ORIGINAL RESEARCH

Antihypertensive Treatment With β-Blockade in Patients With Asymptomatic Aortic Stenosis and Association With Cardiovascular Events

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Background—Patients with aortic stenosis (AS) often have concomitant hypertension. Antihypertensive treatment with a β-blocker (Bbl) is frequently avoided because of fear of depression of left ventricular function. However, it remains unclear whether antihypertensive treatment with a Bbl is associated with increased risk of cardiovascular events in patients with asymptomatic mild to moderate AS.

Methods and Results—We did a post hoc analysis of 1873 asymptomatic patients with mild to moderate AS and preserved left ventricular ejection fraction in the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study. Propensity-matched Cox regression and competing risk analyses were used to assess risk ratios for all-cause mortality, sudden cardiac death, and cardiovascular death. A total of 932 (50%) patients received Bbl at baseline. During a median follow-up of 4.3±0.9 years, 545 underwent aortic valve replacement, and 205 died; of those, 101 were cardiovascular deaths, including 40 sudden cardiovascular deaths. In adjusted analyses, Bbl use was associated with lower risk of all-cause mortality (hazard ratio 0.5, 95% confidence interval 0.3-0.7, $P<0.001$), cardiovascular death (hazard ratio 0.4, 95% confidence interval 0.2-0.7, $P<0.001$), and sudden cardiac death (hazard ratio 0.2, 95% confidence interval 0.1-0.6, $P=0.004$). This was confirmed in competing risk analyses (all $P<0.004$). No interaction was detected with AS severity (all $P>0.1$).

Conclusions—In post hoc analyses Bbl therapy did not increase the risk of all-cause mortality, sudden cardiac death, or cardiovascular death in patients with asymptomatic mild to moderate AS. A prospective study may be warranted to determine if Bbl therapy is in fact beneficial.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00092677. **(*J Am Heart Assoc*. 2017;6: e006709. DOI: 10.1161/JAHA.117.006709.)**

Key Words: aortic valve stenosis • arrhythmia (heart rhythm disorders) • atrial fibrillation • β-blocker • high blood pressure • hypertension

Aortic stenosis (AS) represents a condition of left ventricular (LV) pressure overload resulting in neuroendocrine activation, including a heightened β-adrenergic state, reduced myocyte protein synthesis, and extracellular matrix degradation comparable to heart failure.[1] This cardiovascular-valvular coupling is important because there is little evidence of the ability of cardiotropic drugs to improve outcomes in patients with AS.[2] Moreover, hypertension is a frequent finding in patients with AS, and we have recently shown the importance of lowering blood pressure on reducing adverse

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Accompanying Data S1 and Tables S1 through S3 are available at http://jaha.ahajournals.org/content/6/12/e006709/DC1/embed/inline-supplementary-material-1.pdf

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Received August 10, 2017; accepted September 11, 2017.

Clinical Perspective

What Is New?

- β-Blockade seems safe in patients with mild to moderate aortic stenosis.

What Are the Clinical Implications?

- β-Blockers may be used if patients develop arrhythmias and may be the drug of choice if patients with aortic stenosis develop hypertension.

cardiovascular outcome in patients with asymptomatic AS.[3] Nevertheless, the current guidelines do not specify whether antihypertensive treatment should differ from that used in patients without AS.

β-Blockers (Bbls) are interesting in this regard, as they might reduce oxygen consumption and lower blood pressure to improve survival in AS patients.[4] However, Bbls may also pose a danger of reduced inotropy in AS, and evidence for the safety and efficacy of Bbl use in AS is scarce. This study was therefore undertaken to investigate the association of Bbls with risk of cardiovascular and all-cause mortality as well as of sudden cardiac death during long-term follow-up in the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study, which is, to date, the largest cohort of patients with asymptomatic mild to moderate AS.

Methods

The SEAS study was a randomized, multicenter, double-blind, placebo-controlled study investigating whether intensive lipid lowering with simvastatin plus ezetimibe in combination versus placebo in 1873 patients (45-85 years of age) with asymptomatic AS (defined as echocardiographic aortic valve thickening accompanied by Doppler-measured aortic peak flow velocity between 2.5 and 4.0 m/s, normal LV systolic function, and absence of symptoms according to independent local investigators based on patient interviews) could decrease AS progression and associated risk of cardiovascular morbidity and mortality. Patients were excluded if they had received a diagnosis or had symptoms of coronary artery disease, heart failure, peripheral arterial disease, cerebrovascular disease, or diabetes mellitus or if they had any other condition requiring lipid-lowering therapy. The primary outcome, design, and baseline characteristics of the SEAS study have been published.[5,6] In this report post hoc analyses were used to investigate the association between baseline use of Bbls (as reported by the study investigators at enrollment into the study) and subsequent mortality and cardiovascular outcomes. The SEAS study and its substudies comply with the Declaration of Helsinki; locally appointed ethics committees have approved the research protocol, and informed consent has been obtained. The SEAS trial is registered at http://ClinicalTrials.gov, unique identifier NCT00092677.

