# Optimal Medical Therapy Following Transcatheter Aortic Valve Implantation

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**Limited data exist on optimal medical therapy post-transcatheter aortic valve implantation (TAVI) for late cardiovascular events prevention. We aimed to evaluate the benefits of beta-blocker (BB), renin-angiotensin system inhibitor (RASi), and their combination on outcomes following successful TAVI. In a consecutive cohort of 1,684 patients with severe aortic stenosis undergoing TAVI, the status of BB and RASi treatment at discharge was collected, and patients were classified into 4 groups: no-treatment, BB alone, RASi alone, and combination groups. The primary outcome was a composite of all-cause mortality and rehospitalization for heart failure (HHF) at 2-year. There were 415 (25%), 462 (27%), 349 (21%), and 458 (27%) patients in no-treatment, BB alone, RASi alone, and combination groups, respectively. The primary outcome was lower in RASi alone (21%; adjusted hazard ratio [HR]$_{adj}$: 0.58; 95% confidence interval [CI]: 0.42 to 0.81) and combination (22%; HR$_{adj}$: 0.53; 95% CI: 0.39 to 0.72) groups than in no-treatment group (34%) but no significant difference between RASi alone and combination groups (HR$_{adj}$: 1.14; 95% CI: 0.80 to 1.62). The primary outcome results were maintained in a sensitivity analysis of patients with reduced left ventricular systolic function. Furthermore, RASi treatment was an independent predictor of 2-year all-cause mortality (HR$_{adj}$: 0.68; 95% CI: 0.51 to 0.90), while that was not observed in BB therapy (HR$_{adj}$: 0.94; 95% CI: 0.71 to 1.25). In conclusion, post-TAVI treatment with RASi, but not with BB, was associated with lower all-cause mortality and HHF at 2-year. The combination of RASi and BB did not add an incremental reduction in the primary outcome over RASi alone.**  **(Am J Cardiol 2021;141:62−71)**

Transcatheter aortic valve implantation (TAVI) is an effective treatment for patients with severe aortic stenosis (AS) across all surgical risk categories. Despite the established favorable effects of TAVI on long-term cardiovascular outcomes,[1-5] significant burden of late cardiovascular events remains. Nearly half of patients undergoing TAVI die within 5 years after the procedure, and the cardiac rehospitalization rate is 73%, mostly related to worsening in heart failure.[6,7] Optimal medical therapy may reduce the risk, but evidence supporting this approach is currently limited. Renin-angiotensin system (RAS) inhibition contributes to sustaining protection against left ventricular (LV) hypertrophy and myocardial fibrosis,[8,9] which may be ongoing after aortic valve replacement.[10] In patients with heart failure, beta-receptor blocker (BB) reduces sympathetic overactivity leading to lower incidences of cardiac arrhythmia and sudden cardiac death.[11] After successful TAVI, several studies showed that RAS blockade was associated with mortality reduction;[12-15] however, scarce data exist on the potential benefit of BB and its combination with RAS inhibitors (RASi) on cardiovascular outcomes. Therefore, this study aimed to evaluate the long-term effects of BB, RASi, and their combination on clinical outcomes in a large cohort of patients following TAVI.

## Methods

We retrospectively reviewed medical records of consecutive patients with native severe AS who underwent TAVI at Cedars-Sinai Medical center from January 2013 to November 2017 and included in our TAVI database. We excluded patients if they (1) died during the index hospitalization, (2) were discharged against medical advice, (3) were referred to other hospitals or hospice care, (4) had a contraindication for BB or RASi, or (5) if the data of medication at discharge was missing. The remaining cohort constituted the study population. All patients provided written informed consent for the procedure. The study was approved by the Cedars-Sinai Medical Center Institutional Review Board. Patients were divided into 4 groups according to the status of BB and RASi at discharge. Patients who were prescribed only BB constituted the BB alone group

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See page 70 for disclosure information.

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while those prescribed either angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (with or without sacubitril) or aldosterone antagonist constituted the RASi alone group. Patients who were prescribed both BB and RASi constituted the combination group, whereas those who were not prescribed any BB or RASi constituted the no-treatment group. The prescriptions of BB and RASi at 1-year follow-up were also collected in this database. However, adherence to medications was not assessed in this study.

Comprehensive transthoracic echocardiography (TTE) was performed at baseline and subsequent follow-up. Measurements were obtained according to the American Society of Echocardiography guidelines,[16,17] and systematically reviewed by an experienced reader. In order to evaluate the effect of each discharge medication group on LV remodeling, changes in LV end-diastolic volume (LVEDV) index (LVEDVI), LV mass index (LVMI), and LV ejection fraction (LVEF; using biplane Simpson's method) were analyzed between baseline and 1-year follow-up. LV reverse remodeling and LV adverse remodeling were defined as a >15% decrease and a >10% increase in LVEDVI, respectively,[18] whereas significant LVMI regression was defined as a >10% decrease in LVMI when compared with baseline.[19] The primary outcome was a composite of all-cause mortality and rehospitalization for heart failure (HHF) at 2-year. The secondary outcomes were each component of the primary outcome, 2-year outcomes of acute myocardial infarction, cerebrovascular event, tachyarrhythmia and bradyarrhythmia requiring admission,[20] and LV remodeling at 1-year follow-up. We defined TAVI outcomes and adverse events using the Valve Academic Research Consortium-2 criteria.[21]

