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Reply

Reply: P2Y₁₂-Based Platelet Function Assays Should be Complemented With Cyclooxygenase-Dependent Testing in Framing the Therapeutic Windows for Dual Antiplatelet Therapy

We thank Drs. Gasparovic and Petricevic for their interest in our study (1) and their comments. They strongly suggest that P2Y₁₂-based platelet function assays should be complemented with cyclooxygenase-dependent testing in framing the therapeutic windows for dual antiplatelet therapy. We think that this statement is highly speculative and not supported by the available evidence. Indeed, aspirin resistance has been extensively discussed as a real entity by itself and its association with clinical outcomes. First, response to aspirin assessed by cyclooxygenase-dependent testing has probably been overestimated due to a problem of compliance, and a previous study by our group showed that noncompliance was the main explanation for aspirin resistance, being a rare entity in compliant patients (2). For ischemic risk, some studies suggest the potential impact of aspirin resistance on ischemic events (3), but a recent study assessing the benefit of tailored therapy based on platelet testing of aspirin response failed to show any significant benefit (4). Therefore, testing aspirin response for ischemic prognosis and increasing aspirin dose on the basis of the test results is not supported by available evidence. For bleeding risk, as assessed in our study, to our knowledge, no study has ever linked the variability of aspirin response and bleeding complications in patients undergoing percutaneous coronary intervention after acute coronary syndrome. Therefore, the proposal in their letter is not in line with current data available on platelet monitoring. Also, the major risk of assessing aspirin response could be to use a higher dose in some patients, whereas recent evidence clearly showed that a high dose of aspirin does not provide any ischemic benefit, only a constant increase in bleeding and gastrointestinal events (5).

Accordingly, we performed an additional analysis to confirm previous assumptions. In the present study, aspirin response was assessed by arachidonic acid-induced platelet aggregation (AA-Ag). The rate of aspirin resistance was very low, with only 60 patients (4%) with aspirin resistance defined as AA-Ag above the 30% threshold previously proposed. We did not observe any relationship between AA-Ag and the occurrence of bleeding complications in our population, as suggested by Gasparovic et al. This could also be explained by the biological profile of aspirin response in 1,082 patients (70%) of patients with AA-Ag = 0%. Indeed, to identify a

predictor of bleeding with platelet monitoring, we need to define *hyperresponse*, which is probably impossible with a drug providing 0% in more than two thirds of the patients with the present test.

We appreciate the suggestions of Drs. Gasparovic and Petricevic; however, this statement is supported neither by available evidence nor by the new analysis provided in this letter. Therefore, it was not an omission, and we believe that does not compromise the robustness of the presented data. Following the proposal to integrate the aspirin effect into bleeding risk assessment, the next step might be to use the new P2Y₁₂ blockers as long-term monotherapy without aspirin as currently tested in the GLOBAL LEADERS study (NCT01813435).

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Looking for the Native Annulus After Transcatheter Aortic Valve Replacement?

I read with great interest the recently published paper by Binder et al. (1) that described the impact of post-implantation SAPIEN XT (Edwards Lifesciences Inc., Irvine, California) geometry and positioning on clinical outcome after transcatheter aortic valve replacement (TAVR).

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 plane 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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