Echocardiography

The echocardiographic study protocol, reading procedures, and reproducibility have been published.[7] Briefly, all echocardiograms were read blinded at the SEAS Echocardiographic Core Laboratory, Haukeland University Hospital, Bergen, Norway. Aortic valve area indexed by body surface area was calculated by applying the continuity equation.[8,9] LV dimensions and wall thicknesses were measured on 2-dimensional images according to American Society of Echocardiography guidelines using an anatomically validated formula. The aortic valve area and LV mass, both indexed by body surface area, and the LV ejection fraction were determined by standard 2D-echocardiography.[10,11]

End Points and Adjudication

All end points were evaluated according to a predefined endpoint protocol by an independent end-point classification committee blinded to the randomization as outlined by the SEAS steering committee.[6] The primary outcome in this post hoc substudy was all-cause mortality. Secondary end points were cardiovascular and sudden cardiac death. Exploratory analyses were performed on other end points including major cardiovascular events, a composite of first myocardial infarction, nonhemorrhagic stroke, heart failure, aortic valve replacement (AVR), or cardiovascular death and the individual components of major cardiovascular events as well as coronary artery bypass grafting (CABG) and percutaneous coronary intervention.

Statistical Analysis

SAS statistical software package version 9.4 for PC (SAS Institute Inc, Cary, NC) was used for statistical analysis. Continuous variables are presented as mean±standard deviation and categorical data as number and percentages. Variables not normally distributed are presented as medians with interquartile ranges. Differences in categorical variables were evaluated by chi-squared tests, and thode in continuous variables by the Student t test or Wilcoxon test as appropriate. Changes in echocardiographic parameters, heart rate, and systolic blood pressure according to Bbl therapy were examined by t test on changes in values from baseline to the last recorded. To assess the independent effect of baseline Bbl use on end points, a propensity score for baseline Bbl therapy was quantified by multivariate

logistic regression analysis. Covariates for the propensity model were selected by examining the combination of pertinent predictor variables that resulted in the optimal prediction of baseline Bbl use (see Data S1 and Table S1 for predictor variables). To avoid excluding patients who missed 1 or more baseline variables included in the propensity score, missing variables were imputed according to age- and sex-specific strata. Using the Greedy matching macro (http://www.mayo.edu/research/departments-divisions/department-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros), we matched each case to 1 control on the basis of the propensity score. Kaplan-Meier and Cox regression analyses on the matched data set were performed to approximate the independent effect of baseline Bbl therapy. Competing risk analyses were performed as described by Fine and Gray using all-cause mortality as a competing event to evaluate if the difference in survival altered the risk of nonexclusive end points.[12] Comprehensive sensitivity analyses were performed by (1) tests of interaction between Bbl therapy and baseline variables presumed to have an influence on the effect of Bbl therapy (hypertension at baseline, blood pressure levels [<120, 120-140, and >140 mm Hg], in-study myocardial infarction, AVR, or AS severity); (2) use of multivariable Cox regression; (3) use of an inverse-probability-weighted Cox model (using 1/propensity for Bbl therapy), (4) inclusion of the time-varying effects of AVR with and without CABG as separate effects in the propensity score–matched Cox model; and (5) adjustment of the propensity-matched Cox model with time-updated blood pressure (last prior to end point or censoring) to evaluate if Bbl-induced blood pressure lowering explained the observed survival benefit.

A 2-tailed $P<0.05$ was regarded as statistically significant.

Results

Baseline Characteristics

Among 1873 patients included in the SEAS study, 932 (49.8%) patients received Bbl at baseline. Hypertension was by far the main indication (56%) for Bbl therapy, and metoprolol was the most frequently used Bbl (see Tables S2 and S3 for details).