Continuous variables were tested for distribution normality with the Shapiro−Wilk test and expressed as mean ± standard deviation or median and interquartile range. They were compared using the 1-way analysis of variance test or Kruskal-Wallis test, as appropriate. Categorical variables were expressed as number (percentage) and compared using the chi-square test. Events were reported as counts of the first occurrence per type of event within 2 years of follow-up. Cumulative incidence curves for the composite of all-cause mortality and HHF stratified by treatment group were calculated using Kaplan-Meier estimates and were analyzed using the log-rank test. The effects of hospital discharge prescription of BB and RASi on the clinical outcomes were assessed pairwisely using Cox proportional hazard models and reported as crude hazard ratios (HR) with 95% confidence intervals (CI) and p value from Wald chi-square tests. Then, the HRs were adjusted for diabetes mellitus, history of previous percutaneous coronary intervention, chronic kidney disease ≥stage 3, Society of Thoracic Surgery (STS) score, and LVEF (Supplementary Table 1). As sensitivity analyses, the above crude and adjusted analyses (excluded LVEF variable) for the primary outcome were repeated for patients presenting with LVEF ≤40%. To identify the independent predictors of all-cause mortality at 2-year, a multivariable model was built with candidate variables included if they had p <0.10 in the univariable analysis. In order to assess LV remodeling, LVEDVI, LVMI, and LVEF at baseline and 1-year post-TAVI were compared using related-sample Wilcoxon sign rank test according to medication group at discharge. All analyses were considered significant at a 2-tailed p-value <0.05. The SPSS statistical package, version 24.0, was used to perform all statistical evaluations (SSPS Inc. Chicago, IL).

## Results

We identified 1756 consecutive patients with native severe AS who underwent TAVI during the study period and excluded 72 patients who met the exclusion criteria. The remaining 1,684 patients constituted our study population, which was categorized based on the status of BB and RASi at discharge as no-treatment group in 415 (25%), BB alone group in 462 (27%), RASi alone group in 349 (21%), and combination group in 458 (27%) patients. The distribution of patients from baseline to 1-year follow-up and the distribution of medications are summarized in Online Figures 1 and 2, respectively. Baseline characteristics are provided in Table 1. Patients in the no-treatment group were most likely to be older, had least body mass index, had lowest rates of diabetes mellitus, hypertension, chronic kidney disease ≥stage 3, coronary artery disease, prior coronary artery bypass grafting, and were least likely to take diuretics, anticoagulants, and statins. When compared with other groups, patients in the RASi alone group had the lowest prevalence of prior percutaneous coronary intervention as well as lowest STS score and B-type natriuretic peptide levels. By TTE, patients in the combination group had the lowest LVEF (53.8 ± 16.5 vs 58.7 ± 23.7 in no-treatment, 56.4 ± 14.9 in BB alone, and 59.3 ± 14.4 % in RASi alone groups; p <0.001), highest LVEDV (102.2 ± 45.4 vs 88.9 ± 34.7 in no-treatment, 92.2 ± 38.6 in BB alone, and 92.4 ± 37.6 ml in RASi alone groups; p <0.001), and highest LVMI (118.0 ± 37.8 vs 109.4 ± 32.5 in no-treatment, 111.9 ± 36.3 in BB alone, and 112.8 ± 35.5 g/m$^2$ in RASi alone groups; p = 0.006). For procedural characteristics, patients in the BB alone group were least likely to have the procedure performed via the transfemoral approach (88% vs 95% in no-treatment, 97% in RASi alone, and 94% in combination groups; p <0.001). Procedural complications and outcomes were comparable among all medication groups except for the new left bundle branch block, which was most commonly presented in the no-treatment group (14% vs 12% in BB alone, 7% in RASi alone, and 12% in combination groups; p = 0.021), and new-onset atrial fibrillation which was most frequent in the BB alone group (7% vs 1% in no-treatment, 2% in RASi alone, and 3% in combination groups; p <0.001; Supplementary Table 2).

Event rates with crude and adjusted HR for clinical outcomes are provided in Tables 2 and 3, respectively. During the median follow-up period of 650 days (interquartile range: 284 to 1,004 days), 390 patients died (105 in no-treatment, 130 in BB alone, 60 in RASi alone, and 95 in combination groups). Two hundred and seven patients were readmitted to the hospital with heart failure (54 in no-treatment, 58 in BB alone, 42 in RASi alone, and 53 in combination groups). The primary composite outcome of all-cause mortality and HHF at 2-year was significantly lower in the RASi alone group (21%; adjusted $HR_{adj}$: 0.58; 95%

