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ORIGINAL RESEARCH

Ramipril After Transcatheter Aortic Valve Implantation in Patients Without Reduced Ejection Fraction: The RASTAVI Randomized Clinical Trial

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BACKGROUND: Patients with aortic stenosis may continue to have an increased risk of heart failure, arrhythmias, and death after successful transcatheter aortic valve implantation. Renin-angiotensin system inhibitors may be beneficial in this setting. We aimed to explore whether ramipril improves the outcomes of patients with aortic stenosis after transcatheter aortic valve implantation.

METHODS AND RESULTS: PROBE (Prospective Randomized Open, Blinded Endpoint) was a multicenter trial comparing ramipril with standard care (control) following successful transcatheter aortic valve implantation in patients with left ventricular ejection fraction >40%. The primary end point was the composite of cardiac mortality, heart failure readmission, and stroke at 1-year follow-up. Secondary end points included left ventricular remodeling and fibrosis. A total of 186 patients with median age 83 years (range 79–86), 58.1% women, and EuroSCORE-II 3.75% (range 3.08–4.97) were randomized to receive either ramipril (n=94) or standard treatment (n=92). There were no significant baseline, procedural, or in-hospital differences. The primary end point occurred in 10.6% in the ramipril group versus 12% in the control group (P=0.776), with no differences in cardiac mortality (ramipril 1.1% versus control group 2.2%, P=0.619) but lower rate of heart failure readmissions in the ramipril group (3.2% versus 10.9%, P=0.040). Cardiac magnetic resonance analysis demonstrated better remodeling in the ramipril compared with the control group, with greater reduction in end-systolic and end-diastolic left ventricular volumes, but nonsignificant differences were found in the percentage of myocardial fibrosis.

CONCLUSIONS: Ramipril administration after transcatheter aortic valve implantation in patients with preserved left ventricular function did not meet the primary end point but was associated with a reduction in heart failure re-admissions at 1-year follow-up.

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Key Words: renin-angiotensin ■ TAVR ■ ventricular remodeling

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CLINICAL PERSPECTIVE

What Is New?

- Patients with aortic stenosis may continue to have an increased risk of cardiovascular events after successful transcatheter aortic valve implantation; the administration of ramipril in patients with aortic stenosis with left ventricular ejection fraction >40% after transcatheter aortic valve implantation compared with standard care demonstrated a similar rate of the combined primary end point but a lower rate of heart failure readmissions and greater reduction in left ventricular volumes.

What Are the Clinical Implications?

- Ramipril following transcatheter aortic valve implantation in patients with preserved ejection fraction may reduce rehospitalizations and favors a better remodeling.
- Three-year follow-up is warranted and will help to clarify whether the combined primary end point is met at longer term.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
RAS	renin-angiotensin system
TAVI	transcatheter aortic valve implantation

Some patients with aortic stenosis (AS) may continue to have persistent left ventricular hypertrophy, diastolic dysfunction, and myocardial fibrosis after successful aortic valve replacement, with an increased risk of heart failure (HF), arrhythmias, and death.[1,2] There is evidence to suggest that renin-angiotensin system inhibitors (RASi) may be effective at reducing residual myocardial fibrosis and improving remodeling in patients with AS who have undergone valve replacement surgery.[3,4] Other potential mechanisms of RASi that may contribute to improved outcomes include an antiarrhythmic effect or plaque stabilization in patients with high cardiovascular risk. On the other hand, patients treated with transcatheter aortic valve implantation (TAVI) are often older and with greater burden of cardiovascular disease, greater risk of conduction disturbances, and more arterial pressure lability, which might hinder the use of RASi in clinical practice.[5–8]

Prior retrospective analyses suggest that RASi might improve the prognosis after TAVI in patients with AS even with preserved or mild deterioration of the left ventricular ejection fraction (LVEF),[6–8] but no dedicated prospective and mechanistic analysis has investigated this yet. The main purpose of this study was to explore whether ramipril use improves the outcomes of patients with AS treated with TAVI and provide mechanistic insights by means of cardiac magnetic resonance (CMR) analysis at baseline and follow-up.

METHODS

Trial Design and Oversight

This was a national, multicenter, randomized 1:1 trial assigning patients successfully discharged after TAVI with LVEF >40% to receive standard care (control) versus highest tolerated dose of ramipril. The study rationale design has been previously published.[5] Data are available upon request from a third party.

There was independent monitoring and an independent clinical review committee, and the study received grants from the Instituto de Salud Carlos III (Madrid, Spain) and Sociedad Española de Cardiología but no private fundings warranting independent investigation.

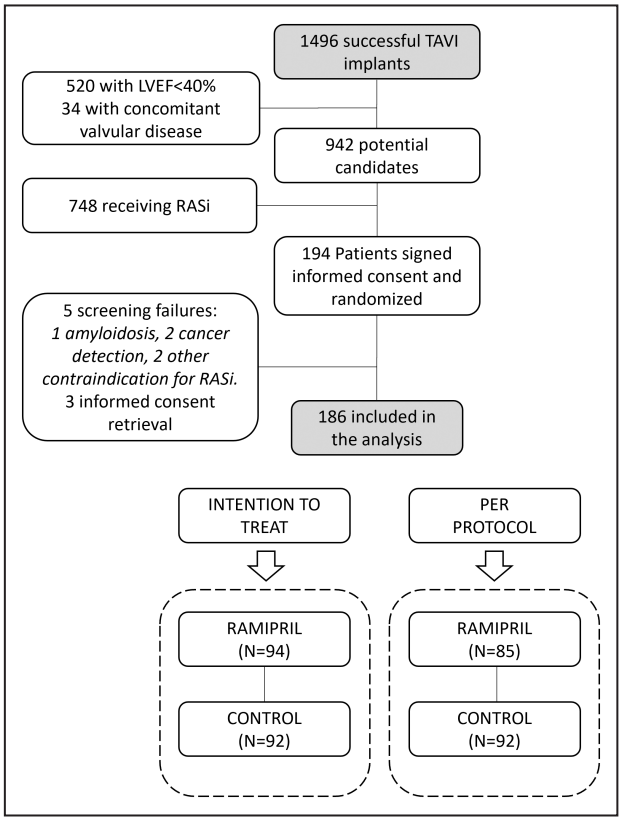

Figure 1. Flowchart of the study.
LVEF indicates left ventricular ejection fraction; RASi, renin-angiotensin system inhibitors; and TAVI, transcatheter aortic valve intervention.

The workflow has been schematically depicted in Figure 1. Briefly, after initial clinical evaluation to determine suitability of the candidate, informed consent was obtained and standard baseline evaluation including transthoracic echocardiography, blood tests, quality of life questionnaires, and 6-minute walking test were performed. After the TAVI procedure, patients were randomized to receive either standard care or an initial dose of ramipril (2.5 mg). A baseline CMR was performed after successful TAVI (predischarge) and repeated at 1-year follow-up unless contraindicated, mainly in case of patients harboring a new permanent pacemaker that was not CMR-compatible. Central analysis of all images was performed by an independent corelab (www.icicorelab.es).

Clinical events were recorded and adjudicated by a scientific committee including a clinical cardiologist, an interventional cardiologist, and a neurologist who were blinded to the therapeutic group. Local ethics committees approved the informed consent that adhered to the directions of the Helsinki Declaration and the legal dispositions 14/2007 and RD 1090/2015 regarding biomedical research.

Patient Selection

The target population included patients >60 years of age with severe AS assessed by transthoracic echocardiography and who successfully underwent TAVI following heart team approval. A successful TAVI procedure following the Valve Academic Research Consortium-2 definition of device success was required.[9]

Patients presenting any of the following conditions were excluded from the study: mitral disease requiring intervention, ventricular ejection fraction ≤40%, prior ST-elevated myocardial infarction or dilated cardiomyopathy, presence of magnetic resonance incompatibilities at baseline (ie, devices, morbid obesity, or claustrophobia), use of drugs for RAS blockade within the past 3 months or intolerance, allergy, or contraindication for their use, including glomerular filtration rate <30 mL/min and persistent hypotension (defined as systolic or diastolic blood pressure <100 or <60 mm Hg, respectively).

Trial Treatment and Follow-Up

Titration of ramipril dose was performed at 1- and 3-month follow-up visits aiming at 10 mg daily if tolerated; in case of symptoms related to dose increase, it was reduced to the previous dose. Patients in the control group did not receive RASi throughout the study; if their blood pressure was beyond recommended parameters (140/90 mm Hg), the physician responsible for treating the patient administered any medication to control it, with the exception of RAS blockers.