Bbl therapy was associated with higher age, systolic and diastolic blood pressure, body mass index, high-density lipoprotein, triglyceride, glucose, peak aortic velocity, LV mass, and left atrial diastolic and systolic volume. In addition, Bbl therapy was associated with a higher prevalence of hypertension at baseline and with use of digoxin, platelet inhibitors, Ca^{2+}-blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, and diuretics, and with previous atrial fibrillation (Table 1). The propensity-matched subset was well balanced on all examined baseline variables (Table 1).

Echocardiographic Variables, Heart Rate, and Blood Pressure in Patients Treated With Bbl

From first to last available in-study value, Bbl-treated patients showed a 2% larger decrease in systolic blood pressure (Figure 1, $P=0.006$) and a 2% greater reduction in LV ejection fraction ($P=0.04$). Change values of LV mass, aortic valve area index, aortic peak jet velocity, and heart rate did not differ between patients receiving and those not receiving Bbl therapy at baseline (all $P>0.38$).

Association of β-Blockade With Outcomes

During a median follow-up of 4.3±0.9 years, 205 died (102 [11%]) in the Bbl group versus 103 [11%] in the control group); of those, 101 suffered cardiovascular deaths (52 [6%]) in the Bbl group versus 49 [5%] without Bbl) (Table 2), and 40 died of sudden cardiac death (15 [2%] in the Bbl group versus 25 [3%] without Bbl).

Bbl was associated with lower risk of all-cause and cardiovascular mortality in inverse-probability-weighted and propensity-matched analyses (Table 3 and Figure 2), as well as sudden cardiac death (Table 3). There was no detectable difference according to Bbl therapy on the risk of myocardial infarction, stroke, or heart failure before AVR or percutaneous coronary intervention in propensity-matched analyses (Table 3). Conversely, Bbl was associated with increased risk of major adverse cardiovascular events, largely driven by a doubling in the use of AVR with and without concomitant CABG (Table 3).

Competing risk analyses with all-cause mortality as a competing event on the propensity-matched subset confirmed the results from the cause-specific Cox models (Table 3). To test whether Bbl associations with mortality were dependent on hypertension at baseline, in-study myocardial infarction, AVR, or AS severity, interaction analyses were performed in propensity-matched Cox models with all-cause mortality as the end point. This showed no interaction of Bbl treatment and risk of all-cause mortality between patients with and those without previous hypertension ($P=0.244$), blood pressure levels ($P=0.3$), in-study myocardial infarction ($P=0.825$), in-study AVR ($P=0.926$), or baseline peak aortic jet velocity ($P=0.140$).

Finally, to test whether Bbl treatment outcome was explained by effects on blood pressure or a higher propensity for AVR and concomitant CABG among patients receiving Blb therapy, additional analyses of the propensity-matched Cox models found that Bbl remained significantly associated with all-cause mortality after adjustment for in-treatment systolic

