventricular (LV) pressure overload and myocardial remodeling can be the presenting symptom of patients with AS and is associated with poor prognosis.[2] To date, transcatheter aortic valve implantation (TAVI) is an effective and less invasive treatment for patients with severe AS across all surgical risk categories.[3−7] Nonetheless, the optimal timing and long-term outcomes of TAVI in patients presenting with HF are still unclear.[8,9] Recent guidelines emphasized the importance of immediate diagnosis and management of patients presenting with acute HF (AHF) in which the efficacy of any intervention or treatment may be time-dependent.[10,11] Thus, we hypothesized that early TAVI strategy might be beneficial in patients with severe AS presenting with AHF since TAVI immediately reduces LV afterload, which is an important contributor to HF in patients with severe AS, and thus may prevent further cardiac and multiorgan damage. However, evidence supporting this approach is currently limited. Therefore, this study aimed to evaluate the characteristics and outcomes of patients with severe AS hospitalized with AHF who underwent TAVI and to investigate the potential benefits of early TAVI strategy in this group.

Methods

We retrospectively reviewed medical records of consecutive patients with native severe AS who underwent TAVI at Cedars-Sinai Medical Center between January 2013 and December 2017 and included them in our TAVI database. We excluded patients if they (1) had hypotension defined as systolic blood pressure <90 mm Hg at the time of admission, (2) had a history of cardiac arrest within 24 hours prior to admission, (3) admitted from the emergency room (ER) by other presenting symptoms without HF, or (4) if the patients were urgently referred after hospitalization from other hospitals. The remaining cohort constituted the study population. All patients provided written informed consent for the procedure. All data for this study were collected from an established interventional cardiology laboratory

[a]Cedars-Sinai Medical Center, Smidt Heart Institute, Los Angeles, California; [b]Queen Sirikit Heart Center of the Northeast, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; [c]Department of Cardiology, Shonan Kamakura General Hospital, Kamakura, Kanagawa, Japan; [d]Department of Cardiology, Tel Aviv Sourasky Medical Center, affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; and [e]Department of Cardiology, Jeonbuk National University Hospital, Jeonju, Republic of Korea. Manuscript received October 12, 2020; revised manuscript received and accepted December 15, 2020.

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*Corresponding author: Tel: (310) 423-3277; fax: (310) 423-0166.
E-mail address: Raj.Makkar@cshs.org (R. Makkar).

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database approved by the Cedars-Sinai Medical Center Institutional Review Board.

Patients were divided into two groups according to the presentation of AHF, in which the diagnosis was made based on Framingham criteria.[12] The final diagnosis of AHF was made by an experienced cardiologist who reviewed the clinical, imaging, and biomarker data and was blinded to the patients' outcomes. Patients admitted from the ER with AHF constituted the AHF group, while those hospitalized for elective TAVI without AHF constituted the elective group. In the AHF group, patients were subcategorized into 2 groups according to the timing of TAVI: the *early TAVI* group included patients who underwent TAVI ≤60 hours after ER arrival, whereas the *non-early TAVI* group included those who underwent TAVI >60 hours after ER arrival. The 60-hour cutoff point was selected based on the association curve between the probability of all-cause mortality at 2-year and the door to TAVI time analyzed in this study. The Get With the Guidelines-HF (GWTG-HF) risk score was calculated for each patient hospitalized with AHF based on race, age, systolic blood pressure, heart rate, blood urea nitrogen, sodium levels, and the presence of chronic obstructive pulmonary disease.[13] The door to TAVI time was defined as the time from ER arrival to the starting time of the TAVI procedure.

Baseline clinical, echocardiographic, and procedural details were recorded for all patients. Transthoracic echocardiography was performed prior to the procedure and subsequent follow-up by experienced sonographers. Measurements were obtained according to the American Society of Echocardiography guidelines[14,15] and were systematically reviewed by echo-cardiologists. Adverse events and in-hospital outcomes were retrospectively reviewed from medical records and judged using the Valve Academic Research Consortium-2 criteria.[16] The primary outcome was all-cause mortality at 30-day and 2-year after TAVI.

Continuous variables were tested for distribution normality with the Shapiro−Wilk test and expressed as mean ± standard deviation or median and interquartile range (IQR). They were compared using the 2-sided Student's *t* test or Wilcoxon rank-sum test, as appropriate. Categorical variables were expressed as number (percentage) and compared using the Pearson Chi-square or Fisher exact test, as appropriate. Cumulative incidence curves for the 30-day and 2-year all-cause mortality were calculated using Kaplan-Meier estimates and were analyzed using the log-rank test. Cox proportional hazards model was used to assess the prognostic capability of TAVI in the AHF setting as well as in the early TAVI subgroup and reported as crude hazard ratios (HR) with 95% confidence intervals (CI) and p value from Wald chi-square tests. The HRs were then adjusted for baseline covariates with a p-value <0.10 in univariable analysis predicting all-cause mortality at 30-day or 2-year, as appropriate. The probability of all-cause mortality at 2-year was calculated for each patient in the AHF group using a cox regression model created from covariates with a p value <0.10 in univariable analysis and chronic kidney disease (CKD) ≥stage 3. The presence of a non-linear association between the door to TAVI time and the probability of all-cause mortality at 2-year was evaluated using a linear regression model with restricted cubic splines of 3, 4, and 5 knots. The goodness-of-fit was compared between models using an analysis of variance. All analyses were considered significant at a 2-tailed p value <0.05. The SPSS statistical package, version 24.0 (SSPS Inc. Chicago, Illinois) and R, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria), were used to perform statistical evaluations.

