



ACE inhibitors in aortic stenosis: no fear just hope

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Aortic stenosis (AS) due to calcification of the aortic valve is a common disease, affecting 2–9% of the elderly.¹ Due to population ageing, AS has become a serious healthcare problem for which the therapeutic options are limited and there are no 'risk-free' procedures applicable yet. Progression of AS is substantially unpredictable and highly variable from patient to patient. In addition, time to symptom onset, the tipping point from which the prognosis declines, is also highly variable. Despite feverish efforts to find reliable findings to predict progression of AS, no universal markers are available to date. Equally imprecise is our current ability to predict mortality and the best timing for surgery in asymptomatic AS. Moreover, treatments capable to slowdown or stop the fibrocalcific process taking place in the valve leaflets are lacking. Such treatments would ultimately allow prevention of haemodynamic progression and stop transition from sclerosis to stenosis, reducing morbidity and mortality.

It has been shown that calcific AS and atherosclerosis are closely related, sharing the same risk factors and common histopathological processes such as endothelial dysfunction, inflammation, fibrosis, and calcification. The existence of these common pathways has triggered studies on lipid-lowering treatments as possible strategies to mitigate AS evolution. However, all the randomized trials with statins failed to show any benefit of these drugs in terms of AS progression and outcomes. These disappointing results confirmed that calcific AS and atherosclerosis could not be targeted similarly. In atherosclerosis, lipid accumulation and inflammation play a central role in plaque formation and rupture, whereas in calcific AS, these seem to be early-phase processes that trigger, precede, and also coexist with bone-like formation processes.² Calcification is the leading actor that determines flow obstruction and poor outcome in AS, while plaque instability is linked to outcome in atherosclerosis. Therefore, statin therapy that lowers the content of lipids and favours plaque fibrosis and stabilization is expected to influence positively outcomes in atherosclerosis, but may not affect outcome in AS with ongoing valve calcification. Positron emission tomography combined with computed tomography (PET/CT) studies using ¹⁸F fluorodeoxyglucose and ¹⁸F-sodium fluoride as tracers have suggested that calcification is the predominant pathogenic process in AS and may be a more suitable target for future therapies aiming to limit AS progression.² No randomized studies testing agents that may influence bone formation pathways are currently available.

The rate of progression from asymptomatic to symptomatic, the occurrence of adverse events, and the need for aortic valve replacement

are influenced not only by the severity of valve obstruction but also by the degree of left ventricular (LV) structural/functional changes in response to chronically increased afterload (i.e. LV remodelling, hypertrophy, myocardial fibrosis, decreased longitudinal function).^{3–5} Hence, the quest of finding treatment strategies that may positively influence outcomes in AS may be extended to treatment strategies designed to preserve myocardial geometry and function.