Outcomes

The primary end point was the composite of cardiac mortality, HF readmission, and stroke at 1 year. Secondary outcomes include each factor of the combined primary end point, functional capacity, and left ventricular remodeling and fibrosis as evaluated by corelab analysis of echocardiography and CMR at 1 year. Follow-up will be extended to 3 years. Arterial pressure, weight, and height were measured before every echocardiographic study. Cavities dimensions, myocardial mass, septal width, ejection fraction (Simpson and Teicholz methods), aortic valve and outflow tract peak velocities, peak and mean gradients, estimated aortic valve area, and aortic regurgitation degree and its location (peri- or intraprosthetic) were measured. The function of the remaining heart valves was also evaluated. Diastolic function was evaluated by measuring E and A waves and their relationship, E′ and A′, and the isovolumetric ventricular relaxation time. In those with baseline and 1-year CMR, the result was evaluated and compared. Right and left ventricular dimensions and function were assessed with SSFP sequences (TrueFISP, bTFE, FIESTA), in 4- and 2-chamber views. Residual aortic regurgitation was also evaluated. Contrast-enhancement analysis with gadolinium was performed to determine the presence and degree of myocardial fibrosis according to segments and disposition (subendocardial, subepicardial, intramyocardial), total fibrotic mass (gr), and its proportion according to total myocardial mass of the left ventricle.

Statistical Analysis and Randomization

Sample size estimation was based on former studies in patients with AS.[10–13] First, the study by Dahl et al[10] included 114 patients and evaluated left ventricular mass after 1 year under treatment or standard of care with a significant greater reduction of mass in the active group. Analysis of these data suggests the need for at least 79 patients in each group. Second, the research by Goel et al[11] retrospectively included 1752 patients and aimed to analyze the impact in mortality; a propensity score subanalysis including 594 patients reported a 5-year mortality rate of 10% in the active group and 22% in the control group. In addition, in the HOPE (Heart Outcome Prevention Evaluation) study,[14] ramipril was stopped in 7% of the patients due to persistent cough. Taking this into consideration and after fixing alpha- and beta-errors of 0.05 and 0.15, respectively, we estimated the sample size for the RASTAVI trial in 336 patients (including 5% of potential missing subjects and 7% dropouts). However, during the analysis of the RASTAVI retrospective cohort[6] including 2785 subject treated with RASi (n=1622) or not

(n=1163), the rates of the combined end point (mortality + HF readmission + stroke) were 47.1% in RASi patients versus 69.4% in the control group at 3-year follow-up, leading to a final sample calculation of 194 patients with preserved ejection fraction randomly assigned to treatment or standard care after a successful TAVI procedure.

The Ene 2.0 (GlaxoSmithKline) was used as an independent system for blocked randomization with balance across groups and blocks of 4 and 6 patients randomly selected. The person performing the randomization, who was contacted by phone call, was unaware of the clinical decision of the patient warranting independent randomization. Data analysis was conducted to evaluate the study results both by intention-to-treat and per protocol. In the intention-to-treat analysis, all participants randomly assigned to the treatment group were included, regardless of their full compliance with the protocol. In the per protocol analysis, those patients in the treatment group who were <30-day under ramipril were excluded from the analysis.

Finally, statistical analysis for categorical variables is expressed both as absolute values and percentages and for continuous variables as median and interquartile range (interquartile range$_{25–75}$). Pearson χ^2 test and Fisher exact test were performed in comparisons between groups with qualitative variables, and Mann–Whitney test in continuous variables. Kaplan–Meier curves were estimated for primary and secondary outcomes and compared with log-rank test. Cox proportional hazards regression with Fine and Gray competing risks was used to estimate risks of the events between ramipril and control arms and is presented as subdistribution hazard ratios with 95% CI.[15] However, because there were no competing risks for all-cause mortality, hazard ratios were estimated with 95% CI. The assumptions of proportional hazards were verified by means of the test of Schoenfeld residuals and checked using the log(–log(survival)) plots. All *P* values are bilateral and were considered statistically significant when <0.05. Statistical analysis was performed with R software, version 4.2.0 (R Project for Statistical Computing).[16]

RESULTS

Trial Population

From February 2018 to July 2021, a total of 186 patients with severe AS successfully treated with TAVI were enrolled in 14 centers in Spain. Median age was 83 years [79–86], 58.1% were women, and mean EuroSCORE-II was 3.75% [3.08–4.97].

Median time between baseline visit and randomization was 4.0 days, interquartile range [3.0–6.5]. Patients were randomized to receive either ramipril (n=94) or standard care (n=92, control group). No significant baseline, procedural, or in-hospital differences existed (Table 1, Tables S1 and S2).

The ramipril treatment had to be withdrawn due to cough in 8.5% and hypotension in 6.4% (Figure 2). These patients were excluded in the per protocol analysis if treatment duration was <30 days, resulting in a group of 85 patients under ramipril and 92 in the control group. No differences existed in baseline, procedural, and acute outcomes between the 2 groups of the per protocol analysis (Table 1, Tables S1 and S2).

Clinical Efficacy and Safety Outcomes

The median dose of ramipril was 5.0 mg and titration within the 1-year follow-up is shown in Figure S1. At 1 year, the primary end point occurred in 10.6% in the ramipril group versus 12% in the control group (*P*=0.776) (Figure 3, Table 2), with no differences in cardiac mortality (1.1% versus 2.2%, *P*=0.619), but a lower rate of readmissions due to HF in the ramipril group (3.2% versus 10.9%, *P*=0.040) (Figure 4). In addition, a dose-dependent effect was detected, with lower rates of the primary end point and of HF readmission at 1 year in patients receiving higher doses of ramipril as compared with those treated with lower doses (Figure 5). Independent predictors of the primary event are described in Table S3. No differences were detected according to sex (Table S4).

Six-minute walking test distance increased from 244.6±113.8 to 306.4±106.1 m (*P* <0.001) with no significant differences between treatment groups (Figure S2). The New York Heart Association class, renal function, and NT-pro-BNP (N-terminal pro-B-type natriuretic peptide) levels were similar in both groups at baseline and at 1-year follow up (Table 2, Table S1).

Imaging Outcomes

Although no differences were found in ventricular volumes at follow-up in the intention-to-treat analysis (Figure S3), better remodeling was found in the ramipril compared with the control group when analyzed per protocol, with end-diastolic and end-systolic left ventricular volumes of 70.5 mm^3 [60.0–96.5] (versus 87.5 mm^3 [64.0–106.0], *P*=0.044) and 26.5 mm^3 [19.2–35.0] (versus 34.5 mm^3 [22.0–45.0], *P*=0.035), respectively (Table 2, Figure 6) by CMR. Also, CMR demonstrated a nonsignificant decrease in the percentage of myocardial fibrosis from 1.63% [0.75–2.21] to 1.51% [0.61–1.98] with no differences between patients in the ramipril (0.91% [0.40–1.59]) and the control group (1.82% [1.03–2.15], *P*=0.113) at 1-year follow-up. Changes in the main parameters measured by CMR are reported in Table 3 and illustrated in Video S1. No differences regarding diastolic function parameters were detected (Figure S4).

Table 1. Baseline Clinical and Echocardiographic Characteristics of the Study Population According to the Treatment Group