Results

We identified 1756 consecutive patients with native severe AS who underwent TAVI during the study period and excluded 209 patients who met the exclusion criteria. The remaining 1547 patients constituted our study population, of which 139 (9%) presented with AHF prior to TAVI (AHF group), and 1408 (91%) underwent elective TAVI (elective group). Patients in the AHF group were further subcategorized based on the timing of TAVI, either early TAVI (N = 43; 31%) or non-early TAVI (N = 96; 69%) groups. A study flow diagram is provided in Figure 1.

Baseline clinical, echocardiographic, and procedural characteristics in the overall cohort are provided in Tables 1, 2, and Supplementary Table 1, respectively. Compared with patients admitted for elective TAVI, patients in the AHF group had higher prevalences of diabetic mellitus and CKD ≥stage3, higher society of thoracic surgeons (STS) score, higher levels of brain natriuretic peptide (BNP), and higher rates of diuretics and sacubitril-valsartan use. By transthoracic echocardiography, patients in the AHF group had larger LV size and LV mass, lower LV ejection fraction (LVEF; 46.0 ± 17.7 vs 58.9 ± 13.6 %; p < 0.001), smaller aortic valve area (0.62 ± 0.20 vs 0.67 ± 0.17 cm^2; p < 0.001), and higher prevalences of concomitant moderate or severe mitral regurgitation, aortic regurgitation, and tricuspid regurgitation. There was no significant difference in periprocedural characteristics between both groups except for a higher rate of postdilatation performed in the AHF group (15% vs 9%; p = 0.022).

Procedural and clinical outcomes in the overall cohort are provided in Supplementary Table 2 and Table 3, respectively. No significant difference in terms of procedural complications between AHF and elective groups was observed, except for the longer length of hospitalization in the AHF group (8 [IQR: 5 to 13] vs 2 [IQR: 2 to 3] days; p < 0.001). At 2-year follow-up, 236 patients died (39 in AHF and 197 in elective groups). All-cause mortality at 30-day was significantly higher in the AHF, compared with the elective groups (8% vs 2%; crude HR: 5.22; 95% CI: 2.53 to 10.77; p < 0.001). After adjusting for age, CKD ≥stage 3, STS score, and LVEF, the HR remained significant (adjusted HR: 3.40; 95% CI: 1.54 to 7.48; p = 0.002; Figure 2). Similar results were observed for all-cause mortality at 2-year, which was significantly higher in the AHF group compared with that of the elective group (33% vs 18%; crude HR: 2.34; 95% CI: 1.66 to 3.30; p < 0.001). After adjusting for covariates with p <0.10 in the univariable analysis (Supplementary Table 3), the HR for all-cause mortality at 2-year remained significant (adjusted HR: 1.81; 95% CI: 1.25 to 2.61; p = 0.002; Figure 2).

In the AHF group, baseline clinical, echocardiographic, and periprocedural characteristics were similar between

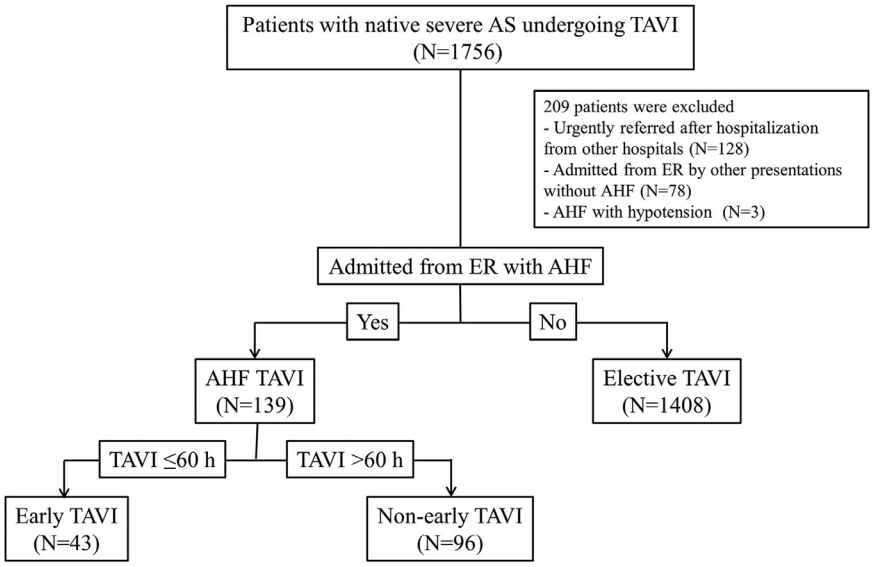

Figure. 1. Study flow diagram. AHF = acute heart failure; AS = aortic stenosis; ER= emergency room; TAVI = transcatheter aortic valve implantation.