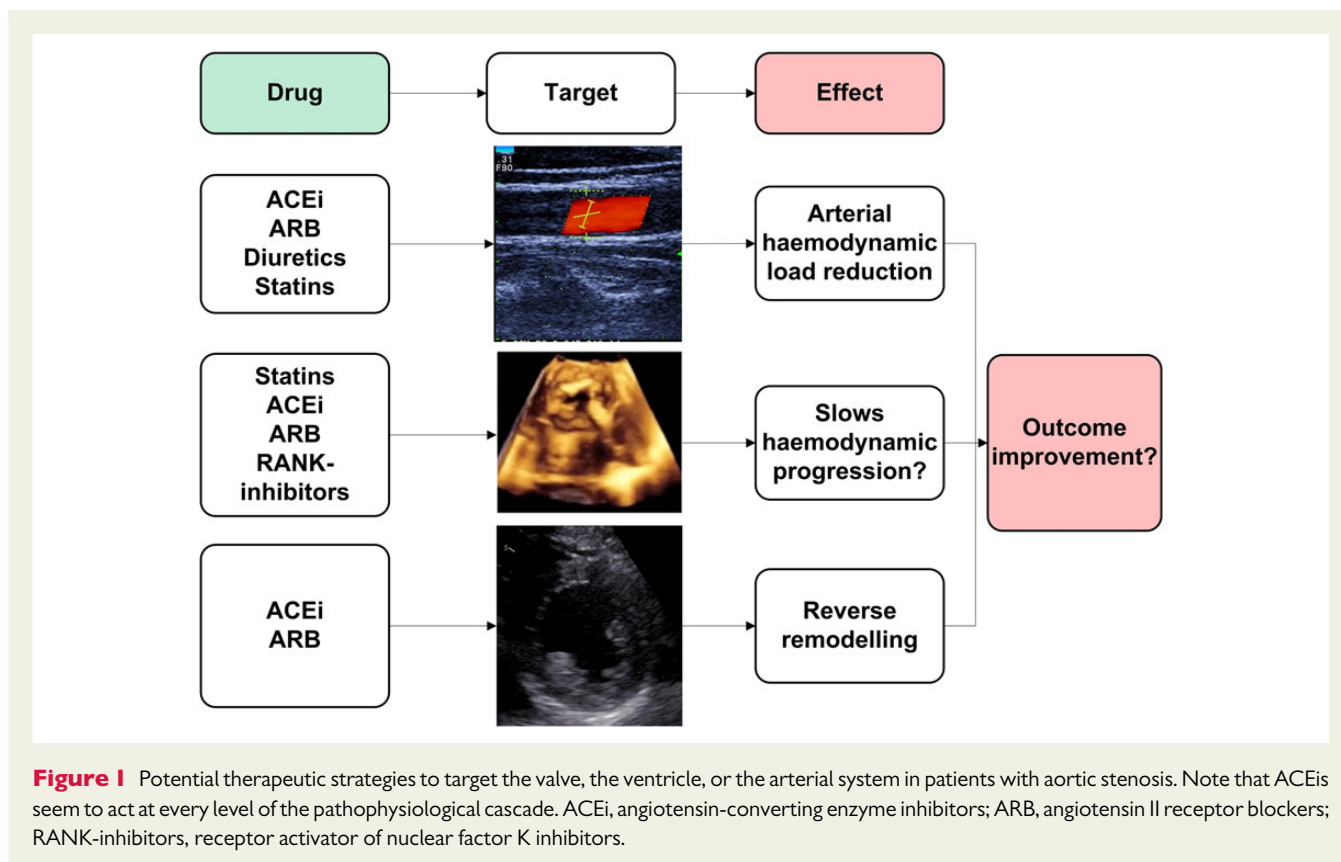
In patients with heart failure and systemic hypertension, angiotensin-converting enzyme inhibitors (ACEis) can regress LV hypertrophy and myocardial fibrosis, irrespective of their blood pressure-lowering effects, particularly through decreased angiotensin II (ATII) levels.⁶ In AS, evolving changes in LV structure are dynamically involved into the progression from compensatory hypertrophy to LV dysfunction and heart failure. Myocyte apoptosis and fibrosis play an important role in this transition. Hence, ACEi, by influencing extracellular matrix content, including the collagen network, could hypothetically revert the LV remodelling process. Recently, a decrease in LV end-systolic volume and brain natriuretic peptide (BNP) was reported in AS patients randomized to ACEis vs. placebo. An ACEi-mediated LV unloading effect with a decrease in systemic vascular resistance and subsequent benefits to the aortic valve and LV function were suggested as potential mechanistic effects.⁷ Although this study included a small number of patients ($n = 44$) and was limited by a short-term follow-up, it confirmed and extended previous retrospective data.⁸ In an animal mice model, administration of ATII resulted in a significant thickening of the aortic valve leaflets, suggesting that ATII may also play a direct role in leaflet fibrosis.⁹ Moreover, in histological studies on human stenotic explanted valves, both ATII and ACE were expressed, supporting their role in valve remodelling in humans.¹⁰ Interestingly, chymase, another enzyme that produces ATII, but not influenced by ACEi, is also expressed in stenotic aortic valves.¹¹ This might partially explain discordant effects of angiotensin receptor blockers (ARB) and ACEi on AS progression.^{10,12,13} In fact, ACEi might not be able to influence the chymase produced ATII in the aortic valve leaflets.^{12,13}

In this issue of the journal, Bull *et al.*¹⁴ examined, in a randomized placebo controlled study (RIAS study), the impact of ramipril, an ACEi, on the degree of LV hypertrophy, the change in LV systolic function, the regression of myocardial fibrosis, and the haemodynamic progression of AS. A total of 100 patients with moderate to severe AS were randomly assigned to ramipril (2.5–10 mg ad) vs. placebo. Assessments of myocardial strain (by the tagging technique), the level of fibrosis (diffuse and replacement), and the myocardial

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perfusion reserve were performed by cardiac magnetic resonance (CMR) at 6- and 12-month follow-up. Haemodynamic progression of AS was assessed by both CMR and transthoracic echocardiography. Exercise tolerance was evaluated by an exercise treadmill test. The results showed a progressive (change over the year) significant reduction in LV mass (primary end point) as assessed by CMR. The secondary end points (changes in parameters of LV physiology, aortic valve area by CMR, BNP levels or exercise tolerance) were not statistically significant between groups.

First merit of this study is to confirm that ACEis are well tolerated and can be safely used in AS. Fears to the use of ACEi in patients with significant AS, theoretical danger of myocardial hypoperfusion and syncope caused by afterload reduction, have been typically associated with underuse of these drugs. ACEi can thus be prescribed with very few risks in AS.