Table 1
Baseline characteristics

| Variable | Total (N=1684) | Medication groups | | | | Overall p value |
|---|---|---|---|---|---|---|
| | | No-treatment (N=415) | BB alone (N=462) | RASi alone (N=349) | Combination (N=458) | |
| Age, years | 81.5±8.6 | 82.9±8.7 | 81.7±8.8 | 81.4±7.7 | 80.0±8.7 | <0.001 |
| Women | 693 (41%) | 164 (40%) | 187 (40%) | 150 (43%) | 192 (42%) | 0.768 |
| Body mass index (kg/m$^2$) | 27.1±5.7 | 26.2±5.4 | 26.9±5.4 | 27.7±6.3 | 27.7±5.7 | <0.001 |
| Diabetes mellitus | 554 (33%) | 100 (24%) | 151 (33%) | 119 (34%) | 184 (40%) | <0.001 |
| Hypertension | 1536 (91%) | 359 (86%) | 421 (91%) | 327 (94%) | 429 (94%) | 0.001 |
| CKD ≥ stage 3 | 1319 (78%) | 303 (73%) | 377 (82%) | 262 (75%) | 377 (82%) | 0.001 |
| Atrial fibrillation | 401 (24%) | 110 (26%) | 115 (25%) | 70 (20%) | 106 (23%) | 0.188 |
| Coronary artery disease | 808 (48%) | 162 (39%) | 234 (51%) | 149 (43%) | 263 (57%) | <0.001 |
| Previous MI | 194 (12%) | 39 (9%) | 57 (12%) | 35 (10%) | 63 (14%) | 0.162 |
| Previous PCI | 377 (22%) | 72 (17%) | 119 (26%) | 58 (17%) | 128 (28%) | <0.001 |
| Previous CABG | 329 (20%) | 53 (13%) | 101 (22%) | 61 (18%) | 114 (25%) | <0.001 |
| Peripheral artery disease | 377 (22%) | 79 (19%) | 112 (24%) | 71 (20%) | 115 (25%) | 0.094 |
| Previous stroke or TIA | 288 (17%) | 66 (16%) | 87 (19%) | 58 (17%) | 77 (17%) | 0.687 |
| COPD | 341 (20%) | 99 (24%) | 100 (22%) | 64 (18%) | 78 (17%) | 0.054 |
| STS score | 5.0 (3.2-7.7) | 5.0 (3.3-7.9) | 5.2 (3.4-8.2) | 4.5 (3.0-6.6) | 5.2 (3.2-7.8) | 0.009 |
| NYHA functional class III/IV | 1575 (94%) | 387 (93%) | 428 (93%) | 331 (95%) | 429 (94%) | 0.645 |
| Discharge medication | | | | | | |
| Diuretics | 807 (48%) | 147 (35%) | 207 (45%) | 175 (50%) | 278 (61%) | <0.001 |
| Antiplatelet | 1459 (87%) | 352 (85%) | 412 (89%) | 309 (88%) | 386 (84%) | 0.070 |
| Anticoagulant | 381 (23%) | 79 (19%) | 110 (24%) | 67 (19%) | 125 (27%) | 0.009 |
| Statin | 1254 (74%) | 256 (62%) | 367 (79%) | 257 (74%) | 374 (82%) | <0.001 |
| BNP (pg/ml) | 235.0 (109.0-536.5) | 228.0 (106.0-498.0) | 260.5 (120.8-606.5) | 160.0 (71.0-401.0) | 271.0 (134.0-596.5) | <0.001 |
| Echocardiographic findings | | | | | | |
| LVEF (%) | 56.9±15.1 | 58.7±23.7 | 56.4±14.9 | 59.3±14.4 | 53.8±16.5 | <0.001 |
| LVEF ≤40% | 288 (17%) | 53 (13%) | 77 (17%) | 45 (13%) | 113 (25%) | <0.001 |
| AVA (cm$^2$) | 0.66±0.18 | 0.66±0.18 | 0.66±0.17 | 0.68±0.18 | 0.66±0.18 | 0.324 |
| Mean aortic valve gradient (mm Hg) | 43.4±13.9 | 44.8±14.6 | 41.6±13.5 | 45.0±13.1 | 42.7±14.0 | 0.001 |
| LV mass index (g/m$^2$) | 113.2±35.8 | 109.4±32.5 | 111.9±36.3 | 112.8±35.5 | 118.0±37.8 | 0.006 |
| LVEDV (ml) | 94.2±39.8 | 88.9±34.7 | 92.2±38.6 | 92.4±37.6 | 102.2±45.4 | <0.001 |
| LVESV (ml) | 43.1±32.0 | 37.4±25.8 | 40.8±30.7 | 38.3±28.4 | 50.3±38.5 | <0.001 |
| LAVI (ml/m$^2$) | 42.0±23.5 | 40.7±19.9 | 43.0±18.9 | 39.4±18.0 | 44.4±32.5 | 0.174 |
| Moderate or severe mitral regurgitation | 427 (25%) | 113 (27%) | 111(24%) | 73 (21%) | 130 (28%) | 0.070 |
| Moderate or severe aortic regurgitation | 243 (14%) | 60 (14%) | 53 (12%) | 45 (13%) | 85 (19%) | 0.016 |
| Moderate or severe tricuspid regurgitation | 334 (20%) | 91 (22%) | 94 (20%) | 55 (16%) | 94 (20%) | 0.172 |

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blocker; AVA = aortic valve area; BB = beta-blocker; BNP = B-type natriuretic peptide; CABG = coronary artery bypass grafting; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; LAVI = left atrium volume index; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MI = myocardial infarction; NYHA = New York heart association; PCI = percutaneous coronary intervention; RASi = renin-angiotensin system inhibitor; STS = the society of thoracic surgeon; TIA = transient ischemic attack.

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

CI: 0.42 to 0.81; p = 0.001), and the combination group (22%; $HR_{adj}$: 0.53; 95% CI: 0.39 to 0.72; p <0.001) compared with the no-treatment group (34%). However, no significant difference of the primary outcome was observed between BB alone and no-treatment groups ($HR_{adj}$: 0.81; 95% CI: 0.62 to 1.06; p = 0.124) as well as RASi alone and combination groups ($HR_{adj}$: 1.14; 95% CI: 0.80 to 1.62; p = 0.461; Figure 1A). The effects of medication groups on all-cause mortality at 2-year were similar to those on the primary composite outcome (Figure 1B), while HHF was significantly lower in the combination group compared with the no-treatment group ($HR_{adj}$: 0.60; 95% CI: 0.38 to 0.96; p = 0.033; Figure 1C). There were no significant differences between groups with respect to the occurrence of acute myocardial infarction, cerebrovascular events, tachyarrhythmia requiring admission, and bradyarrhythmia requiring admission within 2-year follow-up. As shown in Supplementary Table 3 and Online Figure 3, the effect on the primary outcome between groups in pairwise comparison was maintained in a sensitivity analysis of patients with LVEF ≤40%. In a multivariable analysis, RASi prescription at discharge was an independent predictor of reduced all-cause mortality at 2-year ($HR_{adj}$: 0.68; 95% CI: 0.51 to 0.90), while BB therapy was not associated with lower all-cause mortality ($HR_{adj}$: 0.94; 95% CI: 0.71 to 1.25; Table 4).