Table 1
Baseline characteristics in the overall cohort

Variable	Total(N = 1,547)	AHF TAVI(N=139)	Elective TAVI(N = 1,408)	p value
Age (years)	81.6±8.4	82.2±9.6	81.5±8.2	0.402
Male gender	908 (59%)	74 (53%)	834 (59%)	0.171
Body mass index (kg/m^2)	27.2±5.7	27.1±6.2	27.2±5.6	0.771
Diabetes mellitus	506 (33%)	58 (42%)	448 (32%)	0.018
Hypertension	1413 (91%)	122 (88%)	1291 (92%)	0.117
CKD ≥stage 3	1209 (78%)	118 (85%)	1091 (78%)	0.044
Atrial fibrillation	353 (23%)	38 (27%)	315 (22%)	0.183
Coronary artery disease	733 (47%)	61 (44%)	672 (48%)	0.387
Previous MI	170 (11%)	18 (13%)	152 (11%)	0.439
Previous PCI	342 (22%)	25 (18%)	317 (22%)	0.220
Previous CABG	310 (20%)	27 (19%)	283 (20%)	0.850
Peripheral artery disease	353 (23%)	20 (14%)	333 (24%)	0.013
Previous stroke or TIA	279 (18%)	23 (16%)	256 (18%)	0.632
COPD	320 (21%)	34 (24%)	286 (20%)	0.249
STS score	4.9 (3.2-7.5)	6.7 (4.3-10.9)	4.8 (3.1-7.2)	<0.001
NYHA functional class III/IV	1449 (94%)	132 (95%)	1317 (94%)	0.510
Hemoglobin (g/dl)	12.4±1.76	11.2±1.9	12.5±1.7	<0.001
BNP (pg/ml)	220 (100-483)	1013 (446-1991)	389.6 (93-427)	<0.001
Medication at admission				
Beta-blocker	783 (51%)	74 (53%)	709 (50%)	0.517
Diuretics	732 (47%)	93 (67%)	639 (45%)	<0.001
ACEI or ARB	679 (44%)	54 (39%)	625 (44%)	0.209
Sacubitril/valsartan	24 (2%)	5 (4%)	19 (1%)	0.041
Aldosterone antagonist	97 (6%)	10 (7%)	87 (6%)	0.638
Antiplatelet	1027 (66%)	89 (64%)	938 (67%)	0.537
Anticoagulant	345 (22%)	33 (24%)	312 (22%)	0.669
Statin	1042 (67%)	93 (67%)	949 (67%)	0.906

ACEI = angiotensin-converting enzyme inhibitors; AHF = acute heart failure; ARB = angiotensin receptor blocker; BNP = B-type natriuretic peptide; CABG = coronary artery bypass grafting; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; NYHA = New York heart association; PCI = percutaneous coronary intervention; STS = society of thoracic surgeons; TAVI = transcatheter aortic valve implantation.

Values are expressed as number (percentage), mean ± standard deviation, or median (interquartile range).

Table 2
Baseline echocardiographic characteristics in the overall cohort

Variable	Total(N = 1,547)	AHF TAVI(N = 139)	Elective TAVI(N = 1,408)	p value
LVEF (%)	57.7±14.5	46.0±17.7	58.9±13.6	<0.001
LVEF ≤40%	238 (15%)	58 (42%)	180 (13%)	<0.001
Mean aortic valve gradient (mm Hg)	43.5±13.6	42.6±17.4	43.6±13.2	0.547
AVA by continuity equation (cm^2)	0.67±0.18	0.62±0.20	0.67±0.17	<0.001
IVS diameter (cm)	1.31 (1.17-1.46)	1.30 (1.10-1.44)	1.31 (1.18-1.46)	0.108
LVEDD (cm)	4.4 (3.9-4.9)	4.6 (4.1-5.2)	4.4 (3.9-4.9)	0.002
LVESD (cm)	2.9 (2.4-3.5)	3.5 (2.8-4.2)	2.9 (2.4-3.4)	<0.001
LVEDV (ml)	72.5 (53.6-98.0)	90.5 (65.0-113.2)	72.0 (53.0-97.0)	0.003
LVESV (ml)	27.0 (18.0-43.0)	41.8 (24.2-71.6)	26.0 (17.6-41.5)	<0.001
LVMI (g/m^2)	108.4 (87.3-131.5)	117.4 (95.5-141.0)	107.9 (86.7-130.4)	0.001
LAVI (ml/m^2)	37.7 (29.2-50.5)	46.2 (33.9-60.7)	37.3 (29.0-49.7)	0.006
Moderate or severe mitral regurgitation	378 (24%)	54 (39%)	324 (23%)	<0.001
Moderate or severe mitral stenosis	152 (10%)	13 (9%)	139 (10%)	0.844
Moderate or severe aortic regurgitation	226 (15%)	31 (22%)	195 (14%)	0.007
Moderate or severe tricuspid regurgitation	300 (19%)	36 (26%)	264 (19%)	0.042
PASP (mm Hg)	35.0 (27.0-46.0)	44.0 (32.0-53.0)	35.0 (27.0-44.0)	<0.001

AHF = acute heart failure; AVA = aortic valve area; IVS = interventricular septum; LAVI = left atrium volume index; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; LVMI = left ventricular mass index; PASP = pulmonary artery systolic pressure; TAVI = transcatheter aortic valve implantation.

Values are expressed as number (percentage), mean ± standard deviation, or median (interquartile range).

Table 3
Primary outcomes

All-cause mortality	AHF TAVI(N = 139)	Elective TAVI(N = 1408)	HR (95% CI)	p value	Adjusted HR (95% CI)	p value
30-day*	11 (8%)	22 (2%)	5.22 (2.53-10.77)	<0.001	3.40 (1.54-7.48)	0.002
2-year†	39 (33%)	197 (18%)	2.34 (1.66-3.30)	<0.001	1.81 (1.25-2.61)	0.002
All-cause mortality	Early treatment (N = 43)	Non-early treatment (N = 96)	HR (95% CI)	p value	Adjusted HR (95% CI)	p value
30-day‡	2 (5%)	9 (10%)	0.48 (0.10-2.23)	0.349	0.67 (0.14-3.21)	0.617
2-year§	6 (16%)	33 (40%)	0.36 (0.15-0.86)	0.022	0.42 (0.17-1.01)	0.053

AHF = acute heart failure; CI = confidence interval; HR = hazard ratio; TAVI = transcatheter aortic valve implantation.

Values are expressed as number (percentage).

* Adjusted for age, chronic kidney disease ≥stage 3, society of thoracic surgeons score, and left ventricular ejection fraction.

† Adjusted for age, body mass index, coronary artery disease, previous myocardial infarction, previous percutaneous coronary intervention, previous coronary artery bypass grafting, previous stroke or transient ischemic attack, chronic obstructive pulmonary disease, chronic kidney disease ≥stage 3, atrial fibrillation, society of thoracic surgeons score, left ventricular ejection fraction, moderate or severe mitral regurgitation, transfemoral access, and early generation valve.

