Are angiotensin converting enzyme inhibitors beneficial in patients with aortic stenosis?

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Angiotensin converting enzyme (ACE) inhibitors may become an accepted form of treatment for aortic stenosis in the future

Among the various causes for aortic stenosis (AS), so called “degenerative” is the most common and accounts for the majority of aortic valve replacements performed in the USA. Our understanding of “degenerative” AS has dramatically changed in recent years. Previously felt to be a “wear and tear” phenomenon and the mere consequence of the aging process, we now know that “degenerative” AS represents an active disease process with many similarities to atherosclerosis. These similarities include clinical risk factors (hypertension, tobacco use, and raised cholesterol values) and pathologic findings (inflammatory cells, deposition of calcium and atherogenic lipoproteins).

**RAAS AND AORTIC STENOSIS**

In 2002, O’Brien et al reported that angiotensin converting enzyme (ACE) and angiotensin II were present within the aortic valve leaflets in patients with AS and were absent in those with normal aortic valves. These histologic findings provided further evidence that “degenerative” AS involves an active disease process and suggested a possible role for the renin-angiotensin-aldosterone system (RAAS) in disease pathogenesis. The observation that ACE and angiotensin II co-localised within the valve lesions suggested that ACE within the valve was enzymatically active. Helske et al extended these findings by demonstrating that angiotensin II type 1 receptors were also present in stenotic aortic valves and largely absent in normal aortic valves.

**RAAS AND ATHEROSCLEROSIS**

The RAAS and angiotensin II are involved in a number of biologic processes that promote atherosclerosis. Angiotensin II has been detected in coronary plaques, coronary atheterectomy specimens, and primate models of atherosclerosis. In animal and primate models of atherosclerosis, blockage of the RAAS via ACE inhibitors and angiotensin receptor blockers (ARBs) reduces the development of atherosclerotic lesions. Angiotensin II has a number of pro-inflammatory effects that may also be involved in aortic valve disease including acting as a chemotactic agent for monocytes, thereby attracting macrophages into valve lesions, enhancing the uptake of modified low density lipoprotein (LDL) into macrophages, and altering the fibrinolytic system via plasminogen activator inhibitor-1. These deleterious effects of angiotensin II may promote both inflammation and fibrosis and contribute to disease progression within the aortic valve.

Given the clinical and pathologic similarities between AS and atherosclerosis, the presence of components of the RAAS within AS lesions, the role of angiotensin II in atherosclerosis, and the clear benefits of ACE inhibitors in patients with atherosclerosis, it would seem plausible that ACE inhibitors may also be beneficial in patients with AS. However, there is considerable reluctance to administer vasodilator treatment to patients with hemodynamically significant AS. While there is little firm evidence in the literature, vasodilator treatment is thought to be harmful as the stenotic aortic valve orifice may prevent an adequate increase in cardiac output resulting in coronary hypoperfusion and systemic hypotension. Therefore, there is a widely held belief that ACE inhibitors and other forms of vasodilator treatment are contraindicated in the setting of hemodynamically significant AS.

**INITIAL STUDIES OF ACE INHIBITORS AND AORTIC STENOSIS**

The first series of patients to systematically receive an ACE inhibitor for AS was performed by Martinez Sanchez et al in 1996. Twenty two patients with critical AS, seven of whom had congestive heart failure, received the ACE inhibitor captopril. Baseline and sequential hemodynamic assessment with a Swan-Ganz catheter showed beneficial effects with a significant decrease in systemic vascular resistance and cardiac filling pressures and an increase in cardiac index. Several other recent trials have also documented the safety and short term efficacy of ACE inhibitors in patients with AS (table 1). O’Brien et al evaluated 13 elderly patients with mild to moderate AS (aortic jet velocity 2.5–4.0 m/s) and uptitrated the ACE inhibitor ramipril to a maximum dose of 7.5 mg twice a day. Two patients required discontinuation of ACE inhibitor treatment; one for asymptomatic hypotension and one for a reversible increase in creatinine of 0.3 mg/dl. The authors concluded that short term ACE inhibitor treatment was well tolerated. However, the most significant adverse effect was a reversible increase in creatinine.