Variables	N	Global study population (n=186)	Intention-to-treat			Per protocol		
			RASi (n=94)	No-RASi (n=92)	*P* value	RASi (n=85)	No-RASi (n=92)	*P* value
Baseline characteristics								
Age, y	184	83.0 [79.0– 86.0]	83.0 [78.5– 86.0]	84.0 [80.0– 86.0]	0.532	83.0 [79.0– 86.0]	84.0 [80.0– 86.0]	0.823
Female sex	186	108 (58.1%)	53 (56.4%)	55 (59.8%)	0.639	50 (58.8)	55 (59.8%)	0.897
Body surface area, m^2	182	1.74 [1.63– 1.87]	1.74 [1.60– 1.87]	1.74 [1.66– 1.87]	0.418	1.74 [1.60– 1.85]	1.74 [1.66– 1.87]	0.446
Body mass index, kg/m^2	182	27.2 [25.2– 29.6]	26.9 [24.8– 29.0]	28.3 [25.6– 30.3]	0.050	27.0 [25.0– 29.0]	28.3 [25.6– 30.3]	0.068
Hypertension	186	108 (58.1%)	55 (58.5%)	53 (57.6%)	0.901	50 (58.8)	53 (57.6%)	0.870
Dyslipidemia	186	113 (60.8%)	53 (56.4%)	60 (65.2%)	0.217	47 (55.3)	60 (65.2%)	0.177
Diabetes	184	39 (21.2%)	18 (19.4%)	21 (23.1%)	0.537	14 (16.5)	21 (23.1%)	0.273
NYHA functional class III or IV	184	67 (36.4%)	33 (35.1%)	34 (37.8%)	0.707	30 (35.3)	34 (37.8%)	0.733
Previous heart failure	186	72 (38.7%)	39 (41.5)	33 (35.9)	0.431	35 (41.2)	33 (35.9)	0.468
Atrial fibrillation	185	58 (31.3%)	32 (34.0%)	26 (28.6%)	0.423	30 (35.3)	26 (28.6%)	0.339
Previous pacemaker	186	18 (9.7%)	12 (12.8%)	6 (6.5%)	0.150	11 (12.9)	6 (6.5%)	0.148
ICD	186	1 (0.5%)	1 (1.1%)	0 (0%)	0.999	1 (1.2)	0 (0%)	0.480
Prior coronary artery disease	184	37 (20.1%)	18 (19.4%)	19 (20.9%)	0.796	15 (17.9)	19 (20.9%)	0.614
Previous myocardial infarction	186	14 (7.5%)	7 (7.4%)	7 (7.6%)	0.967	6 (7.1)	7 (7.6%)	0.889
Previous PCI	186	31 (16.7%)	14 (14.9%)	17 (18.5%)	0.512	11 (12.9)	17 (18.5%)	0.313
Current coronary artery disease	185	39 (21.1%)	19 (20.2%)	20 (22.0%)	0.769	18 (21.2)	20 (22.0%)	0.897
PCI pre-TAVR	185	20 (10.8%)	8 (8.5%)	12 (13.2%)	0.306	7 (8.2)	12 (13.2%)	0.290
Previous SVR	186	10 (5.4%)	5 (5.3%)	5 (5.4%)	0.999	5 (5.9)	5 (5.4%)	0.999
Previous stroke/TIA	186	22 (11.8%)	10 (10.6%)	12 (13.0%)	0.612	9 (10.6)	12 (13.0%)	0.614
Peripheral vascular disease	186	18 (9.7%)	6 (6.4%)	12 (13.0%)	0.125	6 (7.1)	12 (13.0%)	0.188
COPD	185	12 (6.5%)	7 (7.5%)	5 (5.4%)	0.563	7 (8.3%)	5 (5.4%)	0.446
CKD (CKDEPI) (eGFR <60 mL/min)	186	60 (32.3%)	33 (35.1%)	27 (29.3%)	0.401	28 (32.9)	27 (29.3%)	0.606
NT-proBNP, pg/mL	168	1194 [572– 2371]	1309 [584– 2545]	1136 [582– 2317]	0.502	1352 [572– 2733]	1136 [582– 2317]	0.400
STS score, %	186	2.82 [1.83– 4.07]	2.94 [1.81– 4.30]	2.64 [1.83– 3.84]	0.812	3.10 [1.87– 4.34]	2.64 [1.83– 3.84]	0.688
EuroSCORE II, %	186	3.75 [3.08– 4.97]	3.68 [2.90– 4.71]	3.88 [3.22– 5.24]	0.096	3.66 [2.94– 4.86]	3.88 [3.22– 5.24]	0.164
Barthel Index	157	95.0 [90.0– 100.0]	95.0 [90.0– 100.0]	100.0 [90.0– 100.0]	0.338	95.0 [90.0– 100.0]	100.0 [90.0– 100.0]	0.387
Frailty CGA	148	0.12 [0.08– 0.20]	0.12 [0.09– 0.20]	0.12 [0.08– 0.20]	0.646	0.12 [0.08– 0.20]	0.12 [0.08– 0.20]	0.788
KCCQ 12 score	107	43.8 [41.0– 45.6]	44.2 [41.3– 46.1]	42.9 [40.3– 44.3]	0.435	45.1 [42.1– 47.0]	42.9 [40.3– 44.3]	0.676
CHADS2VASC	185	4.0 [3.0– 5.0]	4.0 [3.0– 5.0]	4.0 [3.0– 5.0]	0.357	4.0 [3.0– 5.0]	4.0 [3.0– 5.0]	0.438
Blood pressure, mm Hg (systolic)	184	126/69	128 [120– 139]	125 [114– 135]	0.459	128 [120– 141]	125 [114– 135]	0.314
Blood pressure, mm Hg (diastolic)	184	126/69	61 [53– 68]	66 [58– 72]	0.182	61 [58– 68]	66 [58– 72]	0.334
Echocardiographic findings at baseline								
Left ventricular ejection fraction, %	174	60.0 [56.0– 65.0]	60.0 [55.0– 65.0]	60.0 [57.5– 65.0]	0.461	60.0 [55.0– 65.0]	60.0 [57.5– 65.0]	0.514
Aortic valve area, cm^2	186	0.9 [0.7– 1.0]	0.9 [0.7– 1.0]	0.9 [0.8– 1.0]	0.999	0.9 [0.7– 1.0]	0.9 [0.8– 1.0]	0.999
Mean transaortic gradient, mm Hg	156	8.0 [6.0– 11.5]	8.0 [6.0– 12.0]	9.0 [6.0– 11.0]	0.849	8.0 [6.0– 12.0]	9.0 [6.0– 11.0]	0.623

(*Continued*)

Table 1. Continued

Variables	N	Global study population (n=186)	Intention-to-treat			Per protocol		
			RASi (n=94)	No-RASi (n=92)	*P* value	RASi (n=85)	No-RASi (n=92)	*P* value
End-diastolic volume, mm^3	112	87.0 [65.5– 103.0]	91.0 [68.0– 110.0]	82.0 [65.0– 100.0]	0.251	89.5 [66.0– 111.0]	82.0 [65.0– 100.0]	0.379
End-systolic volume, mm^3	113	34.0 [25.0– 44.0]	36.0 [29.0– 44.0]	31.0 [23.0– 43.0]	0.311	36.0 [28.0– 44.5]	31.0 [23.0– 43.0]	0.545
Septal hypertrophy, mm	116	13.0 [12.0– 15.5]	14.0 [12.0– 16.0]	13.0 [12.0– 15.0]	0.889	14.0 [12.0– 16.0]	13.0 [12.0– 15.0]	0.546
Left ventricular myocardial mass (g)	115	142 [124–174]	147 [119– 178]	141 [127– 170]	0.799	146 [122– 171]	141 [127–170]	0.801
Aortic regurg. III–IV	168	5 (3.0%)	2 (2.4%)	3 (3.5%)	0.999	2 (2.7)	3 (3.5%)	0.999
Mitral regurg. III–IV	175	3 (%)	2 (2.2%)	1 (1.2%)	0.999	2 (2.5)	1 (1.2%)	0.609
Tricuspid regurg. III–IV	169	12 (7.1%)	7 (8.4%)	5 (5.8%)	0.507	7 (9.3)	5 (5.8%)	0.396
Diastolic dysfunction	143				0.243			0.375
Normal		86 (60.1%)	43 (57.3%)	43 (63.2%)		39 (59.1%)	43 (63.2%)	
Impaired relaxation		46 (32.2%)	28 (37.3%)	18 (26.5%)		23 (34.8%)	18 (26.5%)	
Pseudo-normalized		8 (5.6%)	2 (2.7%)	6 (8.8%)		2 (3.0%)	6 (8.8%)	
Restrictive		3 (2.1%)	2 (2.7%)	1 (1.5%)		2 (3.0%)	1 (1.5%)	
Magnetic resonance at baseline	143							
End-diastolic volume of LV, mL		131 [113–159]	123 [111– 151]	142 [121– 163]	0.094	122 [113– 149]	142 [121– 163]	0.091
End-systolic volume of LV, mL		54.0 [42.0– 74.0]	50.0 [38.5– 61.5]	61.0 [48.0– 79.0]	0.043*	51.0 [39.0– 59.0]	61.0 [48.0– 79.0]	0.048*
LVEF, %		60.0 [53.0– 66.0]	61.0 [55.0– 66.5]	59.0 [48.0– 63.0]	0.188	61.0 [55.0– 66.0]	59.0 [48.0– 63.0]	0.251
Myocardial mass of LV, g		112 [101– 130]	109 [98– 119]	117 [110– 134]	0.018*	109 [98– 119]	117 [110– 134]	0.022*
Maximal septal width of LV, mm		14.0 [12.5– 17.0]	14.0 [12.5– 16.0]	15.0 [13.0– 17.0]	0.489	14.0 [12.3– 16.5]	15.0 [13.0– 17.0]	0.469
End-diastolic volume of RV, mL		108 [94– 127]	107 [93–117]	110 [94.0– 130]	0.485	106 [93– 116]	110 [94.0– 130]	0.653
End-systolic volume of RV, mL		41.0 [35.0– 54.0]	38.0 [34.5– 53.0]	45.0 [35.0– 57.0]	0.603	38.0 [35.0– 52.0]	45.0 [35.0– 57.0]	0.922
RVEF, %		60.0 [54.0– 66.0]	61.0 [56.0– 67.0]	58.0 [52.0– 65.0]	0.247	61.0 [56.0– 66.0]	58.0 [52.0– 65.0]	0.375
Aortic regurgitant volume, mL		4.70 [2.59– 11.6]	3.90 [2.0– 7.30]	5.7 [1.2– 15.0]	0.148	3.8 [1.2– 9.5]	5.7 [1.2– 15.0]	0.130
Aortic regurgitant fraction, %		9.0 [4.0– 15.0]	5.5 [2.0– 14.0]	9.0 [2.0– 27.0]	0.175	5.5 [2.0– 13.5]	9.0 [2.0– 27.0]	0.195