‡ Adjusted for age, gender, and the Get With the Guidelines-Heart Failure risk score.

§ Adjusted for gender, society of thoracic surgeons score, and transfemoral access.

early TAVI and non-early TAVI groups except for a lower rate of CKD ≥stage 3 (74% vs 90%; p = 0.021), higher hemoglobin levels (11.7 ± 1.8 vs 10.9 ± 1.8 g/dl; p = 0.036), and higher volume of contrast media use (92.5 [IQR: 61.2 to 109.0] vs 70.0 [IQR: 46.2 to 100.0] ml; p = 0.021) in the early TAVI group (Tables 4 and 5 and Supplementary Table 4).

Procedural and clinical outcomes in early and non-early TAVI groups are provided in Supplementary Table 5 and Table 3, respectively. No significant difference was observed in terms of procedural complications between early and non-early TAVI groups, except for the shorter length of hospitalization in the early TAVI group (4 [IQR: 3 to 6] vs 11 [IQR: 7 to 16] days; p < 0.001). At 2-year follow-up, 39 patients died (6 in early and 33 in non-early TAVI groups). All-cause mortality at 30-day was not significantly different between early and non-early TAVI groups (5% vs 10%; crude HR: 0.48; 95% CI: 0.10 to 2.23; p = 0.349). After adjusting for age, gender, and Get With the Guidelines-HF risk score, the HR remained insignificant (adjusted HR: 0.67; 95% CI: 0.14 to 3.21; p = 0.617; Figure 3). For the long-term outcome, all-cause mortality at 2-year was lower in the early than non-early TAVI groups (16% vs 40%; crude HR: 0.36; 95% CI: 0.15 to 0.86; p = 0.022). However, the statistical significance was not maintained after adjusting for gender, STS score, and transfemoral approach (adjusted HR: 0.42; 95% CI: 0.17 to 1.01; p = 0.053; Supplementary Table 6, Figure 3).

Association between the door to TAVI time and all-cause mortality at 2-year is shown in Figure 4. Restricted cubic spline modeling with 4 knots was used since this model showed a better goodness-of-fit compared with that from the linear model (p = 0.0005) and showed a comparable goodness-of-fit to the 3-knot and 5-knot model (p = 0.2852 and p = 0.5216, respectively). The association between the door to TAVI time and the probability of all-

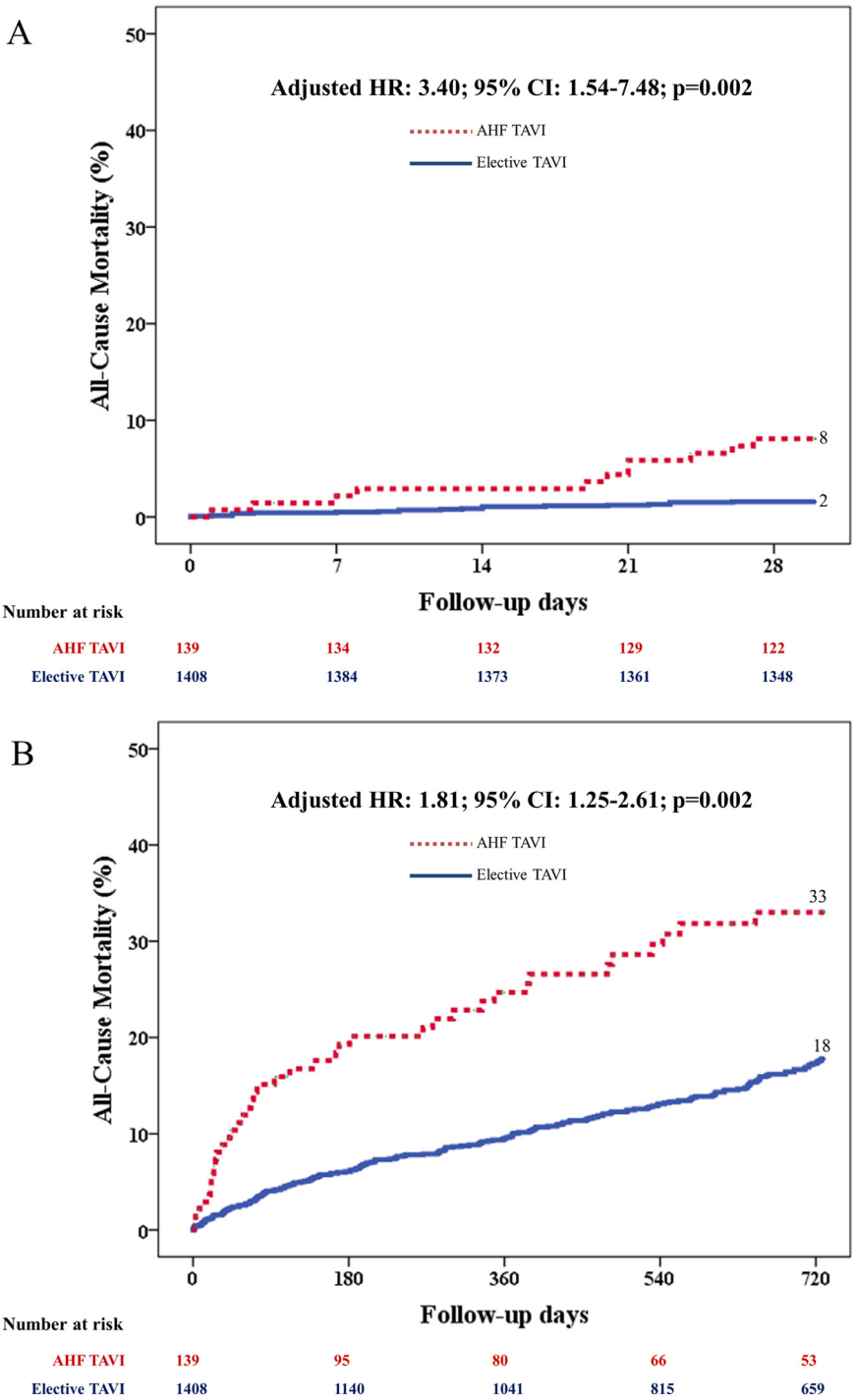

Figure. 2. All-cause mortality for AHF compared with elective TAVI. (A) At 30-day (B) At 2-year CI: confidence interval; AHF, acute heart failure; TAVI, transcatheter aortic valve implantation.

cause mortality at 2-year was not linear, and predicted mortality steeply increased in the first approximately 60 hours from ER arrival, then was steady afterward.

