Short-term hemodynamic effect of angiotensin-converting enzyme inhibition in patients with severe aortic stenosis: A placebo-controlled, randomized study

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Background In patients with severe aortic stenosis (AS), treatment with angiotensin-converting enzyme inhibitors has previously been considered contraindicated. However, there is a lack of clinical evidence to confirm these potential hemodynamic risks and benefits.

Methods Forty-four patients with severe AS (aortic valve area <1 cm^2) were randomized to treatment with trandolapril 22 mg daily/placebo (1:1). Right heart catheterization and echocardiography were performed at rest and during exercise at baseline and on day 3. Follow-up was performed before valve replacement or after a maximum of 8 weeks, when exercise echocardiography was repeated.

Results Compared with placebo, systolic blood pressure and systemic arterial compliance significantly changed at day 3 (–14 ± 11 vs –5 ± 13 mm Hg, $P = .02$, and 0.08 ± 0.16 vs –0.05 ± 0.86 mL/m^2 per mm Hg, $P = .03$, respectively). Changes in left ventricular end systolic volume (LVESV) was nonsignificant (–8 ± 9 vs –3 ± 11 mL, $P = .17$). At a median of 49 days of follow-up, changes in LVESV and N-terminal pro-brain natriuretic peptide were even lower revealing significant differences between the groups (–7.8 ± 2.6 vs –0.5 ± 2.5 mL, $P = .04$, and –19 ± 7 vs 0.8 ± 6 pmol/L, $P = .04$, respectively). No episodes of symptomatic hypotension were noted, and other hemodynamic parameters remained unchanged.

Conclusion Angiotensin-converting enzyme inhibition in severe AS caused a decrease in LVESV and N-terminal pro-brain natriuretic peptide with other hemodynamic parameters preserved both at rest and during exercise implying hemodynamic improvement with left ventricular unloading. (Am Heart J 2014;167:226-34.)

Aortic stenosis (AS) due to calcification of the aortic valve is a common disease, affecting 2% to 9% of the elderly.[1] With increasing life expectancy, the prevalence of AS is expected to rise in the future. Hitherto, no disease-modifying drug has been identified, and the only effective treatment available is aortic valve replacement. Along with progression of the valve stenosis, structural changes of the left ventricle (LV) may occur that allow adaptation to the increase in afterload. This includes development of hypertrophy and eventually fibrosis of LV and the subsequent impairment of systolic and diastolic function. Angiotensin-converting enzyme inhibitors (ACE-Is) might reduce these changes by inhibiting the renin-angiotensin system, and potential benefits to the aortic valve and the LV have been suggested.[2-6] However, there are some concerns about its use. In severe AS, treatment with ACE-I has been considered contraindicated, due to the theoretical possibility that arterial vasodilatation in combination with fixed valve obstruction might result in an increase in the transaortic gradient, resulting in hypotension and thereby myocardial hypoperfusion and a subsequent decrease in cardiac output, especially during exercise. To date, however, there has been no clinical evidence to confirm these potential risks or benefits with respect to hemodynamic characteristics. We performed a prospective double-blinded study investigating the safety and acute