In order to evaluate for changes in LV remodeling post-TAVI, we analyzed TTE data from 853 (51%) patients for whom TTE results were available at baseline and 1-year post-procedure. At 1-year, LVEDVI and LVMI significantly decreased from baseline in the RASi alone (41.1 to 36.9 ml/m$^2$; p = 0.001 and 104.8 to 100.0 g/m$^2$; p = 0.025, respectively), and the combination (42.8 to 38.7 ml/m$^2$;

Table 2
Main outcomes at 2-year follow-up according to medication groups with crude HRs

| Outcomes at 2-year follow-up | Medication groups | | | | Crude HR | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No (N=415) | BB (N=462) | RASi (N= 349) | Both (N=458) | BB vs no | | RASi vs no | | Both vs no | | BB vs RASi | | BB vs both | | RASi vs both | |
| | | | | | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Primary outcome | 107 (34%) | 116 (31%) | 57 (21%) | 81 (22%) | 0.94 (0.73-1.23) | 0.665 | 0.58 (0.42-0.80) | 0.001 | 0.62 (0.47-0.83) | 0.001 | 1.63 (1.19-2.24) | 0.003 | 1.51 (1.14-2.01) | 0.004 | 0.93 (0.66-1.30) | 0.673 |
| All-cause mortality | 75 (24%) | 78 (21%) | 34 (13%) | 57 (16%) | 0.91 (0.66-1.25) | 0.559 | 0.50 (0.33-0.75) | 0.001 | 0.63 (0.45-0.89) | 0.009 | 1.82 (1.22-2.72) | 0.004 | 1.43 (1.02-2.01) | 0.040 | 0.79 (0.52-1.20) | 0.271 |
| HHF | 43 (14%) | 53 (16%) | 31 (11%) | 36 (10%) | 1.08 (0.72-1.61) | 0.725 | 0.79 (0.50-1.25) | 0.313 | 0.70 (0.45-1.08) | 0.108 | 1.36 (0.88-2.13) | 0.169 | 1.55 (1.01-2.36) | 0.043 | 1.13 (0.70-1.83) | 0.607 |
| MI | 10 (4%) | 9 (3%) | 5 (2%) | 5 (1%) | 0.80 (0.32-1.96) | 0.618 | 0.55 (0.19-1.60) | 0.271 | 0.41 (0.14-1.21) | 0.107 | 1.42 (0.47-4.22) | 0.534 | 1.86 (0.62-5.56) | 0.264 | 1.31 (0.38-4.53) | 0.668 |
| Stroke and TIA | 9 (3%) | 10 (3%) | 13 (6%) | 14 (4%) | 0.96 (0.39-2.37) | 0.937 | 1.61 (0.69-3.77) | 0.271 | 1.33 (0.58-3.07) | 0.506 | 0.60 (0.26-1.37) | 0.226 | 0.73 (0.33-1.65) | 0.454 | 1.23 (0.58-2.61) | 0.597 |
| Tachy-arrhythmia readmission* | 5 (2%) | 10 (3%) | 5 (2%) | 9 (2%) | 1.77 (0.60-5.17) | 0.299 | 1.14 (0.33-3.93) | 0.838 | 1.56 (0.52-4.66) | 0.425 | 1.56 (0.54-4.58) | 0.414 | 1.13 (0.46-2.78) | 0.790 | 0.72 (0.24-2.16) | 0.562 |
| Brady-arrhythmia readmission* | 8 (2%) | 9 (2%) | 8 (3%) | 7 (2%) | 0.99 (0.38-2.56) | 0.977 | 1.14 (0.43-3.05) | 0.787 | 0.78 (0.28-2.16) | 0.634 | 0.87 (0.34-2.26) | 0.778 | 1.29 (0.48-3.46) | 0.613 | 1.49 (0.54-4.11) | 0.442 |

BB = beta-blocker; Both = combination group; CI = confidence interval; HHF = rehospitalization for heart failure; HR = hazard ratio; MI = myocardial infarction; No = no-treatment group; RASi = renin-angiotensin system inhibitor; TIA = transient ischemic attack.

Values are expressed as number (percentage).

* Tachyarrhythmia was defined as any cardiac rhythm with heart rate ≥150 beats/minute, and bradyarrhythmia was defined as any cardiac rhythm with heart rate <50 beats/minute.

Table 3
Main outcomes at 2-year follow-up according to medication groups with adjusted HRs

