The quest for an aortic stenosis cure

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The readership of *Heart* will require no introduction to the epidemiology, assessment and treatment of calcific aortic stenosis in 2020. Although transcatheter aortic valve implantation has revolutionised the interventional paradigm and is an unequivocal success, we recognise that a prosthesis is not a cure for aortic valve disease, and that complications—both short- and long-term—cannot be completely abolished. Consequently, although recent clinical research has largely focused on iterative improvements in devices, procedural techniques and risk assessment with a view to optimising the delivery and timing of valve replacement, the search for an effective medical therapy to retard the inexorable progression of aortic stenosis continues.

The only drugs to be tested prospectively in randomised controlled trials as disease modifiers are statins, with conclusively negative results.[1] Observational data have hinted at possible roles for other therapies such as renin–angiotensin–aldosterone system blockade and antiosteoporosis medications (figure 1), but it is not possible to confirm causal relationships and draw actionable conclusions from these non-randomised data. Meanwhile, a deeper understanding of the complex processes governing aortic stenosis has shifted the field away from a purely degenerative disease model, with more emphasis on valve mineralisation, lipoprotein infiltration, active inflammation and tissue remodelling. This has led to the identification of multiple possible therapeutic targets, beyond simple correlations between clinical parameters and disease progression.[2] Dipeptidyl peptidase-4 (DPP-4) has recently been proposed as one such target. DPP-4 inhibitors are most commonly used as oral hypoglycaemics for the treatment of diabetes mellitus. However, DPP-4 cleaves a variety of substrates beyond incretin hormones. The authors of the current study previously demonstrated that valve endothelial cell dysfunction upregulates DPP-4 expression which mediates osteogenic differentiation of valvular interstitial cells via degradation of insulin-like growth factor-1, and that inhibition of DDP-4 with sitagliptin attenuates the progression of aortic valve calcification in an animal model.[3] On this basis, the group has undertaken the present study.

Lee *et al* explore associations between several DPP-4 inhibitors and aortic stenosis progression in a retrospective study, with exploratory pharmacokinetic–pharmacodynamic animal and in vitro modelling.[4] The authors used electronic medical records and echocardiography databases across three Korean tertiary institutions to identify patients with type 2 diabetes, mild or moderate aortic stenosis and a left ventricular ejection fraction >50% who were on diabetic medications, and who had follow-up echocardiography at least 2 years after the index echocardiogram. Patients were classified as either DPP-4 inhibitor non-users or users according to baseline medications, with the latter group further divided into 'favourable' or 'unfavourable' DPP-4 inhibitor use. This classification was based on heart tissue/plasma drug concentration at 4 hours in rats, adjusted for an assumed threshold of anti-calcification efficacy (half maximal effective concentration, derived from in vitro experiments using human valve interstitial cells). Annualised aortic stenosis progression was calculated using the last follow-up echocardiogram available, while 'clinical events' were defined as progression to severe aortic stenosis (peak velocity ≥4 m/s on any follow-up echocardiogram) or aortic valve replacement. Analyses were performed with and without propensity matching for baseline characteristics between favourable DPP-4 inhibitor users and non-favourable DPP-4 inhibitor users or non-users.

Between 2009 and 2016, the researchers screened 1081 patients, of whom 212 were included (115 non-users, 69 unfavourable and 28 favourable DPP-4 inhibitor users). The median aortic valve mean pressure gradient and peak velocity were 18.2±4.5 mm Hg and 2.9±0.3 m/s, respectively. Over two different follow-up time periods (median 3.7 years for echocardiography and 5.0 years for the combined echocardiographic/aortic valve replacement endpoint), the main reported findings were that annualised change in aortic valve velocities and gradients were lower in those using favourable DPP-4 inhibitors at baseline compared with those using unfavourable DPP-4 inhibitors or non-users, and that a smaller proportion of the former group progressed to severe aortic stenosis or had aortic valve intervention. These findings were similar after propensity matching and were independent of several other clinical variables in multivariable regression models.