Continuous variables are presented as mean±SD or median (interquartile range). Categorical data are summarized as numbers (percentage). CGA, indicates comprehensive geriatric assessment; CKD, chronic kidney disease; CKDEPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; EPI, ICD, implantable cardioverter-defibrillator; KCCQ, Kansas city cardiomyopathy questionnaire; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RASi, renin-angiotensin system inhibitors; RVEF. right ventricular ejection fraction; STS, Society of Thoracic Surgeons; SVR, Surgical valve replacement; TAVR, Transcatheter arotic valve replacement; TIA, transient ischemic attack.

*Significant *p*-value (i.e. $p<0.05$).

DISCUSSION

In patients with severe AS, the prosthesis treats the valvular condition but much more is needed to improve the prognosis. RASi targets the other 2 aspects: the myocardium by reversing remodeling and perhaps fibrosis, and the global burden of cardiovascular risk. However, currently the systematic use of RASi as ramipril is not recommended after TAVI when the ejection fraction is preserved. Moreover, concerns regarding the risk of hypotension or renal function decline might discourage its use. The RASTAVI trial is the first study exploring the use of ramipril compared with standard medications in patients with AS and preserved left ventricular function and included systematic echocardiography and CMR at baseline and at 1-year follow-up. The main findings of the study are as follows: (1) The primary end point, a composite of cardiac mortality, HF readmission and stroke at 1-year follow-up, was comparable, and ramipril following TAVI did not impact on global or

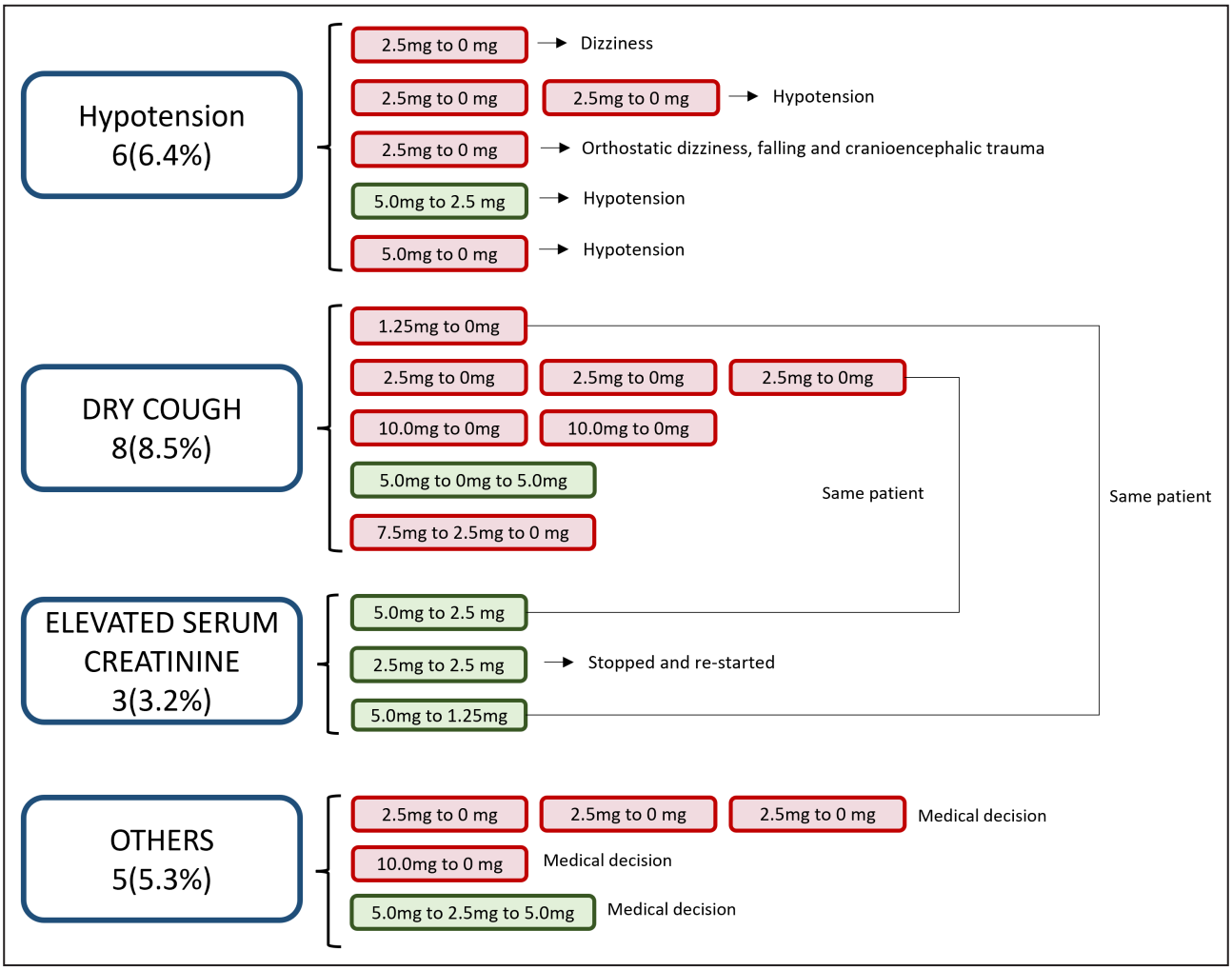

Figure 2. Adverse events related to ramipril.
Each box represents 1 patient (red: adverse event leading to treatment withdrawal; green: adverse event leading to temporary or definitive treatment dose reduction).

cardiovascular mortality, pending the completion of the prespecified 3-year follow-up. (2) However, a decrease in the rate of 1-year HF readmissions was detected, with a significantly lower incidence of the primary end point and the HF readmissions rate in patients receiving the highest dose of ramipril as compared with those treated with lower doses. (3) Functional improvement was similar between treatment groups at 1 year in terms of New York Heart Association class and 6-minute walking test distance, with no differences in renal function or other biomarkers. (4) Episodes of hypotension led to ramipril withdrawn in ≈6% of the patients in the treatment group but no other major events were related to its use, suggesting safety of the therapy in this setting. (5) Patients treated with ramipril presented a significant improvement in left ventricular volumes as assessed by CMR, but no differences were found in terms of regression of ventricular hypertrophy, proportion of myocardial fibrosis, or diastolic function at 1-year follow-up. Whether this last finding will require longer follow-up to demonstrate such regression or, on the contrary, it suggests an irreversible stage of the disease in the elderly patients harboring TAVI remains unknown. The prespecified follow-up at 3 years in the RASTAVI trial will help to shed light in this regard and its potential impact in longer-term mortality.

Benefits of Ramipril Following Transcatheter Aortic Valve Implantation

There are several mechanisms by which RASi might improve the prognosis in patients treated with TAVI.