Table 1. Baseline Characteristics According to β-Blocker Therapy

Variable	Total Population (n = 1873)			Propensity-Matched (n = 1030)		
	No β-Blockade (n=941)	+β-Blockade (n=932)	*P* Value	No β-Blockade (n=515)	+β-Blockade (n=515)	*P* Value
Clinical parameters						
Age, y	66.5±9.9	68.6±9.1	<0.001	67.9±9.4	67.7±9.4	0.83
Men, n (%)	594 (63%)	556 (60%)	0.12	319 (62%)	298 (57%)	0.18
Resting heart rate, min^{-1}	64.9±10.0	65.0±10.6	0.70	66.0±10.5	65.0±10.4	0.10
Systolic blood pressure, mm Hg	142.2±19.0	147.5±21.0	<0.001	145.8±19.1	144.9±20.6	0.49
Diastolic blood pressure, mm Hg	81.2±9.7	82.9±10.7	<0.001	82.3±9.9	82.1±10.9	0.74
Baseline hypertension, n (%)	358 (38%)	607 (65%)	<0.001	292 (57%)	282 (55%)	0.53
Body mass index, kg/m^2	26.4±4.2	27.4±4.4	<0.001	26.8±4.5	27.1±4.4	0.38
Prior atrial fibrillation, n (%)	42 (4%)	135 (14%)	<0.001	41 (8%)	45 (9%)	0.65
Peak aortic jet velocity, m/s	3.0±0.5	3.1±0.5	<0.001	3.1±0.5	3.1±0.5	0.99
Left ventricular ejection fraction, %	65.7±7.0	65.8±7.5	0.92	65.5±7.0	66.2±7.7	0.19
Left ventricular mass index, g/m^2	96.7±26.2	101.8±27.8	<0.001	100.1±27.3	99.6±26.7	0.78
Left atrial diastolic volume, mL	32 (24-38)	35 (27-42)	<0.001	33 (24-38)	34 (25-40)	0.10
Left atrial systolic volume, mL	65 (52-71)	67 (59-78)	<0.001	65 (54-71)	67 (56-73)	0.25
Biochemistry						
Creatinine	92.6±14.7	94.2±15.5	0.03	93.6±15.5	93.7±15.7	0.89
eGFR, mL/min per 1.73 m^2	68.3±12.3	67.4±12.4	0.25	68.3±12.3	67.4±12.4	0.25
Glucose, mmol/mL	5.2±0.7	5.4±0.8	<0.001	5.3±0.8	5.3±0.7	0.92
High-density lipoprotein, mmol/L	1.53±0.44	1.45±0.41	<0.001	1.49±0.43	1.48±0.42	0.79
Low-density lipoprotein, mmol/L	3.61±0.92	3.59±0.91	0.66	3.61±0.94	3.65±0.93	0.54
Apolipoprotein B, mmol/L	1.30±0.26	1.31±0.27	0.35	1.31±0.26	1.31±0.26	0.84
Triglycerides, mmol/L	1.16 (0.90-1.63)	1.29 (1.00-1.83)	<0.001	1.20 (0.92-1.71)	1.25 (0.97-1.80)	0.06
Medicine						
Digoxin, n (%)	9 (1%)	41 (4%)	<0.001	9 (2%)	16 (3%)	0.16
Platelet inhibitor, n (%)*	324 (34%)	530 (57%)	<0.001	252 (49%)	242 (47%)	0.53
Ca^{2+}-blocker, n (%)	172 (18%)	331 (36%)	<0.001	170 (33%)	155 (30%)	0.31
Renin-angiotensin system inhibitor, n (%)	301 (32%)	469 (50%)	<0.001	223 (43%)	239 (46%)	0.32
Diuretics, n (%)	277 (29%)	569 (61%)	<0.001	239 (46%)	230 (46%)	1.00

blood pressure (hazard ratio 0.52, 95% confidence interval 0.43-0.62, *P*<0.001) and time-varying AVR with and without concomitant CABG (hazard ratio 0.54, 95% confidence interval 0.45-0.65, *P*<0.001).

Discussion

This is the first study with a sufficient sample size to evaluate the association of Bbl therapy with cardiovascular end points in asymptomatic mild to moderate AS. The primary finding was that in propensity-matched analyses and inverse-probability adjustment, Bbl therapy was not associated with worse outcome but instead with lower rates of all-cause and cardiovascular death as well as sudden cardiac death. Furthermore, Bbl treatment was not associated with an increased incidence of heart failure before AVR. These findings were confirmed in competing risk analyses with all-cause mortality as a competing event. Thus, this study supports the notion that Bbls are a safe antihypertensive treatment option in patients with asymptomatic mild to moderate AS and preserved LV ejection fraction.

Of note, Bbl was associated with higher rates of major cardiovascular events, almost exclusively driven by a doubling in the use of AVR. This could potentially be driven by reverse causation with Bbl being prescribed to frail patients with higher systolic blood pressure and a more critical condition

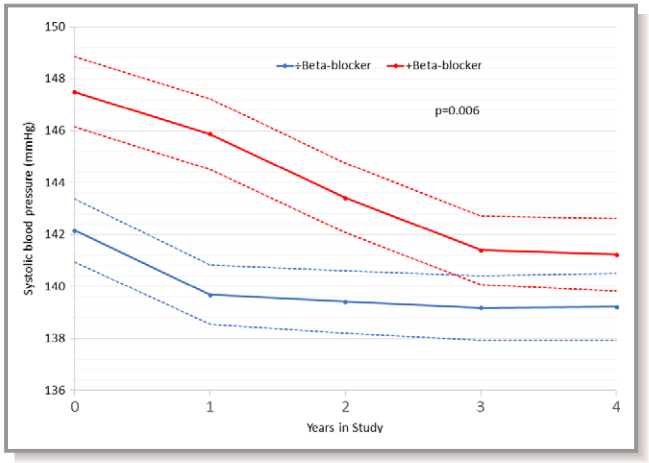

Figure 1. In-treatment systolic blood pressure and confidence intervals according to β-blockade.