| Outcomes at 2-year follow-up | Medication groups | | | | Adjusted HR* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No (N=415) | BB (N=462) | RASi (N= 349) | Both (N=458) | BB vs no | | RASi vs no | | Both vs no | | BB vs RASi | | BB vs both | | RASi vs both | |
| | | | | | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Primary outcome | 107 (34%) | 116 (31%) | 57 (21%) | 81 (22%) | 0.81 (0.62-1.06) | 0.124 | 0.58 (0.42-0.81) | 0.001 | 0.53 (0.39-0.72) | <0.001 | 1.37 (0.99-1.89) | 0.058 | 1.55 (1.16-2.07) | 0.003 | 1.14 (0.80-1.62) | 0.461 |
| All-cause mortality | 75 (24%) | 78 (21%) | 34 (13%) | 57 (16%) | 0.78 (0.57-1.08) | 0.137 | 0.52 (0.35-0.79) | 0.002 | 0.55 (0.39-0.79) | 0.001 | 1.52 (1.01-2.28) | 0.046 | 1.47 (1.04-2.08) | 0.030 | 0.95 (0.62-1.47) | 0.829 |
| HHF | 43 (14%) | 53 (16%) | 31 (11%) | 36 (10%) | 0.93 (0.62-1.39) | 0.714 | 0.77 (0.48-1.23) | 0.279 | 0.60 (0.38-0.96) | 0.033 | 1.18 (0.75-1.84) | 0.483 | 1.61 (1.05-2.47) | 0.030 | 1.37 (0.83-2.24) | 0.216 |
| MI | 10 (4%) | 9 (3%) | 5 (2%) | 5 (1%) | 0.76 (0.31-1.90) | 0.561 | 0.59 (0.20-1.74) | 0.336 | 0.40 (0.13-1.22) | 0.106 | 1.21 (0.40-3.70) | 0.736 | 1.92 (0.64-5.82) | 0.247 | 1.30 (0.36-4.72) | 0.692 |
| Stroke and TIA | 9 (3%) | 10 (3%) | 13 (6%) | 14 (4%) | 1.19 (0.47-3.02) | 0.718 | 1.67 (0.70-3.98) | 0.244 | 1.32 (0.55-3.14) | 0.536 | 0.55 (0.24-1.28) | 0.163 | 0.70 (0.31-1.60) | 0.40 | 1.46 (0.67-3.15) | 0.338 |
| Tachy-arrhythmia readmission† | 5 (2%) | 10 (3%) | 5 (2%) | 9 (2%) | 1.40 (0.48-4.14) | 0.537 | 1.22 (0.34-4.30) | 0.761 | 1.23 (0.40-3.81) | 0.720 | 1.41 (0.48-4.16) | 0.536 | 1.35 (0.54-3.36) | 0.520 | 0.89 (0.29-2.73) | 0.833 |
| Brady-arrhythmia readmission† | 8 (2%) | 9 (2%) | 8 (3%) | 7 (2%) | 0.91 (0.34-2.40) | 0.846 | 1.09 (0.40-2.95) | 0.864 | 0.71 (0.25-2.07) | 0.532 | 0.90 (0.34-2.36) | 0.823 | 1.22 (0.45-3.30) | 0.690 | 1.28 (0.45-3.64) | 0.644 |

BB = beta-blocker; Both = combination group; CI = confidence interval; HHF = rehospitalization for heart failure; HR = hazard ratio; MI = myocardial infarction; No = no-treatment group; RASi = renin-angiotensin system inhibitor; TIA = transient ischemic attack.

Values are expressed as number (percentage).

* Adjusted for diabetes mellitus, history of previous percutaneous coronary intervention, chronic kidney disease stage 3 or higher, STS score, and LVEF.

† Tachyarrhythmia was defined as any cardiac rhythm with heart rate ≥150 beats/minute, and bradyarrhythmia was defined as any cardiac rhythm with heart rate <50 beats/minute.