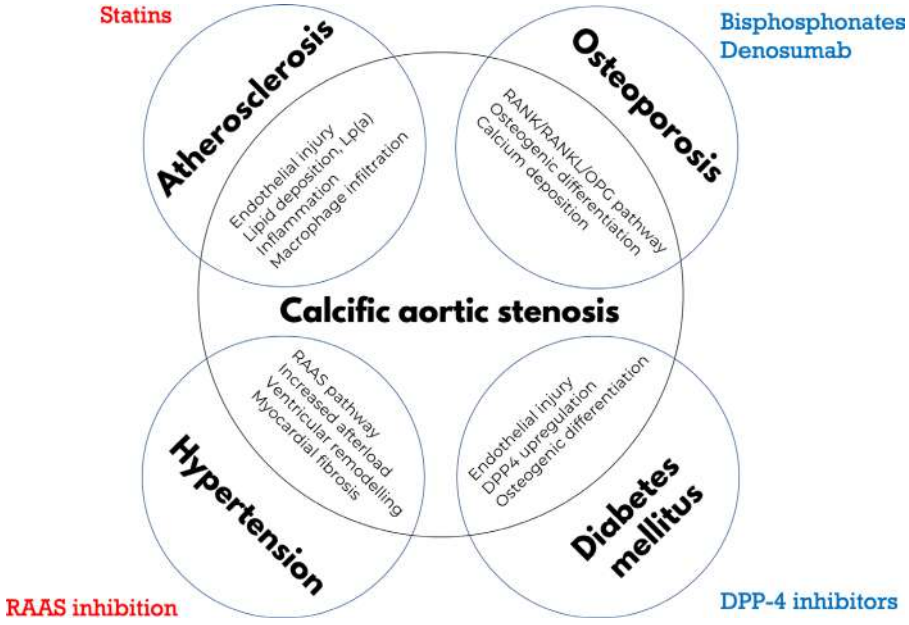

Figure 1 Schematic of proposed shared mechanisms between calcific aortic stenosis and other pathologies which have been investigated in, or are the current target of, clinical studies. Adapted from Dweck *et al*.[6] DPP-4, dipeptidyl peptidase-4; Lp(a), lipoprotein (a); OPG, osteoprotegerin; RAAS, renin–angiotensin–aldosterone; RANKL, receptor activator of nuclear factor-κB ligand.

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The results are interesting and suggest another potential avenue of exploration for disease-modifying medical therapy in aortic stenosis. We commend the authors for their ongoing research in a field which has thus far been unfruitful. However, although there is a dearth of effective medical therapies, we must temper our enthusiasm with a recognition of the limitations of this observational analysis, as acknowledged by the authors. The adjusted heart:plasma ratio as a surrogate for efficacy is arbitrary and based on assumptions regarding heart concentrations of DPP-4 and anti-calcification effective concentrations in rat models. However, heart tissue concentrations (presumably myocardial) are not necessarily related to potential anti-calcification effects in the aortic valve. Furthermore, the threshold used to dichotomise the adjusted heart:plasma ratios was also arbitrary. Although the authors grouped several drugs together as 'favourable' (linagliptin, gemigliptin) and 'unfavourable' (alogliptin, sitagliptin, vildagliptin) for the purposes of this analysis, the most prominent outlier—with an adjusted heart:plasma ratio at least 1000-fold lower than each of the other drugs—was vildagliptin. It is not clear from the data how many patients were receiving each individual drug, and given the small sample size and number of 'events', this binary distinction must be interpreted cautiously.

Most importantly, this study is confounded due to its observational nature. There were substantial between-group differences, which propensity matching can only imperfectly correct for. Multivariable regression modelling was performed for the primary endpoint and results presented for DPP-4 inhibitor use, but it is not clear whether any other covariates also demonstrated significant independent associations with aortic stenosis progression. Furthermore, it is inevitable that there exist other unmeasured confounders that have not been accounted for. For instance, as the authors mention, there were no data regarding compliance to DPP-4 inhibitors, dosage or any medication changes during the follow-up period—potentially crucial information given the hypothesis of this retrospective analysis.

These, and other, limitations are largely extant due to the study design and are not likely to be overcome in this dataset. Ultimately, there exist plausible in vitro data for DDP-4 inhibition in aortic stenosis, with a biological mechanism and now a possible signal for benefit in this retrospective study. This is a hypothesis that is worthy of further testing, as the authors are now doing in the Clinical Study to Evaluate Efficacy and Safety of DA-1229 in Patients With CAVD (DIP-CAVD) (NCT04055883), a double-blind randomised controlled trial that is comparing two doses of evogliptin with placebo in patients with aortic stenosis (peak velocity ≥2.0 and <4.0 m/s, or calcium score ≥300 Agatston units). The primary endpoint is aortic valve calcium volume change on CT at 96 weeks. The importance of conducting this randomised trial is accentuated by recent history: the resoundingly negative randomised trials of statin therapy in aortic stenosis were similarly preceded by promising observational data showing associations between statins and slower progression of calcification or stenosis.[5] Regardless of the results, this will be an important contribution alongside the awaited Study Investigating the Effect of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis (SALTIRE II, NCT02132026) and Bicuspid Aortic Valve Stenosis and the Effect of vItamin K2 on Calcium metabolism on 18F-NaF PET/MRI (BASIK2, NCT02917525) trials.

Truth will out—but in the case of disease-modifying medical therapy for aortic stenosis, where effect sizes may be small and mechanisms complex, only after an adequately powered and well-conducted randomised controlled trial.

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REFERENCES

1 Thiago L, Tsuji SR, Nyong J, *et al*. Statins for aortic valve stenosis. *Cochrane Database Syst Rev* 2016;9:CD009571.
2 Lindman BR, Clavel M-A, Mathieu P, *et al*. Calcific aortic stenosis. *Nat Rev Dis Primers* 2016;2:16006.
3 Choi B, Lee S, Kim S-M, *et al*. Dipeptidyl peptidase-4 induces aortic valve calcification by inhibiting insulin-like growth factor-1 signaling in valvular interstitial cells. *Circulation* 2017;135:1935–50.
4 Lee S, Lee S-A, Choi B, *et al*. Dipeptidyl peptidase-4 inhibition to prevent progression of calcific aortic stenosis. *Heart* 2020;106:1824–31.
5 Marquis-Gravel G, Redfors B, Leon MB, *et al*. Medical treatment of aortic stenosis. *Circulation* 2016;134:1766–84.
6 Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. *J Am Coll Cardiol* 2012;60:1854–63.