**Abbreviations:** ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; AS, aortic stenosis; LDL, low density lipoprotein; RAAS, renin-angiotensin-aldosterone system

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The study by Jiménez-Candil et al\(^\text{23}\) in this issue of *Heart* adds further support to the concept that ACE inhibitors are safe and may provide short term benefit to patients with AS. Twenty patients with AS and hypertension were entered into the study protocol after they tolerated an ACE inhibitor for at least three months. Patients were evaluated at baseline and following drug withdrawal with a Doppler echocardiogram and a symptom limited stress echocardiogram. During ACE inhibitor treatment, patients had a lower systolic and an unchanged diastolic blood pressure at rest, a higher aortic valve Doppler jet velocity, and an unchanged aortic valve area. Exercise stress testing during ACE inhibitor treatment showed a higher stroke volume, no change in the exercise induced increase in systolic blood pressure, and a trend towards a higher diastolic blood pressure. Following withdrawal of ACE inhibitor treatment, exercise duration and energy expenditure were unchanged. Because of concerns regarding the hazards of ACE inhibitor treatment during exercise in AS patients, an important parameter of the study was the exercise blood pressure response. Five patients had an abnormal exercise blood pressure response; in two patients on ACE inhibitor treatment, the abnormal blood pressure response was caused by excessive vasodilation in one patient and a fall in stroke volume in the other patient. In summary, this study demonstrated that ACE inhibitors are generally well tolerated and improve stress haemodynamics in the majority of hypertensive AS patients.

As the authors acknowledge, there are several limitations to this study: (1) patients enrolled in the study protocol had already documented tolerance to an ACE inhibitor for at least three months creating a selection bias and making conclusions regarding the ability of all AS patients to tolerate an ACE inhibitor problematic; (2) the specific ACE inhibitor used was not standardised and six different agents were used; (3) all patients included had coexisting hypertension; and (4) only short term safety and exercise data were evaluated.

**THE FUTURE**

Before ACE inhibitors are considered acceptable treatment for patients with AS, additional studies are required. Randomly selected, large numbers of patients with AS need to be randomised against an ACE inhibitor or placebo in order to determine true rates of tolerability and safety. For patients with significant AS and no cardiovascular symptoms, ACE inhibitor treatment would ideally be well tolerated, safe, and delay the onset of cardiovascular symptoms. For patients with AS, cardiovascular symptoms, and no contraindications to surgical aortic valve replacement, initiating any form of long term medical treatment would be problematic. This group of patients derives significant benefit from surgical replacement of the aortic valve and medical treatment would therefore pose significant risk.\(^\text{24}\) For symptomatic AS patients, it would therefore be difficult to define optimal trial end points—perhaps for patients refusing surgery or those with prohibitive operative risks, ACE inhibitor treatment could be randomised against usual care with clinical end points of severity of heart failure and angina, occurrence of syncope, and time to death.

Many concepts and treatments in the care of cardiovascular patients have changed in recent years. β Blockers which were previously felt to be contraindicated for patients with congestive heart failure and reduced left ventricular function are now standard, first line treatment. While the current studies demonstrating safety and short term efficacy of ACE inhibitors in patients with severe, symptomatic AS to placebo or enalapril,

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**Table 1** Studies evaluating ACE inhibitors in patients with aortic stenosis

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n</th>
<th>Symptoms</th>
<th>EF</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Summary of findings</th>
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<tbody>
<tr>
<td>Martinez Sanchez, 1996</td>
<td>22</td>
<td>Yes</td>
<td>Normal</td>
<td>Critical AS(^*)</td>
<td>AR; CI to RHC; previous ACE use</td>
<td>(1) Captopril up to 25 mg orally three times daily improved cardiovascular filling pressures and haemodynamics</td>
</tr>
<tr>
<td>O’Brien, 2004</td>
<td>13</td>
<td>No</td>
<td>Normal</td>
<td>Mild to moderate AS(^*)</td>
<td>CAD; ▽ LV function; ACEI intolerance; current ACEI use</td>
<td>(2) Ramipril up to 7.5 mg twice daily was well tolerated</td>
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<tr>
<td>Chockalingam, 2004</td>
<td>56</td>
<td>Yes</td>
<td>Normal and reduced</td>
<td>Severe AS; NYHA II or IV</td>
<td>SBP &gt; 90 mm Hg; MBP &lt; 60 mm Hg; severe MS; baseline low BP; ACEI intolerance; Cr &gt; 2.5 mg/dl</td>
<td>(1) BP in 3 of 5 patients with LV dysfunction and ACEI use; (2) Enalapril up to 10 mg twice daily was well tolerated, improved symptoms and 6 minute walk distance</td>
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<tr>
<td>Jiménez-Candil, 2004</td>
<td>20</td>
<td>No</td>
<td>&gt; 45%</td>
<td>Moderate to Severe AS; HTN; current ACE use</td>
<td>Prior cardiac surgery; other valve lesions greater than mild in severity</td>
<td>(1) Exercise induced and/or syncope uncommon with ACEI</td>
</tr>
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ACEI, angiotensin converting enzyme inhibitor; AR, aortic regurgitation; CAD, coronary artery disease; CI, contraindication; Cr, serum creatinine; EF, ejection fraction; HTN, hypertension; LV, left ventricular; MBP, mean blood pressure; MS, mitral stenosis; NYHA, New York Heart Association; RHC, right heart catheterisation; SBP, systolic blood pressure.