First, it may reduce left ventricular hypertrophy irrespective of blood pressure effect. In fact, a randomized trial in asymptomatic patients with moderate or severe AS demonstrated left ventricular mass reduction with RASi despite no differences in blood pressure values.[6] However, it has been demonstrated that the degree of

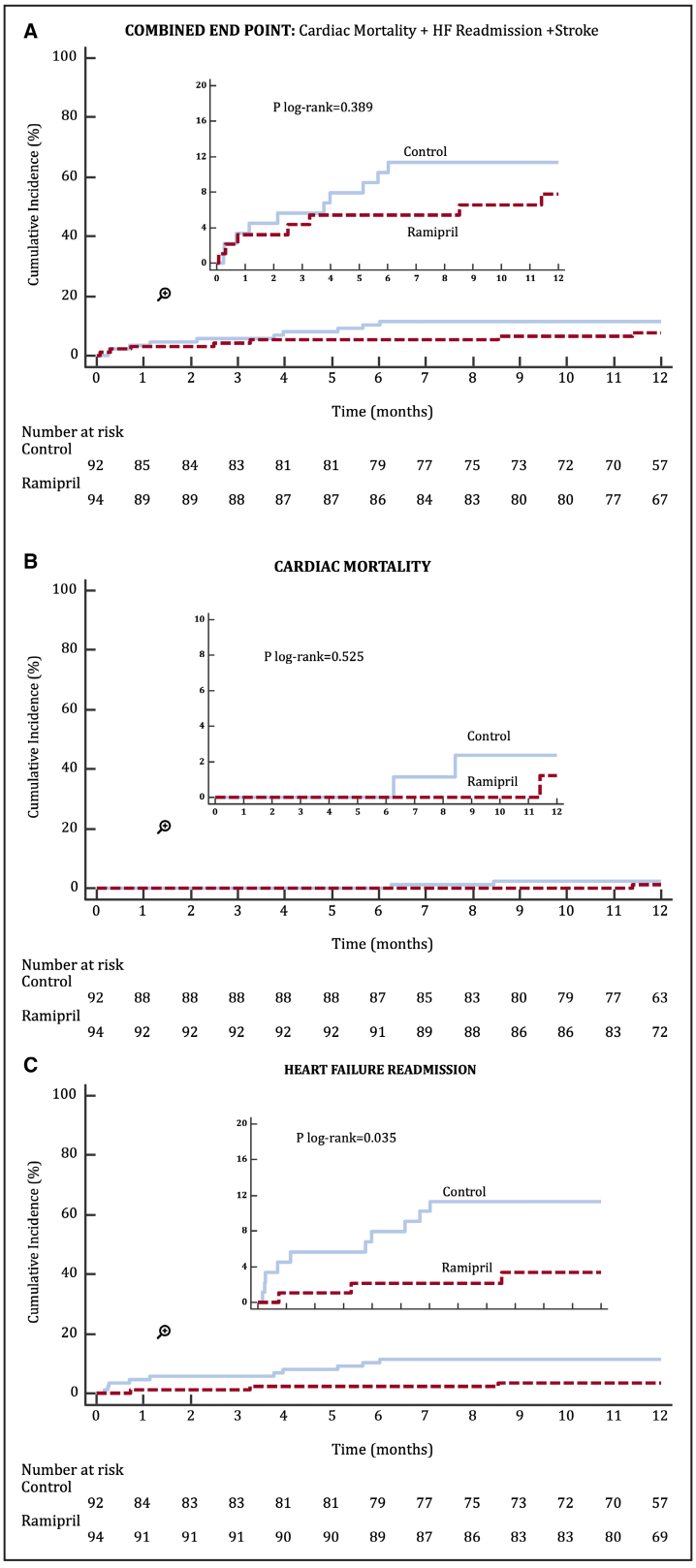

Figure 3. Kaplan–Meier estimates for the combined end point (A), cardiac mortality (B), and heart failure readmissions (C) in the global study population at 1-y follow-up.
HF indicates heart failure.

Table 2. Clinical and Echocardiographic 1-Year Follow-Up Outcomes

Variables	N	Global study population (n=186)	Intention-to-treat			Per protocol		
			RASi (n=94)	No-RASi (n=92)	*P* value	RASi (n=85)	No-RASi (n=92)	*P* value
Clinical findings								
1-y NYHA III–IV	141	13 (9.2%)	8 (11.0%)	5 (7.4%)	0.460	8 (11.8)	5 (7.4%)	0.382
Global mortality	186	7 (3.8%)	4 (4.3%)	3 (3.3%)	0.999	4 (4.7)	3 (3.3%)	0.712
Cardiac mortality	186	3 (1.6%)	1 (1.1)	2 (2.2%)	0.619	1 (1.2)	2 (2.2%)	0.999
Stroke	186	4 (2.2%)	3 (3.2%)	1 (1.1%)	0.621	3 (3.5)	1 (1.1%)	0.352
HF readmission	186	13 (7.0%)	3 (3.2%)	10 (10.9%)	0.040*	3 (3.5)	10 (10.9%)	0.061
Primary end point	186	17 (9.1)	7 (7.4)	10 (10.9)	0.418	7 (8.2)	10 (10.9)	0.552
Δ6-MWT, m	158	65 [−5 to 140]	40 [−7 to 100]	71 [0 to 148]	0.351	40 [−7 to 100]	71 [0 to 148]	0.351
NT-proBNP, pg/mL	95	464 [225 to 1110]	454 [221 to 1181]	472 [228 to 892]	0.949	420 [221 to 1181]	472 [228 to 892]	0.978
KCCQ 12 score	97	52.3 [51.7 to 65.3]	54.1 [53.7 to 66.8]	51.7 [50.0 to 62.7]	0.137	53.7 [52.1 to 65.3]	51.7 [50.0 to 62.7]	0.393
Blood pressure, mm Hg (systolic)	113	135 [124 to 149]	131 [115 to 147]	140 [129 to 150]	0.039*	132 [114 to 148]	140 [129 to 150]	0.051
Blood pressure, mm Hg (diastolic)	113	72 [67 to 79]	71 [66 to 78]	74 [67 to 79.0]	0.366	71.5 [66 to 79]	74 [67 to 79]	0.076
Chronic kidney disease (ClCr <60 mL/min)	129	59 (45.7%)	28 (45.2%)	31 (46.3%)	0.900	25 (43.1%)	31 (46.3%)	0.723
Echocardiographic findings								
Left atrial diameter	50	44.0 [38.0 to 49.0]	43.0 [38.0 to 49.0]	44.5 [39.0 to 51.0]	0.625	43.0 [38.0 to 49.0]	44.5 [39.0 to 51.0]	0.625
Left ventricular end-diastolic diameter	90	46.0 [40.0 to 50.0]	46.0 [40.0 to 49.0]	47.0 [40.0 to 51.0]	0.507	46.0 [40.0 to 49.0]	47.0 [40.0 to 51.0]	0.578
Left ventricular end-systolic diameter	67	31.0 [26.8 to 34.0]	31.0 [27.0 to 34.0]	30.5 [26.0 to 34.0]	0.949	30.5 [26.7 to 34.0]	30.5 [26.0 to 34.0]	0.933
Interventricular septal thickness, mm	90	13.0 [12.0 to 14.0]	13.0 [12.0 to 15.0]	13.0 [12.0 to 14.0]	0.944	13.0 [12.0 to 15.0]	13.0 [12.0 to 14.0]	0.843
Left ventricular myocardial mass, g	89	131 [120 to 143]	135 [115 to 152]	122 [120 to 141]	0.201	135 [118 to 144]	122 [120 to 141]	0.351
Left ventricular ejection fraction, %	115	60.0 [55.0 to 66.0]	60.0 [55.0 to 67.0]	60.0 [55.0 to 66.0]	0.807	60.0 [56.0 to 67.0]	60.0 [55.0 to 66.0]	0.918
Diastolic dysfunction	85							
Normal		47 (55.3%)	24 (55.8%)	23 (54.8%)	0.970	23 (57.5)	23 (54.8%)	0.993
Impaired relaxation		29 (34.1%)	14 (32.6%)	15 (35.7%)		13 (32.5)	15 (35.7%)	
Pseudo-normalized		5 (5.9%)	3 (7.0%)	2 (4.8%)		2 (5.0)	2 (4.8%)	
Restrictive		4 (4.7%)	2 (4.7%)	2 (4.8%)		2 (5.0)	2 (4.8%)	
Peak velocity, m/s	107	1.9 [1.6 to 2.3]	2.0 [1.5 to 2.4]	1.9 [1.6 to 2.3]	0.544	2.0 [1.5 to 2.4]	1.9 [1.6 to 2.3]	0.655
Peak gradient, mm Hg	114	15.0 [10.0 to 21.0]	15.0 [10.0 to 21.0]	16.0 [11.0 to 21.0]	0.950	15.0 [9.0 to 21.0]	16.0 [11.0 to 21.0]	0.774
Mean gradient, mm Hg	112	8.5 [5.0 to 11.0]	8.0 [5.5 to 11.0]	9.0 [5.0 to 11.0]	0.993	8.0 [5.0 to 11.0]	9.0 [5.0 to 11.0]	0.834
End-diastolic volume, mm^3	86	80.5 [61.2 to 102.0]	71.4 [60.0 to 98.0]	87.5 [63.5 to 105.5]	0.098	70.5 [60.0 to 96.5]	87.5 [63.5 to 105.5]	0.062
End-systolic volume, mm^3	86	31.0 [21.0 to 42.0]	26.5 [19.3 to 35.0]	34.5 [22.0 to 44.5]	0.063	26.5 [19.2 to 35.0]	34.5 [22.0 to 44.5]	0.042*
Aortic regurg. III–IV	122	2 (1.6%)	1 (1.6%)	1 (1.7%)	0.999	1 (1.7)	1 (1.7%)	0.999
Mitral regurg. III–IV	122	6 (4.9%)	3 (4.8%)	3 (5.0%)	0.999	3 (5.2)	3 (5.0%)	0.999
Tricuspid regurg. III–IV	117	9 (7.7%)	5 (8.3%)	4 (7.0%)	0.999	5 (8.9)	4 (7.0%)	0.742
SPPA, mm Hg	60	35.0 [27.5 to 44.5]	38.0 [28.0 to 44.5]	34.0 [27.0 to 43.0]	0.491	39.0 [28.0 to 45.0]	34.0 [27.0 to 43.0]	0.426

ClCr indicates Creatinine clearance; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; 6-MWT, 6-minute walking test; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASi, renin-angiotensin system inhibitors; and SPPA, systolic pressure of the pulmonary artery.