such as mildly impaired LV function, atrial fibrillation, and/or subclinical ischemic heart disease. Unfortunately, CT or coronary angiograms were not available to examine the latter assumption further. Another mediating factor could be a possible Bbl-induced functional impairment, which could be misclassified as a symptom of AS progression to elicit earlier AVR.[13]

To compare our findings to previous literature, there are few studies of Bbl therapy in AS patients. In a study of 453 patients with nonsurgically managed severe AS, Varadarajan et al showed that among the patients not undergoing AVR, Bbl was not associated with a survival benefit.[4] Although the present study was comprised of patients with asymptomatic AS, we found no interaction of Bbl treatment with either AS severity or time-varying AVR per se and risk of all-cause mortality.

There are several possible explanations for potential benefits of Bbl therapy in AS patients. First, among older patients with AS, hypertension is common, found in up to 78% of patients.[7] Hypertension significantly modulates LV mass and geometry[14] and is a well-known predictor of increased cardiovascular morbidity and mortality in both the general and AS populations.[15,16] In hypertension, Bbl is known to not only lower the blood pressure but also regress LV mass and alter LV geometry, probably due to the decrease in LV load,[17] which is associated with better survival in hypertensive patients.[14] However, adjustment for in-treatment systolic blood pressure did not change the observed lower rate of mortality, and we did not find interaction with hypertension in the present study. In patients with increased pressure load due to hypertension, Bbl not only regresses LV dimensions in patients with LV hypertrophy but also wall stress and a noninvasive index of myocardial oxygen demand,[18] and the latter was accompanied by lower rates of cardiovascular death and myocardial infarction. This provides indirect support for the conclusion that the known reduction of morbidity and mortality in survivors of myocardial infarction by Bbl treatment[19] could be caused by the reduction of myocardial oxygen demand due to lower blood pressure, heart rate, and myocardial inotropic state. Nevertheless, we were unable to show regression of LV mass in the Bbl-treated patients in the current study despite a significant decrease in arterial blood pressure. This may not be surprising because AS, unlike hypertension, is a major component of increased

Table 2. The Proportion of Patients Meeting End Points According to β-Blocker Therapy

	Total Population (n=1873)			Propensity-Matched (n=1030)		
End Point	No β-Blockade (n=941)	+β Blockade (n=932)	*P* Value*	No β-Blockade (n=515)	+β-Blockade (n=515)	*P* Value*
MCE, n (%)	224 (24%)	464 (50%)	<0.001	160 (31%)	223 (43%)	<0.001
All-cause mortality, n (%)	103 (11%)	102 (11%)	0.90	74 (14%)	37 (7%)	<0.001
Cardiovascular death, n (%)	49 (5%)	52 (6%)	0.65	38 (7%)	14 (3%)	<0.001
Sudden cardiac death, n (%)	25 (3%)	15 (2%)	0.11	19 (4%)	4 (1%)	0.004
AVR, n (%)	156 (17%)	389 (42%)	<0.001	105 (20%)	194 (38%)	<0.001
CABG, n (%)	31 (3%)	138 (15%)	<0.001	26 (5%)	58 (11%)	<0.001
Nonhemorrhagic stroke, n (%)	20 (2%)	42 (5%)	0.006	16 (3%)	15 (3%)	0.90
Myocardial infarction, n (%)	16 (2%)	36 (4%)	0.007	14 (3%)	22 (4%)	0.21
HF before AVR, n (%)	14 (1%)	34 (4%)	0.005	11 (2%)	10 (2%)	0.74
PCI, n (%)	5 (1%)	20 (2%)	0.005	5 (1%)	9 (2%)	0.31
Unstable angina, n (%)	3 (0%)	10 (1%)	0.07	3 (1%)	3 (1%)	0.97

AVR indicates aortic valve replacement; CABG, coronary artery bypass grafting; HF, heart failure; MCE, major cardiovascular events; PCI, percutaneous coronary intervention.
**P*-values reflect univariate Cox regression for the individual end points according to β-blocker therapy.