Discussion

We conducted a retrospective observational study to evaluate the characteristics and outcomes of patients with severe AS undergoing TAVI who presented with AHF and also investigated the potential benefits of early intervention with TAVI in this setting. The main findings of this study are as follows: (1) Patients in the AHF group had higher 30-day and 2-year all-cause mortality compared with those in the elective group; (2) In the AHF group, a trend toward lower 2-year all-cause mortality was observed when TAVI was performed ≤60 hours after admission (early TAVI

Table 4
Baseline characteristics in early and non-early TAVI groups

Variable	Total population(N = 139)	Early treatment(N = 43)	Non-early treatment(N = 96)	p value
Age (years)	82.2±9.6	83.0±8.5	81.9±10.0	0.508
Male gender	74 (53%)	20 (46%)	54 (56%)	0.287
Body mass index (kg/m^2)	27.1±6.2	27.0±7.1	27.1±5.8	0.969
AHF symptom onset (days)	5.0 (1.5-7.0)	5.0 (1.0-8.8)	4.0 (2.0-7.0)	0.834
Diabetes mellitus	58 (42%)	17 (40%)	41 (43%)	0.726
Hypertension	122 (88%)	35 (81%)	87 (91%)	0.125
CKD ≥stage 3	118 (85%)	32 (74%)	86 (90%)	0.021
Atrial fibrillation	38 (27%)	10 (23%)	28 (29%)	0.470
Coronary artery disease	61 (44%)	19 (44%)	42 (44%)	0.962
Previous MI	18 (13%)	5 (12%)	13 (14%)	0.756
Previous PCI	25 (18%)	7 (16%)	18 (19%)	0.726
Previous CABG	27 (19%)	7 (16%)	20 (21%)	0.530
Peripheral artery disease	20 (14%)	4 (9%)	16 (17%)	0.532
Previous stroke or TIA	23 (16%)	5 (12%)	18 (19%)	0.296
COPD	34 (24%)	10 (23%)	24 (25%)	0.825
STS score	6.7 (4.3-10.9)	6.2 (4.1-8.9)	7.0 (4.3-11.8)	0.519
NYHA functional class III/IV	132 (95%)	41 (95%)	91 (95%)	0.890
SBP (mm Hg)	125.4±22.7	127.9±22.5	124.3±22.9	0.386
DBP (mm Hg)	67.0±15.4	65.9±14.9	67.4±15.7	0.587
Heart rate (bpm)	83.1±17.8	83.1±17.3	83.2±18.0	0.982
Intubation at ER	0 (0%)	0 (0%)	0 (0%)	-
Physical findings				
Peripheral edema	99 (71%)	28 (65%)	71 (74%)	0.287
JVD	54 (39%)	14 (33%)	40 (42%)	0.308
Rales	97 (70%)	26 (60%)	71 (74%)	0.109
Laboratory findings				
Hemoglobin (g/dl)	11.2±1.9	11.7±1.8	10.9±1.8	0.036
BNP (pg/ml)	1013.0 (531.0-1844.5)	1070.0 (446.0-2418.0)	1013.0 (565.5-1748.8)	0.890
WBC (cell/mm^3)	7600.0 (6200.0-9700.0)	7600.0 (6400.0-9700.0)	7550.0 (6025.0-9850.0)	0.897
BUN (mg/dl)	27.0 (10.0-42.0)	26.0 (17.0-36.0)	27.0 (20.0-46.5)	0.226
Creatinine (mg/dl)	1.2 (0.9-1.6)	1.0 (0.8-1.4)	1.3 (0.9-1.7)	0.031
Sodium (mEq/l)	140.0 (136.0-142.0)	140.0 (136.0-142.0)	140.0 (137.0-143.0)	0.424
Glucose (mg/dl)	114.0 (97.0-138.0)	111.0 (97.0-133.0)	114.0 (96.2-138.8)	0.600
AST (u/l))	26.0 (18.0-33.8)	26.5 (19.8-31.0)	25.0 (17.8-36.2)	0.939
ALT (u/l)	20.0 (12.0-28.8)	20.0 (14.8-30.2)	20.0 (12.0-28.2)	0.541
Troponin I (ng/ml)	0.07 (0.03-0.15)	0.06 (0.03-0.12)	0.07 (0.03-0.21)	0.957
GWTG-HF risk score	45.8±7.8	44.9±7.0	46.2±8.2	0.389
Medications at admission				
Beta blocker	74 (53%)	23 (54%)	51 (53%)	0.968
Diuretics	93 (67%)	25 (58%)	68 (71%)	0.142
ACEI or ARB	54 (39%)	18 (42%)	36 (38%)	0.626
Sacubitril/valsartan	5 (4%)	1 (2%)	4 (4%)	1.000
Aldosterone antagonist	10 (7%)	3 (7%)	7 (7%)	1.000
Antiplatelet	89 (64%)	31 (72%)	58 (60%)	0.185
Anticoagulant	33 (24%)	7 (16%)	26 (27%)	0.166
Statin	93 (67%)	27 (63%)	66 (69%)	0.490

ACEI = angiotensin-converting enzyme inhibitors; ALT = alanine aminotransferase; ARB = angiotensin receptor blocker; AST = aspartate transaminase; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CABG = coronary artery bypass grafting; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; GWTG-HF = get with the guidelines−heart failure; HF = heart failure; JVD = jugular venous distention; MI = myocardial infarction; NYHA = New York heart association; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; STS = society of thoracic surgeons; WBC = white blood cell.