*Significant *p*-value (i.e. $p<0.05$).

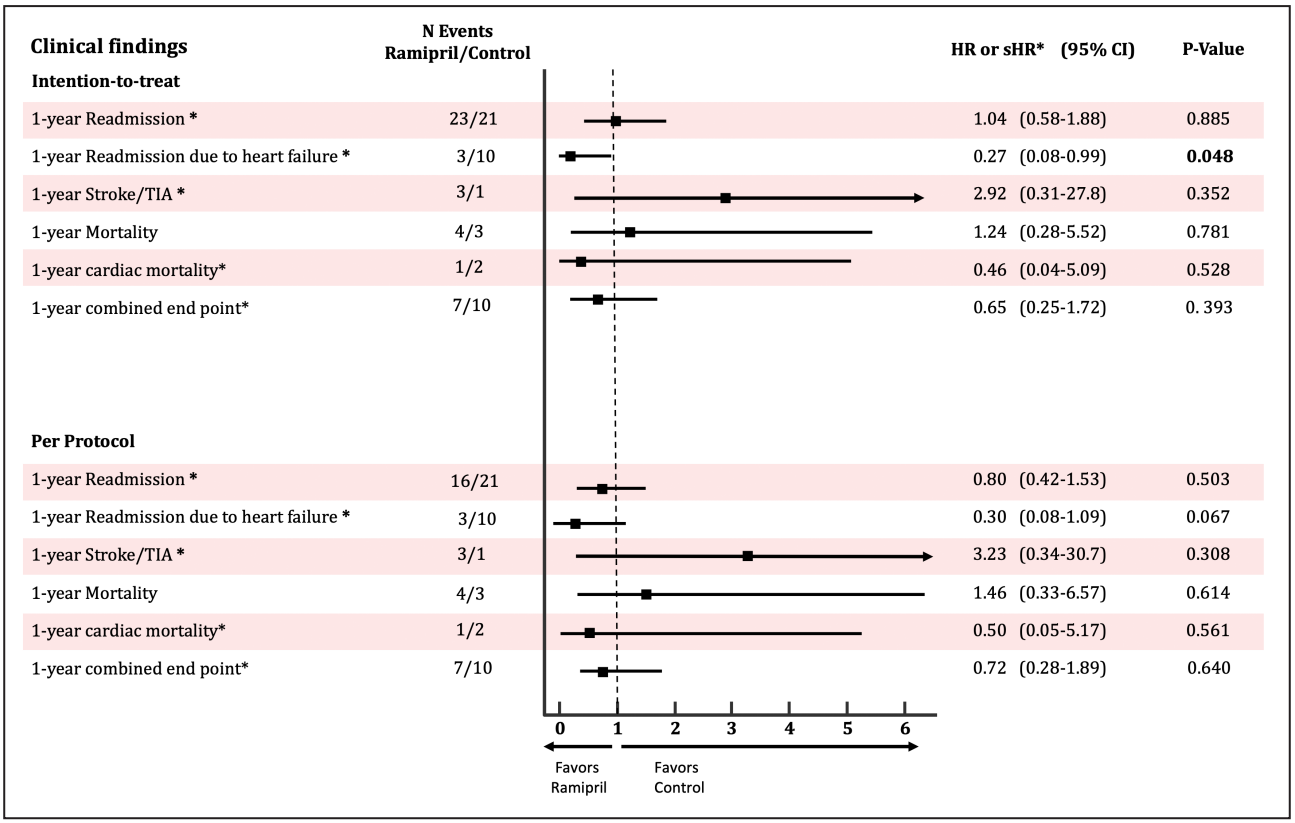

Figure 4. Summary of the main clinical outcomes of the study.
HR indicates hazard ratio; sHR, subdistribution hazard ratio; and TIA, transient ischemic attack. *Outcomes where sHR was used.

hypertrophy poorly correlates with the severity of the stenosis,[2] which suggests alternative mechanisms.

Second, the presence and degree of fibrosis has been associated with worse prognosis in patients with AS.[7] The renin-angiotensin system also plays a crucial role in the generation of fibrosis,[8] and RASi can decrease its degree.[9] Our study did not demonstrate a reduction in myocardial fibrosis at 1 year, but prior research suggests that fibrosis, as opposed to the early reversibility of hypertrophy, might need beyond 6 to 12 months to occur following aortic valve replacement.[10] These medications may inhibit the production of profibrotic factors, such as transforming growth factor-beta and connective tissue growth factor, which are involved in the development of myocardial fibrosis.[14] In addition, RASi may stimulate the production of antifibrotic factors, such as matrix metalloproteinases, which can break down scar tissue. However, after aortic valve replacement up to 26% of patients did not experience reverse remodeling, as demonstrated by late gadolinium enhancement measured by CMR.[7] Recently, Treibel et al[8] also found that focal replacement fibrosis persists 1 year after SAVR. Both studies suggest that, despite the benefits of stenosis relief, myocardial fibrosis is an ongoing problem often irreversible after valve replacement independently associated with poor outcomes.

Third, blood pressure reduction by itself can have a positive effect in the prognosis, not only by reduction in the hypertrophy (which, as mentioned, is an independent effect of RASi) but also because of better control of risk factors.[5] Indeed, in the group of patients treated with ramipril, mean pressure was significantly lower than in the control group (96±31 versus 108±36 mm Hg, P <0.001) as measured in the 1-year follow-up clinical visit. However, pressure reduction is probably not the target of ramipril in normotensive patients harboring a TAVI device, given that prior observational investigations suggested an increase in survival in patients receiving RASi even without differences in blood pressure measurements,[11] and a randomized trial in asymptomatic patients with moderate or severe AS also demonstrated left ventricular mass reduction with no differences in blood pressure values.[6]

In addition, RASi have an antiarrhythmic effect caused by an increase of potassium blood levels. AS represents an arrhythmogenic substrate, and prior research with captopril already demonstrated a reduction in the arrhythmic risk.

Another more controversial effect of RASi is mediated by a reduction in the degree of calcification of the aortic valve.[13] Due to the artifact caused by the prosthesis in the imaging tests, this hypothesis cannot

