the recently published results from the National Health and Nutrition Examination Survey, which demonstrated that individuals with diabetes (age ≥65 years) with an HbA_{1c} >8.0% had an increased risk of all-cause and cause-specific mortality compared with subjects with diabetes with an HbA_{1c} <6.5% (4). In a multiethnic Asian diabetes cohort, worsening HbA_{1c} and extremely high initial HbA_{1c} levels were associated with increased risk of long-term comorbidities and death, whereas the risk of CVD and death was not significantly greater in patients with diabetes with a moderately increased HbA_{1c} (mean, 8.5%) compared with those with an HbA_{1c} of 7.0% (5).

To the best of our knowledge, this is the first nationwide prospective Chinese diabetes cohort exploring the associations between HbA_{1c} and macrovascular outcomes. The advantage of our study is the prospective design, its large sample size, centralized measurement of HbA_{1c}, and adjustment for potential confounders. The study was conducted before the widespread availability of SGLT2 inhibitors and GLP-1 receptor agonists, which could yield cardiovascular benefits beyond glycemic therapy. Potential limitations of our study are the single measurement of HbA_{1c} at baseline and lack of long-term longitudinal HbA_{1c} trends.

The findings from our observational study support the idea that better glycemic control (HbA_{1c} <8.0%) is important for reducing CVD and mortality. We believe that larger, longer duration studies are needed to define the optimal HbA_{1c} for prevention of macrovascular complications.

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PCSK9 Involvement in Aortic Valve Calcification

High levels of proprotein convertase subtilisin/kexin 9 (PCSK9) (>305 ng/ml) have been recently associated, along with insulin resistance and lipoprotein-associated phospholipase A_2 activity, with aortic bioprosthesis calcification and able to predict hemodynamic valve deterioration (1). Interestingly, high levels of PCSK9 have been previously shown also to correlate with the presence of calcific aortic valve stenosis (CAVS) (2), and an early study showed that carriers of the PCSK9 R46L loss-of-function genetic variant might have a low CAVS risk (3).

In the present analysis, we took advantage of the PCSK9 knockout mouse model to explore the link between PCSK9 and aortic valve calcification (AVC). In addition, in human specimens, we evaluated if there was an association between AVC and PCSK9 valve content.

First, whole aortic valve tissue extracts from 12-month-old *Pcsk9*$^{-/-}$ mice and wild-type (WT) fed a standard chow diet (n = 5/group) were used to assess AVC by calcium colorimetric assay kit (Biovision, Mountain View, California). AVC was 5 times lower in

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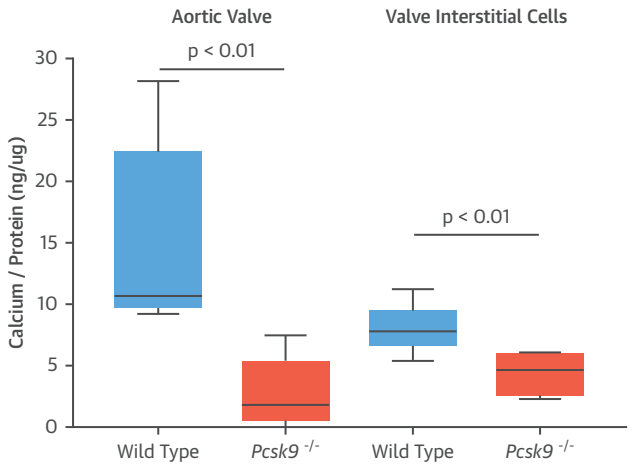
FIGURE 1 PCSK9 and Calcification



Total calcium content in aortic valve leaflets and in valve interstitial cells from *Pcsk9*$^{-/-}$ and wild-type mice. The **central line** illustrates the median, and **box limits** indicate the 25th and 75th percentiles.

Pcsk9$^{-/-}$ than in WT mice (2.72 ± 2.9 vs. 14.99 ± 7.9 ng Ca^{2+}/μg proteins, respectively; p = 0.008) (Figure 1). Although plasma cholesterol levels were ~30% lower in *Pcsk9*$^{-/-}$ than in WT mice, the concentration of ApoB-containing lipoproteins is very low in WT mouse plasma, and their contribution to AVC in this experimental setting is unknown. Second, valve interstitial cells (VIC) isolated from both mouse groups were used to evaluate the in vitro calcification potential related to PCSK9-deficiency in basal condition and on a calcification-promoting medium (i.e., 10 mM β-glycerophosphate and 50 μg/ml ascorbic acid). Results showed that, after 7 days of culture, *Pcsk9*$^{-/-}$ VICs (untreated) calcified to a lesser extent than WT VICs (4.37 ± 1.6 vs. 8.04 ± 1.7 ng-Ca^{2+}/μg-proteins, respectively; p = 0.0003) (Figure 1). Interestingly, 10 mmol/l β-glycerophosphate and 50 μg/ml ascorbic acid treatment, although inducing calcification in both groups, exerted a significantly lower calcification rate in *Pcsk9*$^{-/-}$ VICs compared with WT VICs (41.85 ± 12.4 vs. 55.89 ± 12.1 ng-Ca^{2+}/μg-proteins, respectively; p = 0.01).