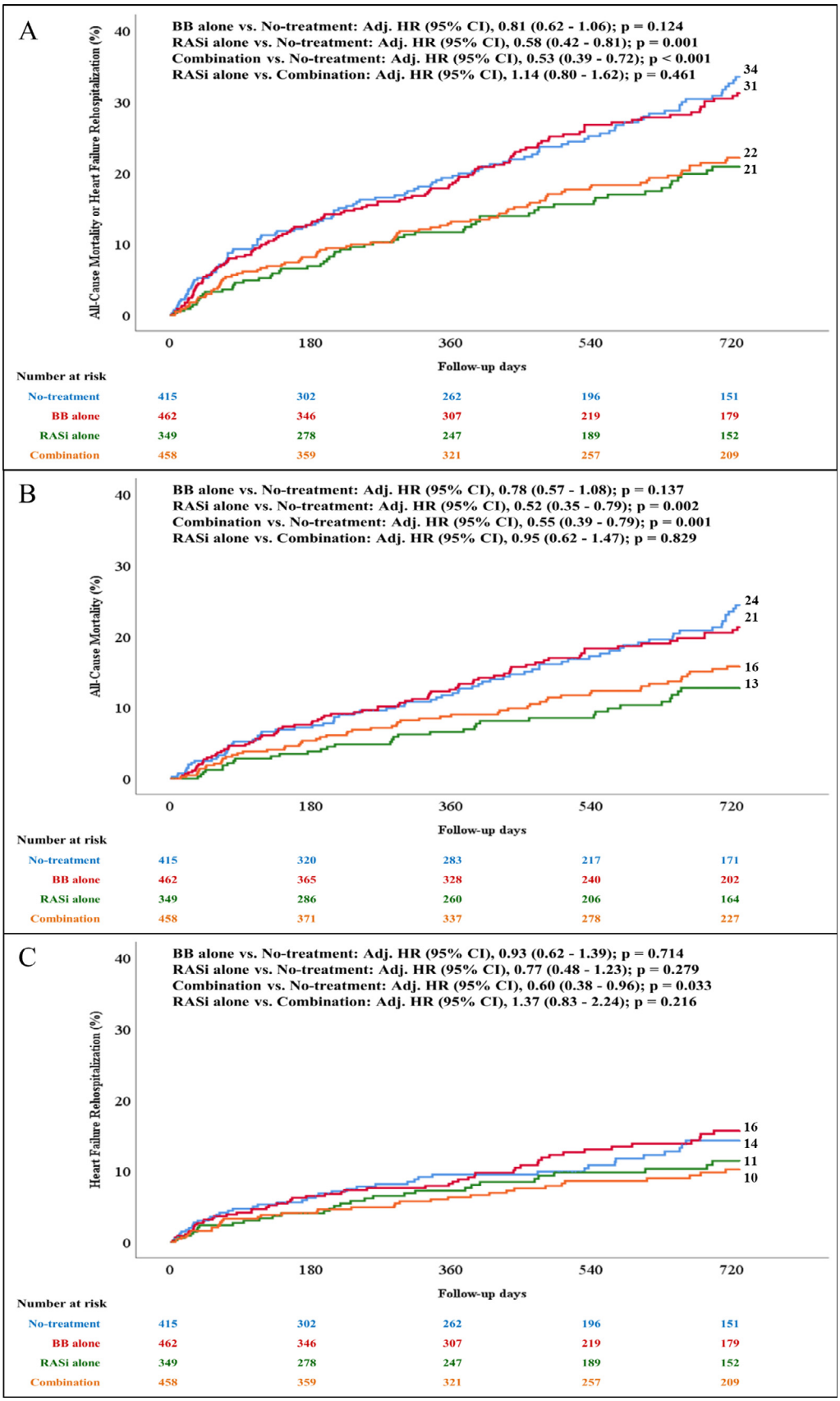


Figure 1. Kaplan-Meier estimates of the primary outcome and its components at 2-year follow-up. (*A*) The composite outcome of all-cause mortality and HHF. (*B*) All-cause mortality. (*C*) HHF. Adj = adjusted; BB = beta-blocker; HHF = rehospitalization for heart failure; RASi = renin-angiotensin system inhibitor.

Table 4
Predictors of all-cause mortality at 2-year follow-up

| Variable | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | HR (95% CI) | p value | Adjusted HR | p value |
| BB at discharge | 1.01 (0.78-1.30) | 0.948 | 0.94 (0.71-1.25) | 0.673 |
| RASi at discharge | 0.60 (0.47-0.78) | <0.001 | 0.68 (0.51-0.90) | 0.007 |
| Age | 1.03 (1.02-1.05) | <0.001 | | |
| Male | 1.29 (0.99-1.58) | 0.057 | 1.48 (1.08-2.01) | 0.013 |
| BMI | 0.95 (0.92-0.97) | <0.001 | | |
| CAD | 1.30 (1.01-1.68) | 0.040 | | |
| Previous MI | 1.57 (1.11-2.21) | 0.010 | | |
| Previous PCI | 1.49 (1.13-1.96) | 0.004 | 1.55 (1.08-2.23) | 0.017 |
| Previous CABG | 1.18 (0.88-1.59) | 0.270 | | |
| PAD | 1.19 (0.89-1.58) | 0.242 | | |
| Previous stroke/TIA | 1.32 (0.98-1.80) | 0.070 | | |
| Diabetes mellitus | 1.25 (0.96-1.62) | 0.092 | 1.44 (1.06-1.96) | 0.020 |
| COPD | 1.78 (1.36-2.34) | <0.001 | 1.56 (1.14-2.12) | 0.005 |
| CKD stage ≥ 3 | 2.09 (1.42-3.07) | <0.001 | 1.65 (1.09-2.49) | 0.017 |
| Atrial fibrillation | 1.40 (1.06-1.85) | 0.017 | 1.43 (1.06-1.94) | 0.020 |
| STS score | 1.08 (1.06-1.10) | <0.001 | 1.06 (1.04-1.09) | <0.001 |
| LVEF | 0.98 (0.97-0.99) | <0.001 | | |
| Moderate or severe MR | 2.10 (1.60-2.76) | <0.001 | 1.61 (1.20-2.17) | 0.002 |
| Moderate or severe MS | 1.30 (0.87-1.96) | 0.200 | | |
| Non-TF access | 2.37 (1.64-3.42) | <0.001 | | |
| Early generation valve* | 1.78 (1.38-2.29) | <0.001 | 1.40 (1.05-1.88) | 0.022 |
| PVL ≥ mild degree | 1.39 (1.06-1.82) | 0.017 | 1.34 (1.01-1.78) | 0.043 |

BB = beta-blocker; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MR = mitral regurgitation; MS = mitral stenosis; NYHA = New York heart association; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PVL = paravalvular leakage; RASi = renin-angiotensin system inhibitor; STS = society of thoracic surgeon; TF = transfemoral; TIA = transient ischemic attack.

* Early generation valve defined as CoreValve, Sapien original, and Sapien XT.

p = 0.009 and 111.6 to 107.4 g/m$^2$; p = 0.013, respectively) groups, whereas the similar effect was not observed in the BB alone and no-treatment groups. Notably, no significant change was observed in each medication group in terms of LVEF between baseline and 1-year follow-up (Figure 2 and Supplementary Table 4). Furthermore, a higher percentage of reverse LV remodeling and LVMI regression was observed in RASi alone and combination groups when compared with no-treatment and BB alone groups, but this did not reach statistical significance (p = 0.303 and p = 0.165, respectively; Online Figure 4).

## Discussion

The main findings of this study are as follows: (1) Compared with patients with no treatment, RASi prescription at discharge was associated with lower composite outcome of all-cause mortality and HHF. This association was not significant for BB; (2) Combination therapy with RASi and BB did not add any significant benefits over RASi alone; (3) These effects were independent of LVEF and were similar even in patients with reduced LV systolic function (Figure 3).