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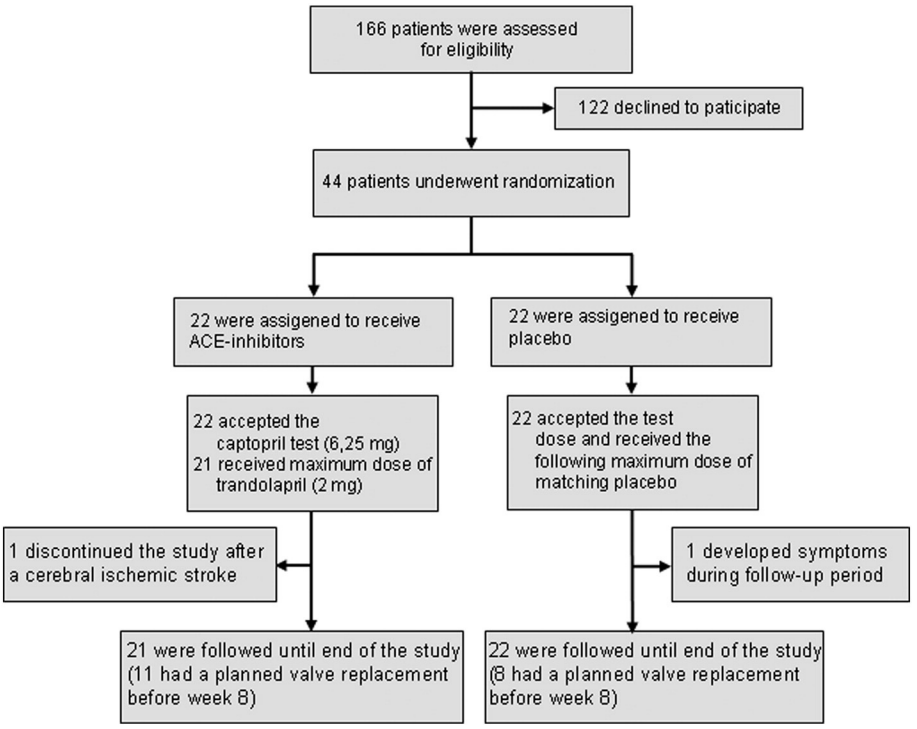
Figure 1



Consort diagram.

hemodynamic effects of ACE-I treatment in patients with severe symptomatic and asymptomatic AS.

Methods

Study population

Patients with *severe AS*, defined as an aortic valve area <1 cm^2, being in sinus rhythm and without symptoms at rest, who had been referred for aortic valve replacement were recruited at the Department of Cardiology, Rigshospitalet, Denmark, between November 2005 and December 2009. Patients were grouped as symptomatic or asymptomatic. Symptomatic individuals were those with angina pectoris, dizziness, syncope at exertion, or those who were classified as New York Heart Association (NYHA) functional classes II to IV by a study-independent cardiologist. We excluded patients with mitral regurgitation; those unable to perform exercise testing; and those with resting a systolic blood pressure (BP) <100 mm Hg, known renal artery stenosis or creatinine >200 μmol/L, or who had received treatment with ACE-Is or angiotensin receptor blockers during the previous month. We recorded the complete medical history, including the presence of diabetes, hypertension, and chronic obstructive pulmonary disease. A coronary angiogram was performed as part of the planned diagnostic workup of the patients, and the extent of coronary artery disease was recorded. Patients were consecutively screened, by which process we identified 166 eligible individuals, of whom 44 agreed to participate in this extensive protocol (Figure 1). The invasive nature of the study was the main reason for patient refusal. The study is registered at www.clinicaltrials.gov, with the ClinicalTrials.gov Identifier: NCT00252317.

End points

The prespecified primary end point was the acute hemodynamic effects of ACE-I treatment, including systolic and diastolic parameters, at rest and during exercise, measured invasively by a Swann-Ganz catheter (cardiac output [CO], stroke volume [SV], and pulmonary capillary wedge pressure [PCWP]) and noninvasively by echocardiography (LV ejection fraction, LV end systolic volume [LVESV], and E/e'). The primary safety end point was symptomatic hypotension, including syncope or a systolic BP <90 mm Hg or a drop in systolic BP of >40 mm Hg during treatment. Secondary outcomes were changes in systemic BP, systemic arterial compliance (SAC), valvuloarterial impedance (Z_{VA}), N-terminal pro-brain natriuretic peptide (NT-proBNP), and exercise capacity. All noninvasive parameters were measured again at follow-up, when reports of adverse events were also recorded.

Study design

The study was performed as a randomized, placebo-controlled, double-blinded trial. Patients were randomized in a 1:1 fashion in blocks of 12 to receive either an ACE-I or a placebo (Figure 1). Randomization was performed by the Copenhagen County Hospital Pharmacy, and the trial was fully monitored according to the rules for good clinical practice operating in the