Values are expressed as number (percentage), mean ± standard deviation, or median (interquartile range).

group) compared with that in the non-early TAVI group, although 30-day all-cause mortality was comparable between the two groups.

AHF is a dreaded sequela of severe AS associated with repeated hospitalization and poor outcome.[2] In many cases, TAVI is not performed during the index HF hospitalization. Clinicians often prefer a period of stabilization and "cooling down" of patients with decompensated HF prior to TAVI; however, drop death may occur during the waiting period.[17] Thus, limited data exist on the optimal timing and outcomes of semi-urgent TAVI performed in AHF setting. Previous studies reporting outcomes of urgent or emergent TAVI consisted of the mixed patient population,[9,18,19] which makes the results not generalizable for patients presenting

Table 5
Baseline echocardiographic characteristics in early and non-early TAVI groups

Variable	Total Population(N = 139)	Early Treatment(N = 43)	Non-Early Treatment(N = 96)	p value
LVEF (%)	46.0±17.7	45.8±18.5	46.0±17.4	0.955
LVEF ≤40%	58 (42%)	18 (42%)	40 (42%)	0.983
Mean aortic valve gradient (mm Hg)	42.6±17.4	41.6±19.7	43.1±16.2	0.631
AVA by continuity equation (cm^2)	0.62±0.20	0.60±0.21	0.63±0.19	0.369
IVS diameter (cm)	1.30 (1.10-1.44)	1.30 (1.20-1.45)	1.30 (1.05-1.44)	0.591
LVEDD (cm)	4.6 (4.1-5.2)	4.6 (4.1-5.2)	4.5 (4.2-5.3)	0.723
LVESD (cm)	3.5 (2.8-4.2)	3.6 (2.6-4.4)	3.3 (2.8-4.2)	0.769
LVEDV (ml)	90.5 (65.0-113.2)	91.0 (66.9-147.5)	90.0 (60.1-109.8)	0.752
LVESV (ml)	41.8 (24.2-71.6)	50.5 (22.0-92.5)	34.0 (24.2-66.9)	0.527
LVMI (g/m^2)	117.4 (95.5-141.0)	121.5 (101.2-148.7)	116.6 (94.4-137.7)	0.252
LAVI (ml/m^2)	46.2 (33.9-60.7)	47.7 (35.1-64.2)	45.8 (32.4-56.2)	0.333
Moderate or severe mitral regurgitation	54 (39%)	15 (35%)	39 (41%)	0.521
Moderate or severe mitral stenosis	13 (9%)	4 (9%)	9 (9%)	1.000
Moderate or severe aortic regurgitation	31 (22%)	11 (26%)	20 (21%)	0.534
Moderate or severe tricuspid regurgitation	36 (26%)	9 (21%)	27 (28%)	0.371
PASP	44.0 (32.0-53.0)	43.5 (30.0-52.2)	48.0 (33.0-55.0)	0.285

AHF = acute heart failure; AVA = aortic valve area; IVS = interventricular septum; LAVI = left atrium volume index; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; LVMI = left ventricular mass index; PASP = pulmonary artery systolic pressure; TAVI = transcatheter aortic valve implantation.

Values are expressed as number (percentage), mean ± standard deviation.

with AHF. To the best of our knowledge, this is the largest study that evaluated the short and long-term outcomes of TAVI, specifically in AHF setting. In this study, patients in the AHF group had higher rates of cardiac comorbidities, higher STS score, lower LVEF, as well as greater prevalences of concomitant other valvular heart defects compared to those in the elective group. Although more unfavorable baseline characteristics were observed in the AHF group, procedural complications were comparable between AHF and elective TAVI groups. This result was different from a previous study on urgent TAVI, showing higher procedural related complications compared to elective TAVI.[8] One possible explanation is that patients with extremely high risk, such as those in cardiogenic shock or post-cardiac arrest, were excluded from our study.

Despite a similar rate of procedural complications, patients in the AHF group had worse all-cause mortality at 30-day and 2-year than those in the elective group. It is possible that the worse baseline characteristics may have led to a negative impact on prognosis during follow-up. However, after adjustment for baseline differences, TAVI in the AHF setting remained significantly predictive of all-cause mortality at 30-day and 2-year. Currently, the timing of TAVI is a matter of extensive research and debate. A new staging system for patients with AS based on the extent of cardiac damage has been suggested that goes beyond the severe or not severe and symptomatic or asymptomatic paradigm.[20] Patients who present with AHF likely have more advanced AS stage resulting in worse short and long-term outcomes. Thus, it is crucial to identify and treat patients with AS earlier before the development of overt HF for the better recovery of cardiac function and improve prognosis.[21] The potential benefit of early TAVI strategy is currently being evaluated in several ongoing randomized trials (EARLY TAVI NCT03042104, TAVI UNLOAD NCT02661451).