Table 3. Propensity-Adjusted and Propensity-Matched Hazard Ratios for Adverse End Points According to β-Blocker Therapy Use

	Full Data Set (n=1873)			Propensity-Matched (n=1030)	
End Point	Univariate	Multivariable	IPTW	Univariate	Competing Risk*
MCE, n (%)	2.5 (2.1-2.9, *P*<0.001)	2.4 (2.0-2.9, *P*<0.001)	1.7 (1.4-2.0, *P*<0.001)	1.5 (1.2-1.8, *P*<0.001)	1.5 (1.2-1.8, *P*<0.001)
All-cause mortality, n (%)	1.0 (0.7-1.3, *P*=0.90)	0.9 (0.6-1.3, *P*=57)	0.6 (0.4-0.8, *P*=0.002)	0.5 (0.3-0.7, *P*<0.001)	NA
Cardiovascular death, n (%)	1.1 (0.7-1.6, *P*=0.65)	0.9 (0.5-1.4, *P*=0.50)	0.6 (0.4-1.0, *P*=0.03)	0.4 (0.2-0.7, *P*<0.001)	0.4 (0.2-0.7, *P*=0.001)
Sudden cardiac death, n (%)	0.6 (0.3-1.1, *P*=0.11)	0.6 (0.2-1.3, *P*=0.21)	0.3 (0.2-0.7, *P*=0.003)	0.2 (0.1-0.6, *P*=0.004)	0.2 (0.1-0.6, *P*=0.004)
AVR, n (%)	2.9 (2.4-3.5, *P*<0.001)	2.0 (1.6-2.5, *P*<0.001)	2.1 (1.7-2.5, *P*<0.001)	2.0 (1.6-2.5, *P*<0.001)	2.1 (1.6-2.6, *P*<0.001)
CABG, n (%)	4.7 (3.2-6.9, *P*<0.001)	4.5 (2.8-7.1, *P*<0.001)	2.6 (1.7-4.0, *P*<0.001)	2.2 (1.4-3.5, *P*<0.001)	2.3 (1.4-3.7, *P*<0.001)
Nonhemorrhagic stroke, n (%)	2.1 (1.2-3.6, *P*=0.006)	2.0 (1.4-4.0, *P*=0.049)	1.2 (0.6-2.1, *P*=0.60)	0.9 (0.4-1.8, *P*=0.90)	0.9 (0.5-1.9, *P*=0.86)
Myocardial infarction, n (%)	2.3 (1.3-4.1, *P*=0.007)	1.9 (0.9-4.0, *P*=0.11)	1.3 (0.7-2.6, *P*=0.40)	1.5 (0.8-3.0, *P*=0.21)	1.6 (0.8-3.1, *P*=0.17)
HF before AVR, n (%)	2.4 (1.3-4.5, *P*=0.005)	3.7 (2.0-6.8, *P*<0.001)	1.2 (0.6-2.4, *P*=0.58)	0.9 (0.4-2.0, *P*=0.74)	0.9 (0.4-2.2, *P*=0.84)
PCI, n (%)	4.0 (1.5-10.7, *P*=0.005)	5.3 (1.5-18.6, *P*=0.009)	2.0 (0.7-5.7, *P*=0.21)	1.8 (0.6-5.2, *P*=0.31)	1.8 (0.6-5.4, *P*=0.29)
Unstable angina, n (%)	3.3 (0.9-12.1, *P*=0.07)	3.73 (0.78-17.84, *P*=0.10	1.5 (0.4-6.2, *P*=0.55)	1.0 (0.2-4.8, *P*=0.97)	1.0 (0.2-5.0, *P*=0.99)

AVR indicates aortic valve replacement; CABG, coronary artery bypass grafting; HF, heart failure; IPTW, inverse probability of treatment–weighted Cox regression analysis; MCE, major cardiovascular events; NA, not applicable (patients are matched as shown in Table 1); PCI, percutaneous coronary intervention.
*Fine and Gray estimates of the subdistribution of risk using all-cause mortality as a competing event.

LV load and stimulus to LV hypertrophy in AS patients not directly affected by Bbl therapy.

Second, there is evidence that severe valvular disorders produce humoral and cytokine activation similar to heart failure, suggesting a potential role for neurohormonal blockade with Bbls.[20,21] In a study with 14 patients undergoing transcatheter aortic valve implantation and 14 matched controls, Dumonteil et al showed that AS patients had increased sympathetic nervous system activity associated with a decrease in sympathetic baroreflex gain, and that AVR normalized these parameters. Hence, progression and prognosis of AS could be related to both hemodynamic impairment and sympathoexcitation with additional impairment of baroreflex restraint of sympathetic tone. This autonomic dysfunction may contribute to high incidences of sudden death, mortality, and morbidity in AS patients and also be a target for Bbl therapy.[22]