Because these in vitro data suggested a VIC-related PCSK9 effect in AVC, we then assessed, as a proof of concept, the presence of PCSK9 in human aortic valves with and without calcification (n = 5/group). Automated capillary electrophoresis Western blotting (ProteinSimple, San Jose, California) analysis showed that PCSK9 was indeed highly expressed in calcified aortic valves compared with noncalcified ones (+4.9 ± 0.5 log2 fold-change; p = 0.004).

Interestingly, enzyme-linked immunosorbent assay (R&D, Minneapolis, Minnesota) revealed that human VICs isolated from calcified aortic valves expressed and secreted PCSK9 (0.54 ± 0.07 and 2.51 ± 0.33 ng/ml, respectively), which positively correlated with the VIC calcification potential assessed after 7 days of in vitro culture (ρ = 0.96; p = 0.009). Conversely, PCSK9 mRNA and protein levels were not detectable in valve endothelial cells.

Overall, we showed that: 1) old *Pcsk9*$^{-/-}$ mice have lower AVC than WT mice; 2) *Pcsk9*$^{-/-}$ VICs are partially protected from in vitro calcification; 3) PCSK9 is highly expressed in human calcified aortic valves; and 4) human AVC might be caused by VIC-related PCSK9 expression. Taken together, these data strongly support a direct effect of PCSK9 on CAVS development and progression, although it remains to be established if PCSK9 may facilitate calcification by acting intracellularly or extracellularly.

In the last decades, all efforts aimed at finding medical therapy or therapeutic agents that could prevent or stop the progression of CAVS have failed because of the paucity of underlying mechanisms (4). Furthermore, it is currently debated whether the mechanisms for bioprosthesis deterioration, because of leaflet calcification, are similar to the ones involved in native AVC. Our results suggest that VIC-associated PCSK9-mediated mechanisms could be relevant only to the native AVC, whereas circulating PCSK9 might influence both types of calcification.

Hence, PCSK9 inhibition therapy, in addition to its positive effects in patients with coronary artery disease, could also be efficient in patients with CAVS and then represents a novel pharmacological treatment for these patients. This hypothesis will be confirmed in currently ongoing and future clinical trials where the therapeutic approaches to inhibit PCSK9 may carry added value to control AVC.

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First-in-Human Use of Coronary Sinus Reducer in Patients With Refractory Angina

Chronic angina, refractory to medical and interventional therapies, is a common and disabling medical condition and a major public health problem. The prevalence of chronic angina is high not only in patients who are not candidates for revascularization, but also in patients following previous revascularization. In addition to chronic total occlusion, the diffuseness of the disease also makes them poor candidates for routine intervention.

The coronary sinus (CS) Reducer is a novel effective therapy for patients suffering from chronic refractory angina. The Reducer is a transcatheter, balloon-expandable metal mesh, designed to create a focal narrowing in the lumen of the CS to generate a pressure gradient across it. In the presence of myocardial ischemia, the Reducer forces redistribution of blood from the less ischemic subepicardium to the more ischemic subendocardium of the left ventricle. Currently available randomized controlled trial and clinical reports demonstrate the safety profile of the device and its efficacy in relieving angina and improving quality of life (1,2). However, long-term data regarding the integrity, patency, and efficacy of the Reducer are not available. In this study, we evaluate the position, patency, and integrity of the Reducer and clinical status and angina severity 12 years after implantation.

We conducted a prospective, nonrandomized, single-arm anatomic and clinical evaluation of patients who underwent Reducer implantation at our medical center as part of the first-in-human clinical study (3). Ten patients with chronic refractory angina and reversible myocardial ischemia were electively implanted with the Reducer in 2005 with follow-up at 6 months and 3 years. The primary outcome at 12 years was confirmation of the position, integrity, and patency of the reducers by computed tomography angiography (CTA). CTA results were analyzed by the medical center and an independent core laboratory. We evaluated proper location of the Reducer in the proximal segment of the CS at 2 to 4 cm distal to the ostium; patency of the Reducer; and the presence of strut fractures, distortion, or dislocation of the Reducer. The diameters of the Reducer were measured at the proximal and distal ends as well as the narrowed center. All data collected were compared with the CTA performed at 6 months post-implantation. Secondary outcomes were improvement in Canadian Cardiovascular Society (CCS) angina class and prevalence of major adverse cardiac events.

Of the 10 patients treated with Reducer, 7 were available for follow-up at 12 years. All Reducers were positioned properly in the proximal segment of the CS, with no migration, occlusion, or thrombosis (**Figure 1**). Additionally, no strut fractures, deformity, or distortions were detected with appropriate blood flow through all Reducers. The mean diameters of the Reducers at 12 years were proximal 7.8 ± 1.13, distal 6.24 ± 1.47, and mid 1.78 ± 0.34 mm, comparable with the diameters measured at 6 months CTA of proximal 8.2 ± 0.7 ($p = 0.441$), distal 5.81 ± 1.52 ($p = 0.6$), and mid 1.6 ± 0.16 ($p = 0.229$). CTA analyses of the medical center and of the core laboratory were similar.

Of the 10 patients, 3 experienced major adverse cardiac events during follow-up; 1 underwent coronary artery bypass graft surgery at 18 months and is still alive. Two patients died of cardiac causes at 11 years. One patient, although alive, did not participate in the 12-year follow-up. At 12 years, all 7 patients reported sustained improvement of angina class compared with baseline status. Four patients (57%)