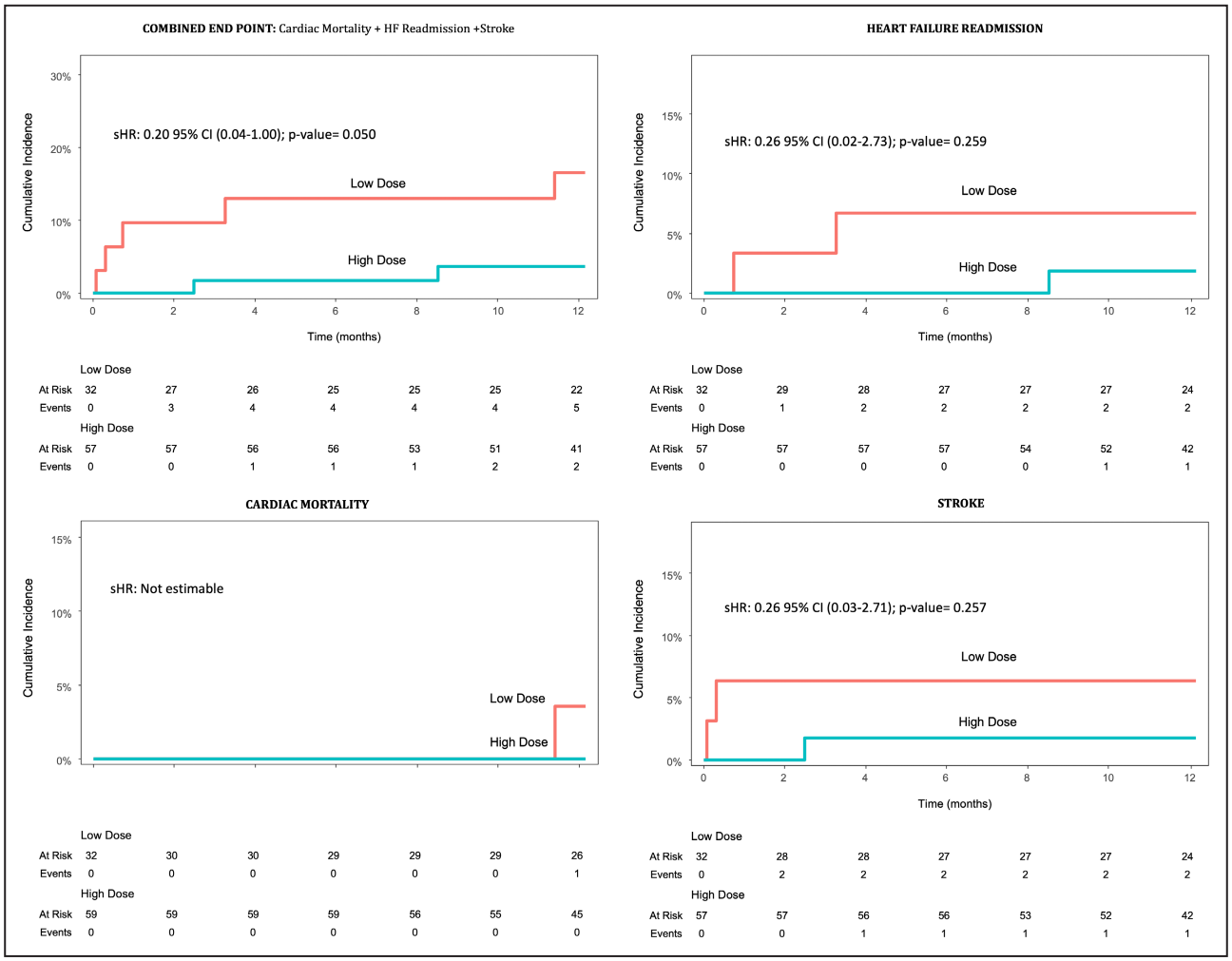

Figure 5. Outcomes according to ramipril dose in the treatment group.
HF indicates heart failure; and sHR, subdistribution hazard ratio.

be confirmed but it could help to achieve better long-term results in terms of prosthesis expansion and hemodynamics.

Finally, the HOPE study demonstrated that RASi can decrease the risk of myocardial infarction and ischemic stroke by stabilization of atherosclerotic plaques as an independent mechanism.[14] How plaque stabilization occurs is still unknown, but it has been suggested that it might be caused by an increase in the synthesis of collagen type 3.[17–19]

Long-Term Outcomes

No benefit was seen in mortality at 1-year follow-up with the use of ramipril in our investigation. Previous research suggested benefit in cardiovascular mortality that was particularly appreciated at 3-year follow-up.[6] Inohara et al[20] analyzed 21 312 Medicare patients, and there was a suggestion of lower risk of mortality in the short-term and lower risk of HF in patients receiving a prescription of RASi at hospital discharge. With a longer follow-up of 2 years, Ochiai et al[13] also demonstrated, in a cohort of 560 patients who underwent TAVI, lower mortality amongst patients treated with RASi. The benefit might be more limited, however, in patients with preserved ejection fraction as those included in our research. Our serial imaging evaluation helped in understanding how reverse left ventricular remodeling might be underlying the improved prognosis in this population. The reduction of HF readmissions is a remarkable finding; although those with lower LVEF at discharge presented a greater HF readmission rate at 1 year (33.3% versus 6.2%, hazard ratio=7.066 [95% CI, 1.386–36.031]; *P*=0.019), they were equally distributed amongst the ramipril and the control group, suggesting that the effect of ramipril on readmissions is independent from the post-TAVI LVEF. The analysis also suggested this independent effect of ramipril when adjusted, taking into consideration the CHADS2VASC or the STS scores. In addition, a greater rate of readmissions was detected in the first 6 months after discharge. Several factors might explain this trend

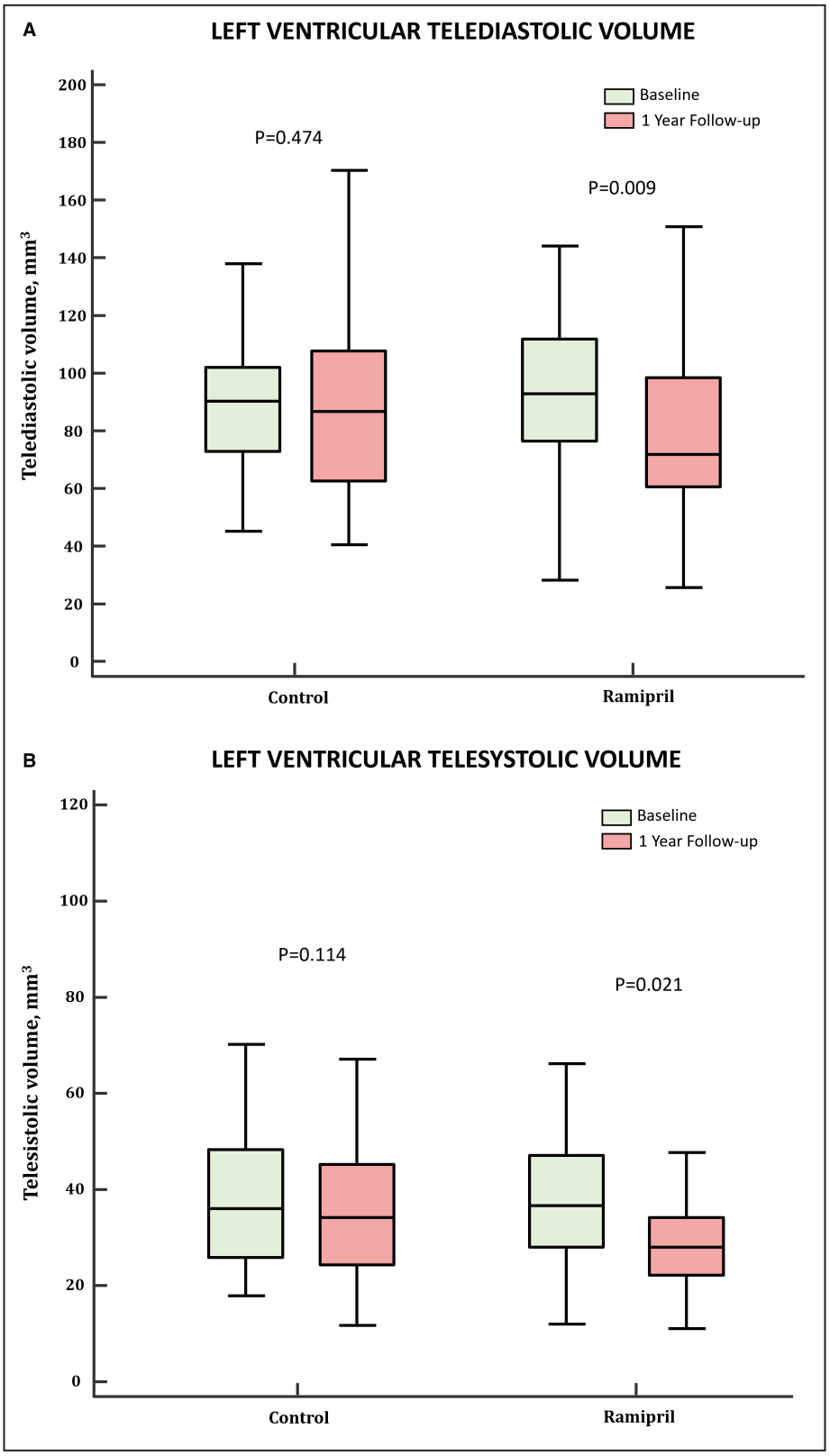

Figure 6. Outcomes according to ramipril dose in the treatment group.
(A) Left ventricular telediastolic volume and **(B)** left ventricular telesystolic volume. HF indicates heart failure; and sHR, subdistribution hazard ratio.