Third, hemodynamically significant AS results in LV hypertrophy and eventually in LV systolic and diastolic dysfunction and overt clinical heart failure. AS may also predispose to mitral regurgitation and left atrial enlargement leading to atrial fibrillation[23] and increase the risk of sudden death,[24] the most feared event in the watchful waiting strategy in asymptomatic AS patients. In the SHIFT (Systolic Heart failure treatment with the sinoatrial node inhibitor ivabradine Trial),[25] ivabradine was associated with an 18% lower risk of the primary composite end point of cardiovascular death or hospitalization for worsening heart failure in patients with heart failure. Our group previously demonstrated that increased heart rate is associated with adverse outcomes in patients with asymptomatic AS[26]; thus, the lower mortality among Bbl-treated patients in the present study might be due, at least in part, to Bbl heart rate–reducing properties.

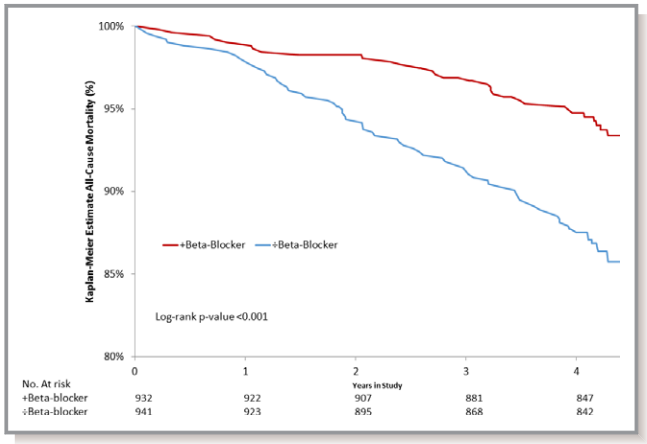

Figure 2. Kaplan-Meier plot for all-cause mortality in the propensity-matched subset.

Finally, Bbl therapy has been a cornerstone secondary prevention therapy for patients with myocardial infarction since large randomized controlled trials conducted in the 1970s and 1980s demonstrated substantial reductions in mortality, mostly driven by sudden cardiac death.[27] It therefore is possible that even though SEAS patients were free from overt coronary disease, Bbl may have prevented clinical events due to unrecognized concomitant coronary atherosclerosis.

Data on cardiovascular outcome using different antihypertensive drug regimens in patients with AS are scarce; we have previously reported from the SEAS data set that treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was not associated with increase or improvement in all-cause or cardiovascular mortality as well as sudden cardiac death even though treatment with this drug class did reduce blood pressure and LV hypertrophy.[28] Our previous report on angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and our current study on Bbl are in sharp contrast to our preliminary report on antihypertensive treatment with diuretics, suggesting increased all-cause and cardiovascular mortality in patients with asymptomatic AS.[29] Thus, the present study refutes the concept that Bbl treatment of hypertension is hazardous in AS patients and supports current clinical practice to use Bbls when needed in AS patients. However, randomized controlled studies are missing on other antihypertensive drugs in head-to-head comparison with Bbl.

Limitations

Our study is a post hoc analysis of a randomized controlled trial rather than a prespecified trial of Bbl effects. The preventive association of Bbl on mortality could possibly be explained by Bbl patients using other antihypertensive drugs, calcium channel blockers, statins, aspirin, and other medical treatment. However, other medical treatments were included in analyses, and our propensity-matched data set was shown to be well balanced with regard to all concomitant therapies. Nevertheless, there are still covariates that are difficult to balance, such as doctor preferences. In addition, there is a risk of unmeasured confounding, such as selection bias with Bbl being completely avoided in the sickest patients. However, the SEAS study population included ambulatory patients with normal LV ejection fraction without overt atherosclerotic disease. Unfortunately, we could not perform any meaningful analyses of in-study add-on Bbl treatment because patients' characteristics were not ascertained when patients went on and off Bbl therapy. Finally, because variable Bbl use was reported by the individual study investigators, it was not possible to independently control whether patients were in fact on Bbl therapy.

Conclusions

In this large study of asymptomatic patients with mild to moderate AS, Bbl therapy, in contrast to clinical concern, was associated in adjusted analyses with lower rates of cardiovascular and all-cause mortality as well as sudden cardiac death in propensity-matched analyses. Thus, use of Bbl as antihypertensive therapy is safe in patients with asymptomatic AS.

