Aortic stenosis was first described by the French surgeon and anatomist Lazare Rivière in 1663. While the last decade has seen impressive advances in our ability to treat aortic valve stenosis invasively and percutaneously, significant issues remain with regards to the optimal timing of valve replacement, periprocedural risks and long-term durability. There therefore remains major interest in developing medical treatments to halt or slow progression of aortic stenosis, which could obviate the need for surgical intervention altogether. A stitch in time saves nine; however, no pharmacotherapies are currently proven to be effective for the treatment of calcific aortic valve stenosis (CAVS).

Atherogenic apolipoprotein B-containing lipoproteins, such as low-density lipoprotein (LDL) and lipoprotein(a) (Lp(a)), have clearly been implicated in the pathogenesis of aortic stenosis, particularly in the early initiation phase. However, LDL cholesterol lowering with statins or ezetimibe failed to modify progression of aortic valve stenosis in multiple randomised clinical trials (SEAS, SALTIRE and ASTRONOMER). Attention has instead switched to Lp(a), with a growing body of epidemiology, genetics and prospective imaging studies having built a convincing case for elevated Lp(a) levels being associated with calcific aortic valve stenosis in a very large-scale dataset. The goal of these Mendelian randomisation analyses is to assess the effect of life-long exposure to—in this case—elevated Lp(a) activity, thereby providing an unconfounded estimate of the effect of Lp(a) activity on CAVS risk. Collaborating with colleagues from Europe and the USA, they were able to combine eight cohorts of European descent and accrue an impressive number of 10 137 CAVS cases and 434 585 controls. Nevertheless, they did not find an association between any Lp-PLA2 activity raising variant at the PLA2G7 locus and CAVS, nor an association with aortic valve CT calcium scores in the CHARGE consortium. These findings conclude that Lp-PLA2 is not a causal risk factor for CAVS but a biomarker at best.

Where does this study leave us? Given the growing healthcare burden of CAVS, there is a clear need to better understand the underlying disease mechanisms in order to help identify potential biological targets. Strong evidence points towards elevated Lp(a) levels and its associated OxPL as causal risk factors for CAVS, suggesting that targeting this lipid-driven, inflammatory pathway has a real chance to translate into therapy capable of mitigating disease. The current study suggests that this association is not mediated by Lp-PLA2 and underlines the importance of scrutinising whether biological factors within pathophysiological pathways are merely biomarkers or actually represent a feasible and causal target. More direct targeting of Lp(a) and OxPL would therefore appear to hold more potential as an effective treatment strategy. Emerging antisense oligonucleotides are capable of potently lowering Lp(a) levels in patients and are currently being tested in cardiovascular outcome trials in atherosclerosis.

Similar randomised controlled trials are patiently awaited in CAVS. Indeed, while observation studies are of value in improving our understanding of the biology of aortic stenosis and in helping us to select the most promising targets for further investigation, randomised controlled trials are necessary to provide robust evidence of efficacy and long-term durability.

### Table 1  Ongoing randomised clinical trials of medical therapies in aortic stenosis

| Study | Target | Treatment |
|-------|--------|-----------|
| Lipid-driven inflammation pathways | | |
| PCSK9 inhibitors in the progression of aortic stenosis (NCT03051360) | ApoB-containing lipoproteins; PCSK9. | Biweekly injection of PCSK9 inhibitor versus placebo. |
| Early Aortic Valve Lipoprotein (a) Lowering (NCT02109614) | Lipoprotein(a). | Daily extended-release niacin 1500–2000 mg versus placebo. |
| Calcification pathways | | |
| SALTIRE II – Study Investigating the Effect of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis (NCT02132026) | Mineral metabolism. | ▶ Alendronic acid (n=50) versus placebo tablets (n=25). |
| | | ▶ Denosumab (n=50) versus placebo injections (n=25). |
| BASIK2 – Bicuspid Aortic Valve Stenosis and the Effect of vitamin K2 on Calciummetabolism on 18F-NaF PET/ MRI (NCT02917525) | Vitamin K2-Matrix Gla protein. | Daily vitamin K2 360 µg (n=22) versus placebo (n=22). |

1Department of Vascular Medicine, Amsterdam University Medical Centers, Amsterdam, North Holland, Netherlands.
2British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK.

Correspondence to Dr Kang H Zheng, Department of Vascular Medicine, Amsterdam UMC, AMC, Amsterdam, The Netherlands; k.h.zheng@amsterdamumc.nl
controlled trials are ultimately required to provide definitive evidence of efficacy. These studies are both time consuming and relatively expensive, but the potential market for an effective treatment for aortic stenosis is huge and unburdened by any effective competitors. Several such RCTs currently underway (table 1), as some 353 years after its first description we still patiently await an effective medical treatment for aortic stenosis.

Twitter Kang H Zheng @Zheng_KH and Marc R Dweck @MarcDweck

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