The main finding of the authors is that low implantation depth is associated with clinically significant new conduction disturbances and permanent pacemaker implantation. Although this result was previously reported by our team (2), the authors should be congratulated because the statistical power of their study is much better than ours (89 vs. 34 patients). However, the methodology for measuring the primary endpoint (i.e., the implantation depth of the stent with multidetector computed tomography), raises some questions. Indeed, the authors explained at the end of the Methods section that "the distance from the stent frame inflow to the aortic annulus (most basal insertion of the native aortic leaflets) was measured." A proper assessment of the native annulus before TAVR is already a difficult and a still debated challenge; therefore, a proper assessment after TAVR seems very difficult or unfeasible. Indeed, when we made these measurements in our study (2), we clearly noted that post-implantation multi-detector computed tomography implies a complex mixture of artifacts associated with native calcifications and stent frame, particularly at the most basal insertion of the native aortic leaflets, which is not visible except when the stent frame is implanted in a high position. This is the reason why the implantation depth was evaluated in our study with reference to the floor of the sinuses of Valsalva.

Because this endpoint reflects the main result of their study, I think that the authors should precisely state, with a dedicated figure, the methodology used to measure the depth of implantation to ensure good reproducibility and comparability with previous and future studies on this interesting topic.

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Reply

Reply: Looking for the Native Annulus After Transcatheter Aortic Valve Replacement?

We thank Dr. Caudron for his interest in our paper (1) that evaluated post-deployment geometry and its impact on conduction disturbances, hemodynamic performance, and paravalvular regurgitation. We have also read with great interest his many previous contributions to the field. Dr. Caudron raises concerns regarding the difficulty in evaluating the location of the aortic annulus/aortic valve ventricular plane on post–transcatheter aortic valve implantation (TAVI) multidimensional computed tomography (CT) imaging and raises questions as to the strength of the findings of our study. In fact, Dr. Caudron implies that even the native annulus may not be reproducibly evaluated on pre-procedural CT: "A proper assessment of the native annulus before TAVI is already a difficult and still debated challenge." We respectfully disagree with this sentiment. We and other groups (2–4) have for the last 5 years consistently shown that the basal ring and annular geometry can be evaluated in a granular and reproducible fashion prior to TAVI. These 3-dimensional measurements of the annulus have been shown to display high intraclass correlation coefficients in multiple studies and have received consensus support to be used to assist transcatheter heart valve selection. Importantly, these measurements have not only been confirmed to be reproducible, they have also been shown to be invaluable in guiding transcatheter heart valve sizing and have allowed the improvement in TAVI-related clinical outcomes (5,6).

With regard to the issue of localization of the annular plain on post-TAVI imaging, we agree that with only post-TAVI CT imaging this is very difficult and would undoubtedly suffer from reproducibility issues. However, unlike in Caudron et al. (7), we were not limited to post-TAVI CT imaging but rather had both pre- and post-transcatheter aortic valve replacement CT imaging for all cases. The baseline CT imaging prior to TAVI provided us an important mask to allow for the identification of the aortic valve ventricular plane on the pre-transcatheter aortic valve replacement CT exam and to colocalize it on the post-TAVI CT. Although we did not perform formal reproducibility analyses, as there was only 1 reader of all of these studies, we strongly feel that the methodological differences in our study with pre- and post-TAVI CT imaging are real strengths of our analysis and afforded us a unique opportunity to perform the measurements and analyses presented in our paper (1).

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Is Time of Renal Hypoperfusion an Important Variable in Determining Response to Renal Artery Revascularization?

The CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial found that stent implantation did not provide any benefit beyond optimal medical therapy in the occurrence of death or adverse cardiovascular or renal events in patients with moderately severe atherosclerotic renal artery stenosis (1). There was a modest, consistent difference in systolic blood pressure favoring the stent group, but this did not result in a decrease in adverse clinical outcomes. These findings are consistent with the ASTRAL (Angioplasty and Stenting for Renal Atherosclerotic Lesions) trial (2) and the STAR (Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progression of Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery) trial (3).

Over the years, studies of renal artery intervention have been criticized for small sample size, the use of angioplasty alone rather than stenting, high treatment-crossover rate, and enrollment of patients with renal artery lesions that were not hemodynamically significant. CORAL is the largest study of renal artery intervention and anticipated all of these potential criticisms. Even though the threshold for enrollment in CORAL was lowered to include stenosis of ≥60%, a subgroup analysis limited to patients with stenosis ≥80% did not show any benefit to stent implantation.

Why have the clinical trials of stenting of atherosclerotic renal artery stenosis failed to show improved clinical outcomes? One variable that might play an important role in determining the benefit of revascularization is the time of renal hypoperfusion. In the 2-kidney-1-clip model, abrupt onset of decreased renal perfusion is associated with renin-angiotensin system activation, leading to sodium and water retention. Over time, the renin-angiotensin system returns to baseline levels and the intact normal kidney compensates to excrete sodium and water by pressure natriuresis (4). Transient activation of the renin-angiotensin system leads to elevated oxidative stress, sympathoadrenergic activation, and impaired vasoactive responses within both the kidney and the systemic microcirculation (5). Moreover, animal studies show that persistent ischemia leads to irreversible kidney damage and development of a chronic kidney disease phenotype (6). Similar renal damage is seen in humans; the majority of patients with renal artery stenosis have renal parenchymal changes including interstitial fibrosis, tubular atrophy, glomerulosclerosis, periglomerular fibrosis, and a variety of arteriolar abnormalities (7). Finally, there is evidence that short-term elevation in angiotensin II levels can accelerate the development of atherosclerosis and lead to changes in the arterial wall that persist even after angiotensin levels return to baseline (8,9). It is unclear to what extent, if any, that these adverse renal and vascular effects respond to revascularization.

Data from animal models suggest that renal parenchymal damage and aortic atherosclerotic changes begin soon after renal hypoperfusion. These effects worsen over time and many of the changes are irreversible. Further studies are needed to determine whether there is a "window of time" in humans during which revascularization is beneficial and whether it can be identified with biomarkers or renal imaging.

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