Acknowledgments

We thank the SEAS study investigators. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Sources of Funding

The SEAS study was funded by an unrestricted grant from Merck & Co, Inc. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the article and its final contents.

Disclosures

Drs Boman, Nienaber, Ray, Rossebø, and Wachtell were on the SEAS steering committee and received honoraria from Merck & Co, Inc, the funding sponsor of the SEAS study. The remaining authors report no conflicts.

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SUPPLEMENTAL MATERIAL

Data S1.

Predictors used for building propensity score for beta-blocker therapy.

Age, sex, baseline systolic and diastolic blood pressure, baseline hypertension, prior mitral valve incompetence, prior atrial fibrillation, prior supraventricular tachycardia, prior arrhythmia, prior palpitations, prior sinus bradycardia, prior angina pectoris, prior left bundle branch block, prior ventricular hypertrophy, baseline left atrial systolic and diastolic volume, baseline left ventricular end-diastolic volume, left ventricular internal diastolic diameter, systolic posterior wall thickness, baseline aortic peak velocity, stress-corrected mid wall shortening, left ventricular outflow-tract mean velocity, PQ-interval, QTc-interval, baseline universal ST-segment depression, baseline medical treatment including: angiotensin converting enzyme-inhibitor, diuretics, calcium antagonist, angiotensin receptor blocker, aspirin or other platelet inhibitor; baseline biochemistry including baseline fasting plasma remnant-like particle cholesterol, hematocrit, creatinine, alkaline phosphatase, creatinine phosphokinase, high density lipoprotein, sodium, total bilirubin, white blood cells, high sensitivity C-reactive protein, chloride, thyroid-stimulating hormone, glucose, aspartate aminotransferase.

Table S1. Most important predictors of beta-blocker therapy: ranked by standardized coefficients.

Analysis of Maximum Likelihood Estimates			
Parameter	**chi-square**	**p-value**	**Standardized coefficients***
Baseline hypertension	69.6269	<.0001	-0.3006
Concomitant ASA/other platelet inhibitor	50.7172	<.0001	-0.2754
Concomitant diuretics	62.9185	<.0001	-0.2392
Prior atrial fibrillation	35.629	<.0001	-0.1914
Prior angiotensin receptor blocker	17.7232	<.0001	0.1291
Prior aspirin or other platelet inhibitor	10.4506	0.0012	0.1243
Aortic peak velocity (m/s)	15.4572	<.0001	0.1147
Prior supraventricular tachycardia	8.9624	0.0028	-0.0936
High density lipoprotein	9.2468	0.0024	-0.0902
Prior Arrhythmia	6.5118	0.0107	-0.0827
Systolic blood pressure (mmHg)	5.6171	0.0178	0.0725
Prior ACE inhibitor	4.6823	0.0305	0.0692
Baseline glucose (mmol/l)	4.693	0.0303	0.064

Standardized coefficients are coefficients adjusted so that that may be interpreted as having the same, standardized scale and the magnitude of the coefficients can be directly compared (ranked). The greater the absolute value of the standardized coefficient, the greater the predicted change in the probability of the outcome given a standardized change in the corresponding predictor variable, holding constant the other predictors in the model.

Abbreviations – ASA: acetylsalicylic acid, ACE: Angiotensin converting enzyme.

Table S2. Indications of beta-blocker treatment.

Indication	%
Hypertension	55.8
Atrial fibrillation	17.5
Arrhythmia* or palpitations	9.8
Angina	3.4
Aortic stenosis	1.5
Heart Failure	1.5
Tremor	1.2
Acute myocardial infarction	1
Atherosclerosis	0.7
Migraine	0.7
Aorta aneurism	0.3
Aortic valve replacement	0.3
Dyspnea	0.2
Other/unspecified	7.6

* Including sick sinus syndrome, sinus tachycardia, ventricular extrasystoles, ventricular tachycardia and unspecified tachycardia.

Table S3. Beta-blocker types.

Indication	%
Metoprolol	48
Bisoprolol	19
Atenolol	16
Sotalol	6
Carvedilol	5
Propranolol	3
Nebivolol	1
Pindolol	<1
Celiprolol	<1
Talinolol	<1
Betaxolol	<1
Acebutolol	<1

Antihypertensive Treatment With β–Blockade in Patients With Asymptomatic Aortic Stenosis and Association With Cardiovascular Events

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J Am Heart Assoc. 2017;6:e006709; originally published November 27, 2017;
doi: 10.1161/JAHA.117.006709
The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980