Second, this study showed that ramipril had the potential to reduce LV mass at 1-year follow-up, irrespective of its blood pressure-lowering result. This effect was surprisingly independent of any significant change in myocardial fibrosis severity. The ramipril group also showed a trend towards a slower progression of AS, as assessed by CMR planimetered aortic valve area. Nonetheless, the lack of any statistically significant difference regarding haemodynamic progression of AS between groups might be related to the use of an ACEi with little effects on the aortic valve leaflets metabolic activity, the methodology used to assess subtle changes in valve stenotic status, limited follow-up period, or underpowered sample size.

Third, the RIAS study was not designed to evaluate the effects of ramipril on outcome. It concerned a small number of patients

followed up over 1 year. A larger trial is thus required to determine whether the observed physiological changes (i.e. LV hypertrophy regression) are confirmed and might translate into improved clinical outcomes. In such a larger randomized trial, the evaluation of new biomarkers of extracellular matrix turnover, the use of imaging modalities targeting aortic valve metabolic activity (inflammation, lipid accumulation) (PET/CT), and a direct comparison ACEi/ARB might strengthen the added value of medical treatment in AS. The ongoing ROCK-AS trial (NCT00699452) using candesartan (ARB) vs. placebo in AS will only partially address this appeal.

In conclusion, the use of ACEi in AS might modulate the complex interplay between the LV, the valve, and the systemic vascular system (Figure 1). However, although the data of the RIAS study are promising, routine use of ACEis in patients with asymptomatic AS cannot be systematically recommended at this time.

Conflict of interest: none declared.

References

- Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM *et al.* Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. *J Am Coll Cardiol* 2013;**62**:1002–12.
- Dweck MR, Jones C, Joshi NV, Fletcher AM, Richardson H, White A *et al.* Assessment of valvular calcification and inflammation by positron emission tomography in patients with aortic stenosis. *Circulation* 2012;**125**:76–86.
- Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL *et al.* Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. *Circulation* 1997;**95**:2262–70.

4. Cioffi G, Faggiano P, Vizzardi E, Tarantini L, Cramariuc D, Gerdts E *et al.* Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. *Heart* 2011;**97**:301–7.
5. Herrmann S, Stork S, Niemann M, Lange V, Strotmann JM, Frantz S *et al.* Low-gradient aortic valve stenosis myocardial fibrosis and its influence on function and outcome. *J Am Coll Cardiol* 2011;**58**:402–12.
6. Brilla CG, Funck RC, Rupp H. Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. *Circulation* 2000;**102**:1388–93.
7. Dalsgaard M, Iversen K, Kjaergaard J, Grande P, Goetze JP, Clemmensen P *et al.* Short-term hemodynamic effect of angiotensin-converting enzyme inhibition in patients with severe aortic stenosis: a placebo-controlled, randomized study. *Am Heart J* 2014;**167**:226–34.
8. Nadir MA, Wei L, Elder DH, Libianto R, Lim TK, Pauriah M *et al.* Impact of renin-angiotensin system blockade therapy on outcome in aortic stenosis. *J Am Coll Cardiol* 2011;**58**:570–6.
9. Cote N, Pibarot P, Pepin A, Fournier D, Audet A, Arsenault B *et al.* Oxidized low-density lipoprotein, angiotensin II and increased waist circumference are associated with valve inflammation in prehypertensive patients with aortic stenosis. *Int J Cardiol* 2010;**145**:444–9.
10. O'Brien KD, Shavelle DM, Caulfield MT, McDonald TO, Olin-Lewis K, Otto CM *et al.* Association of angiotensin-converting enzyme with low-density lipoprotein in aortic valvular lesions and in human plasma. *Circulation* 2002;**106**:2224–30.
11. Helse S, Lindstedt KA, Laine M, Mayranpaa M, Werkkala K, Lommi J *et al.* Induction of local angiotensin II-producing systems in stenotic aortic valves. *J Am Coll Cardiol* 2004;**44**:1859–66.
12. Capoulade R, Clavel MA, Mathieu P, Cote N, Dumesnil JG, Arsenault M *et al.* Impact of hypertension and renin-angiotensin system inhibitors in aortic stenosis. *Eur J Clin Invest* 2013;**43**:1262–72.
13. Rosenhek R, Rader F, Loho N, Gabriel H, Heger M, Klaar U *et al.* Statins but not angiotensin-converting enzyme inhibitors delay progression of aortic stenosis. *Circulation* 2004;**110**:1291–5.
14. Bull S, Loudon M, Francis J, Joseph J, Gerry S. A prospective, double-blind, randomised controlled trial of the angiotensin converting enzyme inhibitor Ramipril In Aortic Stenosis (RIAS trial). *Eur Heart J Cardiovasc Imaging* 2015;doi:10.1093/ehjci/jev043.