Other than evaluating the prognosis of patients who underwent TAVI in AHF setting, the present study tried to investigate whether early TAVI is associated with a more favorable outcome. We selected the 60-hour cutoff to define early TAVI since the restricted cubic splines model plot showed a steep increase after approximately the first 60 hours from ER arrival in the probability of all-cause mortality at 2-year evaluated with door to TAVI time. Thus, we speculated that the 60-hour point should be an optimal time point to differentiate the effect of early and non-early TAVI on mortality outcomes. From the result of our study, early TAVI showed lower all-cause mortality at 2-year, while baseline characteristics between early and non-early TAVI groups were relatively balanced except for the rate of CKD and hemoglobin levels. This finding implies that early treatment with TAVI may itself have some potential benefits resulting in a better long-term outcome. Recently, several studies showed the benefit of early treatment for AHF, which may be explained by that myocardial damage is a progressive phenomenon in the acute phase among patients with AHF and that early treatment mitigating this organ damage might consequently improve outcomes.[22,23] For clinical implication, our findings suggested that in patients with severe AS hospitalized with AHF, early TAVI within 60 hours from ER arrival should be considered as it may lower the risk of all-cause mortality at 2-year.

Several limitations of the present study warrant consideration. First, this was a retrospective observational study in a single center. The diagnosis of AHF and the data of door to TAVI time were made and collected retrospectively. Furthermore, confounding factors that we did not expect may not have been accounted for in our analyses. Second, the diagnosis of AHF in this study was made based on Framingham criteria evaluated with imaging and

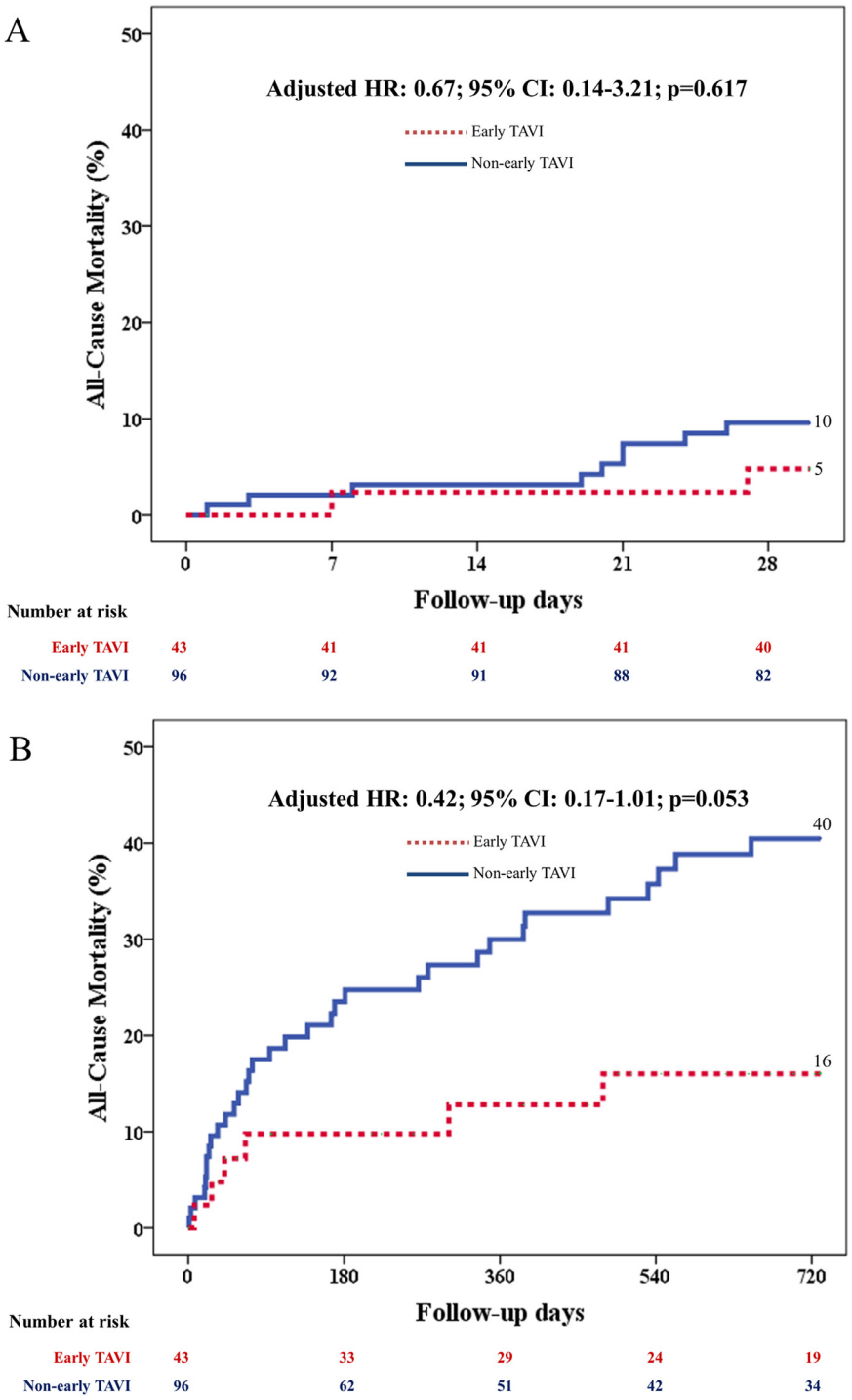

Figure. 3. All-cause mortality for early TAVI compared with non-early TAVI in AHF setting (A) At 30-day (B) At 2-year CI: confidence interval; AHF, acute heart failure; TAVI, transcatheter aortic valve implantation.

biomarker data, which may not be similar to the AHF definition from the ACC/ESC guidelines. Third, the mortality rate from AHF in this study may not represent that of the general population with severe AS presenting with AHF since patients with AHF who had cardiogenic shock, cardiac arrest, or died before TAVI were excluded from this study. Fourth, given its observational nature, it should be noted that only an association, not causality, was demonstrated in the present study. Finally, the number of events per adjusting variable (EPV) in a proportional hazard regression analysis was <10 in the analyses of 30-day outcomes. Thus, the result of adjusted HR should be interpreted with caution in those analyses. These limitations indicate that our study results are only hypothesis-