\(^*\)Aortic valve area < 0.75 cm\(^2\), peak to peak gradient > 50 mm Hg; aortic valve Doppler jet velocity 2.5 to 4.0 m/s; aortic valve area < 0.75 cm\(^2\), mean aortic gradient > 50 mm Hg or aortic valve Doppler jet velocity > 4.5 m/s; aortic valve Doppler jet velocity > 2.5 m/s, aortic valve area < 1.2 cm\(^2\).

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The surprising finding of this study was that 30% of patients screened for study entry were already receiving an ACE inhibitor—suggesting that either their treating physician was unaware of the diagnosis of AS, or that AS patients were tolerating an ACE inhibitor without issue such that discontinuation was not necessary. Chockalingam et al\(^\text{22}\) randomised 56 patients with severe, symptomatic AS to placebo or enalapril. At one month, patients were evaluated for the occurrence of hypotension, the Borg index of dyspnoea, and six minute walk distance. Patients receiving enalapril had a significant improvement in New York Heart Association (NYHA) functional class, distance. Patients receiving enalapril had a significant improvement in New York Heart Association (NYHA) functional class, distance. Three of five patients with left ventricular systolic dysfunction experienced significant hypotension requiring discontinuation of enalapril. The authors concluded that ACE inhibitors were well tolerated and associated with improvements in functional capacity in patients with symptomatic AS. They advised caution in patients with left ventricular systolic dysfunction and baseline hypotension.

**CURRENT STUDY OF ACE INHIBITORS AND AORTIC STENOSIS**

The study by Jiménez-Candil et al\(^\text{23}\) in this issue of *Heart* adds further support to the concept that ACE inhibitors are safe and may provide short term benefit to patients with AS. Twenty patients with AS and hypertension were entered into the study protocol after they tolerated an ACE inhibitor for at least three months. Patients were evaluated at baseline and following drug withdrawal with a Doppler echocardiogram and a symptom limited stress echocardiogram. Following withdrawal of ACE inhibitor treatment, exercise duration and energy expenditure were unchanged. Because of concerns regarding the hazards of ACE inhibitor treatment during exercise in AS patients, an important parameter of the study was the exercise blood pressure response. Five patients had an abnormal exercise blood pressure response; in two patients this occurred while taking an ACE inhibitor, and in three patients while not taking an ACE inhibitor. For the two patients on ACE inhibitor treatment, the abnormal blood pressure response was caused by excessive vasodilation in one patient and a fall in stroke volume in the other patient. In summary, this study demonstrated that ACE inhibitors are generally well tolerated and improve stress haemodynamics in the majority of hypertensive AS patients.
inhibitors in AS are preliminary, these agents may become an accepted form of therapy in the future.

REFERENCES

IMAGES IN CARDIOLOGY

Distal embolisation in percutaneous saphenous vein graft intervention despite use of a polymer covered stent

A 73 year old woman presented with angina 22 years after saphenous vein grafts. All three grafts were in excellent condition, with the exception of a severe stenosis in the proximal portion of the circumflex graft (panel A). For elective percutaneous coronary intervention (PCI), a FilterWire distal protection device was deployed in the body of the graft before pre-dilatation with a 2.5 × 15 mm Maverick balloon. Aiming to minimise the risk of distal embolisation, a (self expanding nitinol) Symbiot polymer covered stent (4.0 × 20 mm) was deployed (panel B). These stents require post-inflation to optimise deployment. Following stent inflation (4.0 × 15 mm Extensor) a new filling defect (white arrow) was immediately apparent within the stent at its proximal end (panel C). Filling defects (white arrows) were also present within the FilterWire device (black arrows) (panel C). The in-stent debris was presumed to be material extruded from the proximal margin of the covered stent after high pressure inflation and was displaced to the FilterWire by multiple passages of a deflated balloon and a single further inflation. Recovered atherothrombotic debris is shown in panel D. The end angiographic result was excellent with normal flow (panel E).

This case demonstrates the potential for distal embolisation despite covered stent use, and further emphasises the importance of distal protection strategies in vein graft intervention.

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