Long-standing AS can lead to myocardial dysfunction, which may not be reversible even after stenosis relief.[10] Thus, the treatment of severe AS goes beyond the aortic valve and is primarily directed to alleviate the increased LV wall stress and prevent adverse myocardial remodeling, which may trigger future cardiovascular events. In this study, compared with patients not receiving any medication, patients who received RASi (with or without BB) after TAVI showed a significant reduction in the primary outcome at 2-year. Furthermore, RASi treatment was also associated with lower mortality, which the result persisted after multivariable adjustment. One can speculate that these results are confounded because of selection bias as more stable patients can be expected to be more likely to receive RASi at discharge. Patients in the RASi alone group were slightly younger and had lower STS scores at baseline than those in the no-treatment group; however, they had higher rates of cardiovascular comorbidities. Our results are consistent with those of previous studies, showing favorable effects of RASi treatment on long-term survival of patients post-TAVI.[12-15] RASi has antifibrotic properties, which can promote LV reverse remodeling through the inhibition of angiotensin II.[9,22] Our findings support this protective mechanism, as we found a significant decline of LVEDVI and LVMI at 1-year post-TAVI in patients prescribed with RAS blockade with or without BB. Recently, Chau et al. found that in patients with LV hypertrophy, LVMI regression at 1-year post-TAVI was associated with lower death at 5-year.[19] This finding emphasizes the importance of myocardial reverse remodeling after TAVI as a marker for better long-term outcomes.

In contrast to RASi, BB failed to show a significant reduction in the primary outcome at 2-year when compared with no-treatment, as well as not being an independent predictor of 2-year all-cause mortality. When compared with the no-treatment group, patients treated with BB alone were younger but had higher comorbidities. However, the lack of

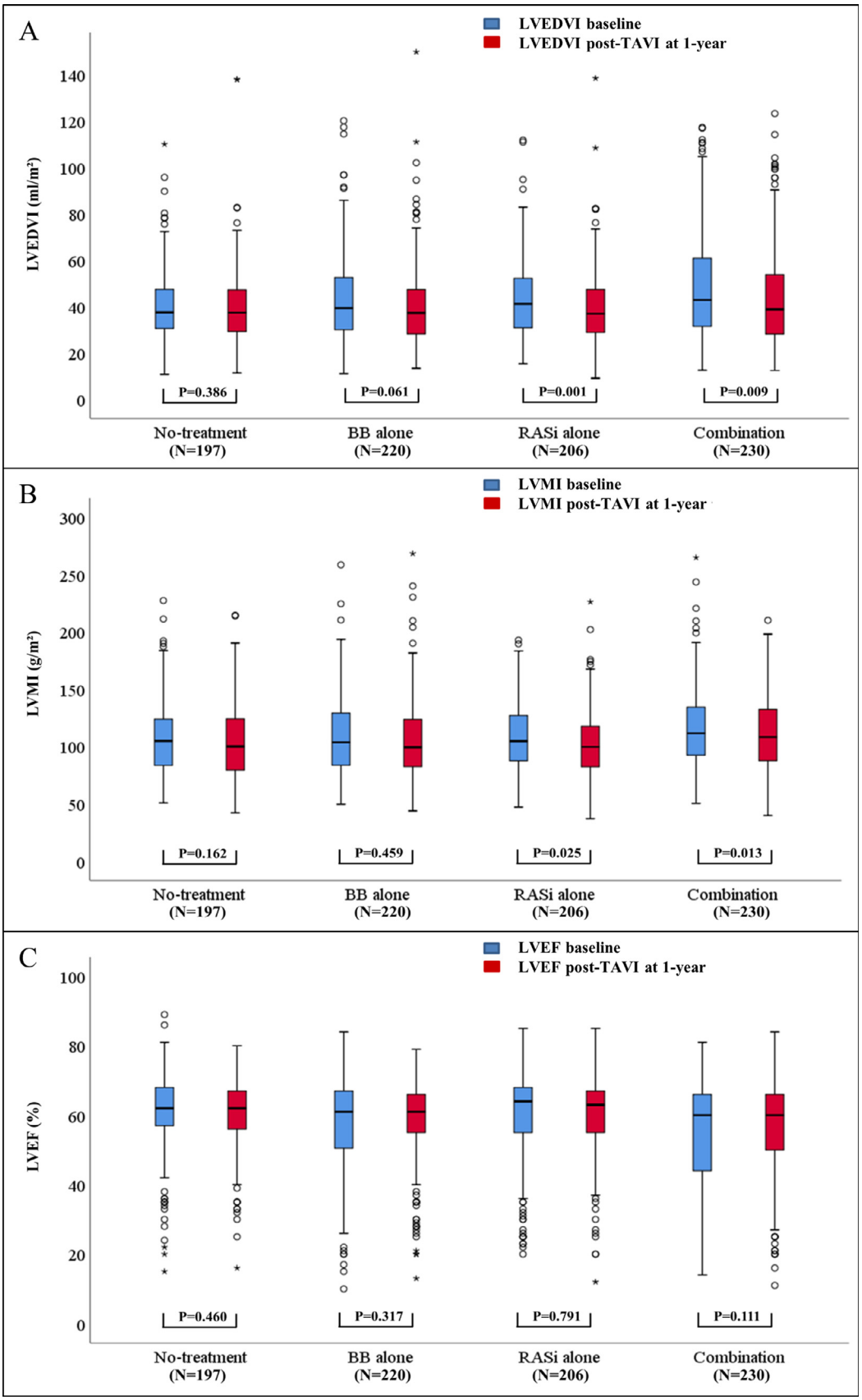


Figure 2. Left ventricular remodeling at 1-year follow-up in patients who underwent TAVI according to medication groups. (*A*) LVEDVI. (*B*) LVMI. (*C*) LVEF. BB = beta-blocker; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; RASi = renin-angiotensin system inhibitor; TAVI = transcatheter aortic valve implantation.