Table 3. Changes from Baseline to 1-y Follow-Up in Cardiac Magnetic Resonance Parameters

Variables	Global study population (n=186)	Intention-to-treat			Per protocol		
		RASi (n=94)	No-RASi (n=92)	*P* value	RASi (n=85)	No-RASi (n=92)	*P* value
Cardiac magnetic resonance							
Δ End-diastolic volume of LV, mL	−12.0 [−25.0 to 2.50]	−13.0 [−23.5 to 5.0]	−11.0 [−26.0 to 1.0]	0.059	−13.0 [−23.5 to 5.0]	−11.0 [−27.0,2 to 0]	0.043*
Δ End-systolic volume of LV, mL	−6.0 [−17.0 to 2.0]	−9.0 [− 17.5 to 0]	−6.0 [−13.5 to 3.5]	0.390	−9.0 [− 17.5 to 0]	−6.0 [−14.0 to 4.0]	0.034*
Δ LVEF, %	2.0 [−2.0 to 8.0]	2.0 [−2.0 to 8.0]	1.5 [−0.5 to 8.5]	0.625	2.0 [−2.0 to 8.0]	1.5 [−0.5 to 8.5]	0.808
Δ Myocardial mass of LV, g	−15.5 [−31.0 to −4.0]	−11.5 [−24.0 to −3.0]	−21.3 [−34.5 to −6.0]	0.187	−12.5 [−27.5 to −3.5]	−21.3 [−34.5 to −6.0]	0.265
Δ Maximal septal width of LV, mm	−1.0 [2.0 to 0.0]	−1.0 [−2.0 to 0.0]	−1.0 [−2.0 to 0.0]	0.867	−1.0 [−1.8 to 0.0]	−1.0 [−2.0 to 0.0]	0.953
Δ End-diastolic volume of RV, mL	−4.50 [−20.0 to 11.0]	−3.0 [−23.0 to 13.0]	−6.5 [−19.0 to 7.5]	0.475	−4.5 [−23.0 to 12.5]	−6.5 [−19.0 to 7.5]	0.640
Δ End-systolic volume of RV, mL	−2.0 [−9.0 to 6.0]	−2.0 [−10.0 to 6.0]	−2.5 [−8.5 to 5.5]	0.987	−2.5 [−11.0 to 6.0]	−2.5 [−8.5 to 5.5]	0.748
Δ RVEF, %	0.0 [−3.0 to 6.0]	0.5 [−3.0 to 6.0]	0.0 [−3.5 to 5.5]	0.868	0.5 [−3.0 to 6.0]	0.0 [−3.5 to 5.5]	0.730
Δ Aortic regurgitant volume, mL	−0.6 [−2.97, 1.99]	0.11 [−1.15, 1.91]	−1.30 [−4.10, 3.24]	0.276	0.11 [1.15, 1.91]	−1.30 [−4.10, 3.24]	0.276
Δ Aortic regurgitant fraction, %	−1.0 [−5.0 to 4.0]	0.0 [−3.0 to 4.0]	4.0 [−6.5 to 4.5]	0.215	0.0 [−3.0 to 4.0]	4.0 [−6.5 to 4.5]	0.215
Δ Aortic regurgitant volume, mL (descending aorta)	−0.6 [−3.9 to 2.2]	−1.30 [−3.2 to 1.1]	0.15 [−4.6 to 4.8]	0.499	−1.30 [−4.0 to 0.8]	0.15 [−4.6 to 4.8]	0.448
Δ Aortic regurgitant volume, % (descending aorta)	−1.0 [−6.0 to 4.0]	−1.0 [−4.0 to 1.0]	0.0 [−8.0 to 6.5]	0.579	−1.0 [−4.0 to 1.0]	0.0 [−8.0 to 6.5]	0.522
Δ Myocardial fibrosis mass, g	−0.42 [1.69 to 0.11]	−0.53 [−3.15 to −0.11]	−0.10 [−1.69 to 0.11]	0.594	−0.53 [−3.15 to −0.11]	−0.10 [−1.69 to 0.11]	0.594
Δ Percentage of myocardial fibrosis according to global LV mass, %	−0.25 [−1.34 to 0.32]	−0.62 [−1.84 to 0.34]	0.18 [−0.34 to 0.57]	0.143	−0.62 [−1.84 to −0.34]	0.18 [−0.34 to 0.57]	0.143
Echocardiography							
Δ Left atrial diameter	2.5 [−3.0 to 7.0]	0.5 [−2.0 to 5.0]	5.5 [−5.0 to 8.5]	0.999	0.5 [−2.0 to 5.0]	5.5 [−5.0 to 8.5]	0.999
Δ Left ventricular end-diastolic diameter	1.5 [−6.0 to 4.0]	−1.0 [−6.0 to 3.0]	3.0 [−5.5 to 4.5]	0.177	−0.5 [−5.5 to 3.0]	3.0 [−5.5 to 4.5]	0.242
Δ Left ventricular end-systolic diameter	0.5 [−4.0 to 4.0]	−2.0 [−4.5 to 4.0]	1.0 [−2.0 to 4.0]	0.385	−1.0 [−4.0 to 5.0]	1.0 [−2.0 to 4.0]	0.578
Δ Interventricular septal thickness, mm	0.0 [−2.0 to 1.0]	0.0 [−3.0 to 2.0]	0.0 [−2.0 to 1.0]	0.836	0.0 [−3.0 to 2.0]	0.0 [−2.0 to 1.0]	0.987
Δ Left ventricular ejection fraction, %	0.0 [−5.0 to 8.0]	1.0 [−4.5 to 8.0]	0.0 [−5.0 to 7.0]	0.699	1.0 [−5.0 to 8.0]	0.0 [−5.0 to 7.0]	0.729
Δ Peak velocity, m/s	0.0 [−0.4 to 0.3]	−0.1 [−0.4 to 0.3]	0.0 [−0.35 to 0.20]	0.739	−0.1 [−0.4 to 0.2]	0.0 [−0.35 to 0.20]	0.559
Δ Peak gradient, mm Hg	0.0 [−5.0 to 3.0]	−1.0 [−6.0 to 2.0]	0.0 [−5.0 to 3.5]	0.268	−1.0 [−6.0 to 1.0]	0.0 [−5.0 to 3.5]	0.177
Δ Mean gradient, mm Hg	−1.0 [−3.0 to 2.0]	1.0 [−4.0 to 1.0]	0.0 [−2.0 to 2.0]	0.113	−1.0 [−4.0 to 1.0]	0.0 [−2.0 to 2.0]	0.056
Δ End-diastolic volume, mm^3	−10.4 [−31.2 to 12.0]	−15.0 [36.2 to −8.0]	3.5 [−27.5 to 16.5]	0.079	−15.0 [−37.6 to −8.5]	3.5 [−27.5 to 16.5]	0.044*
Δ End-systolic volume, mm^3	−6.0 [−12.2 to 2.0]	−8.8 [−15.5 to −1.5]	5.0 [−12.0 to 5.0]	0.284	−9.8 [−16.0 to −5.0]	5.0 [−12.0 to 5.0]	0.205

LVEF indicates left ventricular ejection fraction; RASi, renin-angiotensin system inhibitors; and RVEF, right ventricular ejection fraction. Δ was calculated as 12-mo follow-up minus baseline.

*Significant *p*-value (i.e. $p<0.05$).

to early readmissions, including nosocomial infections, postbleeding anemia, or new-onset arrhythmias that are known predictors of HF decompensation.[21]

Limitations

The open-label design and the lack of placebo group due to pragmatic design entailed a risk of reporting bias regarding the trial outcomes. The coronavirus disease 2019 pandemic affected the outpatient clinic follow-up routine and may have resulted in underassessment of laboratory data and mild-to-moderate clinical events. In this regard, we reported lack of differences between the study groups during the outbreak of the coronavirus disease.[22] The trial-drug discontinuation may have had competing risks in relation to the outcomes we studied, and we did not perform competing-risk analyses. Our trial results apply only to patients with symptomatic AS, preserved left ventricular function, and deemed candidates for TAVI, involving a population of selected older adults. These results may not apply to younger patients at lower operative risk or patients with asymptomatic AS. Patients with LVEF between 40% and 50% might have had indication of angiotensin-converting enzyme inhibitor according to current evidence, but only represented 12.5% of the sample with even distribution amongst groups, precluding further conclusions.

In conclusion, the administration of ramipril after TAVI in patients with preserved LVEF did not meet the primary end point but was associated with a reduction in the 1-year HF re-admission rate without significant differences in mortality or reverse myocardial fibrosis at 1 year. The higher dose of ramipril was associated with a lower rate of the primary end point and HF readmissions as compared with lower doses. Predetermined 3-year follow-up will be performed to confirm these findings.

ARTICLE INFORMATION

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Drs San Román and Amat-Santos designed and supervised the Study. All authors supervised the development of the study within their institutions. Itziar Gómez and Manuel Carrasco-Moraleja performed the interim and final statistical analysis. All authors approved the final version.

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Disclosures

None.

Supplemental Material

Data S1
Video S1

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