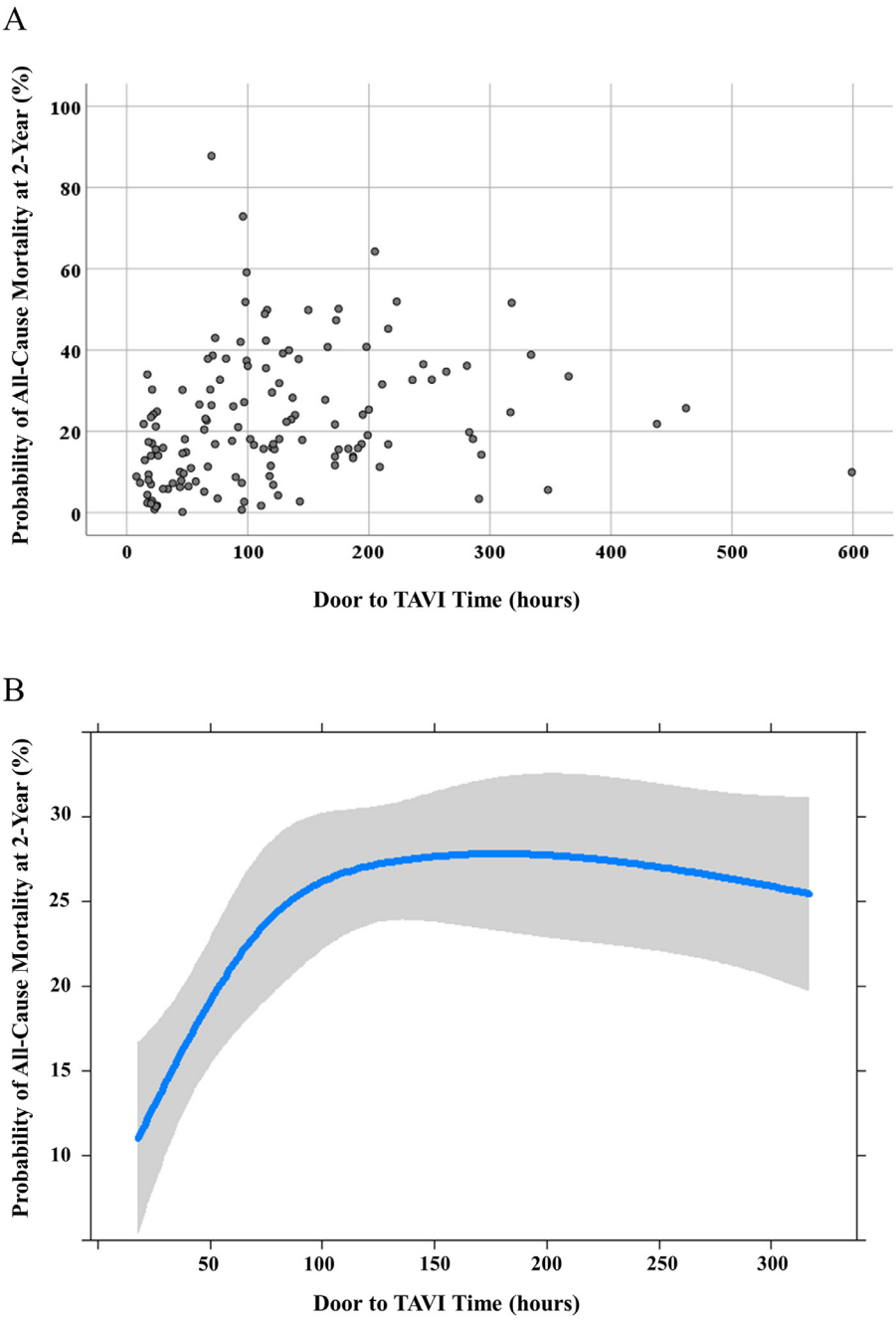

Figure. 4. Probability plot for all-cause mortality at 2-year in AHF setting (A) Scatter plot between the door to TAVI time and the probability of all-cause mortality at 2-year (B) Association between the door to TAVI time and the probability of all-cause mortality at 2-year using restricted cubic spline model with 4 knots The solid blue line represents the estimated probability of all-cause mortality at 2-year, the light grey shaded area is a 95% confidence interval. AHF, acute heart failure; TAVI, transcatheter aortic valve implantation.

generating; however, it is virtually impossible to randomize patients to a delayed-treatment group from an ethical perspective. A future prospective study is desirable to confirm the results of this study.

In conclusion, TAVI in patients with AHF was associated with worse short and long-term outcomes. In AHF setting, early TAVI did not significantly reduce all-cause mortality at 30-day; however, it showed a strong trend for lowering all-cause mortality at 2-year.

Authors' Contributions

Danon Kaewkes: conceptualization, methodology, formal analysis, investigation, writing -original draft. Tomoki Ochiai: conceptualization, methodology, writing - review & editing. Nir Flint: conceptualization, writing - review & editing. Vivek Patel: investigation, writing - review & editing. Jigar Patel: investigation, writing - review & editing. Isic Kim: writing - review & editing. Yusuke Enta: writing

- review & editing. Jubin Joseph: writing - review & editing. Sung-Han Yoon: conceptualization, writing - review & editing. Tarun Chakravarty: writing - review & editing. Mamoo Nakamura: writing - review & editing. Wen Cheng: writing - review & editing. Raj Makkar: conceptualization, methodology, writing - review & editing, supervision.

Disclosures

Dr. Makkar has received grant support from Edwards Lifesciences Corporation; is a consultant for Abbott Vascular, Cordis, and Medtronic, and holds equity in Entourage Medical. Dr. Chakravarty is a consultant, proctor, and speaker for Edwards Lifesciences and Medtronic; he is a consultant for Abbott Lifesciences, and he is a consultant and speaker for Boston Scientific. Other authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.046.

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