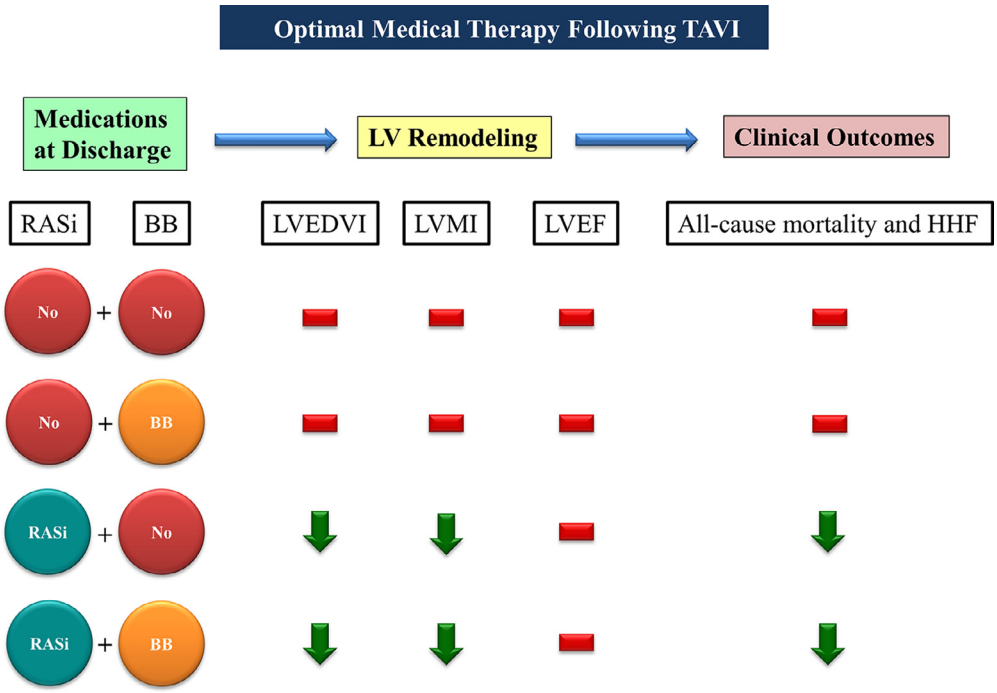


Figure 3. Central illustration. BB = beta-blocker; HHF = rehospitalization for heart failure; LV = left ventricle; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVMI = left ventricular mass index; RASi = renin-angiotensin system inhibitor; TAVI = transcatheter aortic valve implantation.

protective effect of BB remained after multivariable adjustment. BB has potential beneficial properties in reducing cardiovascular mortality and HHF, as it slows heart rate, increases diastolic filling time, improves myocardial perfusion, and has an antiarrhythmic effect. Theoretically, these benefits should apply to post-TAVI patients. However, no significant benefit of BB on the primary and secondary outcomes has been observed in this study. There are several possible explanations for this finding. First, as BB has been proven to be more effective in patients with reduced LVEF, the high prevalence of patients with preserve LVEF in our study may affect BB's response. Second, most BB does not block the $\beta$1-adrenergic receptor at both the high and the low-affinity sites. Thus, the chronic unblocked low-affinity $\beta$1-adrenergic receptor may mediate persistent cardiostimulation overtime, causing adverse myocardial remodeling even in patients treated with BB.[23] Third, the type of BB may have influenced the results. In 1 study, carvedilol showed higher degrees of reverse remodeling and lowered cardiovascular events compared with metoprolol.[24]

Compared with the no-treatment group, combination treatment with BB and RASi was associated with lower rates of the primary outcome. However, this benefit did not persist when compared combination therapy to RASi alone. This finding may imply that the beneficial effects on myocardial fibrosis reduction and reverse myocardial remodeling facilitation are far greater in RASi than BB therapy. The significant reduction in LVEDVI and LVMI observed in RASi but not in BB groups during follow-up supports this hypothesis. Furthermore, the primary outcome results were maintained in a sensitivity analysis of patients with LVEF $\leq$40% despite BB, RASi, and their combination are the proven medications for patients with heart failure with reduced LVEF. A possible explanation is that most of the patients in this study had preserved LVEF, which may obscure the effect of BB, showing differences in outcome in the sensitivity analysis. For clinical implications, our findings suggested that in the absence of contraindications, RASi should be considered in all patients post-TAVI at discharge as it may lower the risk of HHF and mortality. In addition, combination therapy did not add significant benefit over RASi alone.

Several limitations of the present study warrant consideration. First, this was a single-center, retrospective observational study. Confounding factors that we did not expect may not have been accounted for in our analyses. Second, medications at discharge other than RASi and BB, such as statin and antiplatelet therapies, which may affect the clinical outcomes post-TAVI,[25,26] were not included in this study's analyses. Third, the number of events per adjusting variable in proportional hazard regression analyses was <10 in some analyses of secondary outcomes. Thus, the result of HR should be interpreted with caution in those analyses. Finally, several patients lost to follow-up in this study, and there is a possibility that some patients might discontinue or receive study medications during the follow-up period. This limitation emphasized that a randomized control trial is necessary to confirm the result of this study.

In conclusion**,** RASi treatment following TAVI, but not BB, was associated with a lower rate of mid-term composite outcome defined as all-cause mortality and HHF. Combination therapy with BB to RASi did not add any significant benefit over RASi alone.

## 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. Sahar Mahani: Investigation, Writing - Review & Editing. Isic Kim: Investigation, Writing - Review & Editing. Dhairya Patel: Writing - Review & Editing. Tracy Salseth: Writing - Review & Editing. Michelle Friedman: Writing - Review & Editing. Sung-Han Yoon: Conceptualization, Writing - Review & Editing. Siddharth Singh: 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.2020.11.010.


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