

## Aortic regurgitation after TAVI: focus on calcium in the aortic valve and root

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Aortic regurgitation (AR), mostly paravalvular, has been frequently reported after transcatheter aortic valve implantation (TAVI)<sup>1,2</sup>. The incidence of moderate and severe AR after TAVI ranges between 2% and 24%<sup>1,2</sup>. The increased risk of 30-day and one-year mortality associated with moderate and severe AR<sup>1</sup> has prompted many researchers to investigate the underlying mechanisms associated with this complication. Non-invasive imaging modalities, particularly multidetector-row computed tomography (MDCT), have provided important insights into this field.

Several anatomical and morphological characteristics of the aortic valve and root have been associated with increased risk of AR after TAVI<sup>3-5</sup>. Large, eccentric aortic annulus and bicuspid aortic valve anatomy have been associated with increased risk of significant AR across the series<sup>3-5</sup>. Indeed, undersized prostheses relative to the aortic annulus dimensions may lead to significant AR<sup>5</sup>. Furthermore, bicuspid aortic valve anatomy challenges the deployment of the transcatheter valves, particularly self-expandable valves, leading to asymmetrical deployment and incomplete aortic annulus sealing by the prosthesis that may be the origin of paravalvular AR<sup>3</sup>. However, the role of valvular calcification on the risk of AR is more controversial, since a certain amount of calcification may be needed to ensure effective anchoring of the prosthesis into the aortic root, while excessive, bulky calcifications may impede full expansion of the prosthesis, creating gaps between the native annulus and the prosthesis frame that lead to AR<sup>2,4,6-8</sup>.

In this issue of EuroIntervention, Buellesfeld et al have elegantly analysed the impact of the location of aortic valve calcifications distributed over the aortic annulus and left ventricular outflow tract (LVOT) on post-TAVI AR<sup>9</sup>. The presence of calcifications at the annulus and LVOT for each valve cusp sector was

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analysed on contrast-enhanced MDCT data of 177 patients with severe aortic stenosis undergoing TAVI (63% self-expandable and 37% balloon-expandable valves). A semiquantitative analysis was performed taking into consideration the extent and bulkiness of calcifications<sup>10</sup>. Immediately after valve deployment, the severity of AR was assessed with angiography following the classification of Sellers et al<sup>11</sup>, and additional balloon dilatation of the prosthesis was performed in 50 patients while a valve-in-valve manoeuvre was performed in five patients to reduce the grade of AR. The final incidence of more-than-mild AR was 23%. Patients with more-than-mild AR had a larger aortic valve annulus, less frequently an oversized prosthesis, and a more severely calcified aortic annulus and LVOT compared with patients with no or mild AR. Overall calcification of the aortic annulus and LVOT and any regional (per cusp level) calcification of the LVOT were independently associated with the occurrence of significant AR after TAVI. These results confirm previous studies describing the association between aortic calcification and significant AR after TAVI<sup>4,6-8</sup>.

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Early studies used semiquantitative classifications<sup>10</sup> or quantitative methods based on the Agatston score to assess the amount of aortic valve calcification<sup>4,8</sup>. For example, Unbehaun et al<sup>8</sup> evaluated semiquantitatively (4-point scale) and quantitatively (Agatston calcium score) the amount of calcifications of the landing zone including the LVOT, aortic annulus and valvular cusps on MDCT data of 307 patients undergoing transapical TAVI. Each 100-unit increment of the Agatston calcium score was associated with increased risk of AR (odds ratio 1.09,  $p=0.03$ ). In addition, asymmetric cusp calcification and severe calcification of the landing zone were strongly associated with increased risk of AR. Other studies have focused on the location and morphology of the calcifications in the aortic valve providing further understanding of the association between aortic valve calcium and AR after TAVI<sup>6,7</sup>. Using contrast-enhanced MDCT and specific quantitative, post-processing software that enables regional analysis of the volume of calcium at the aortic cusps (edge and body) and commissures, and at the aortic wall, Ewe and co-workers showed that the presence of severe calcification of the commissures was highly predictive of the presence of paravalvular AR originating from the corresponding commissure, as assessed with periprocedural transoesophageal echocardiography<sup>6</sup>. In addition, Feuchtner et al have recently shown that only the protruding but not the “adherent” calcifications of the aortic valve and root were associated with the occurrence of paravalvular AR<sup>7</sup>. Using contrast-enhanced MDCT, aortic valve calcifications were defined as protruding when the thickness of the calcification exceeded its extension and “adherent” when the extension was larger than the thickness. While protruding calcifications may impede full sealing of the aortic annulus by the prosthesis frame, “adherent” calcifications in the landing zone would favour appropriate apposition of the frame into the aortic annulus being less associated with significant AR after TAVI<sup>7</sup>.

Despite using different methodologies and classifications of aortic valve and root calcification, these studies indicate that an excess of calcium may preclude optimal apposition of the valve into the aortic root<sup>4,6-8</sup>. Eventually, it may be important also to evaluate the association between the amount of aortic root calcification and the final deployment of the prosthesis. The use of MDCT post TAVI may shed light on the underlying mechanisms of AR<sup>12,13</sup>. However, one should be cautious about indicating this imaging technique after TAVI due to the risk of contrast nephropathy in this elderly population with associated comorbidities. Advances in three-dimensional imaging techniques (integration of MDCT and echocardiography) that permit simulations of the deployment of the valve into the aortic root and show the spatial relationship of the device and the aortic root calcifications may help us anticipate the results of TAVI and plan the implantation strategy to minimise the risk of AR.

In pursuing further the research of the determinants and the clinical implications of significant AR after TAVI, several issues need to be considered. First, the definition of significant AR should be standardised. The relatively wide variability of the incidence of significant post-TAVI AR across the various series may be explained by the different methodologies of assessment of AR<sup>4,6,8</sup>. While some series have reported on AR based on angiographic evaluation, other series

have used periprocedural transoesophageal echocardiography which permits differentiation between transvalvular and paravalvular AR<sup>4,6,8</sup>. The Valve Academic Research Consortium-2 document has summarised the criteria which define significant AR after TAVI, following the recommendations of the American Society of Echocardiography and the European Association of Echocardiography<sup>14</sup>. Based on echocardiographic techniques, these criteria comprise several morphological and haemodynamic aspects of the regurgitant jet (i.e., circumference of the prosthesis occupied by the jet, jet density, width and deceleration time and regurgitant volume), valve structure and motion and haemodynamic consequences on the left ventricle<sup>15</sup>. In the present study, Buellesfeld and co-workers assessed the severity of AR with angiography which does not allow the differentiation between transvalvular and paravalvular AR. The use of echocardiography would have provided additional insights by correlating the location of the most severe calcifications with the origin of the regurgitation. Second, prospective randomised studies selecting the prosthesis design and size based on three-dimensional imaging data (including annulus dimensions and aortic root calcification) and other factors that may influence the TAVI results (i.e., height of the coronary ostia, left ventricular function) are needed to establish the role of MDCT, transoesophageal echocardiography and magnetic resonance imaging in the patient selection process and procedural planning. In a recent prospective, multicentre controlled trial including 266 patients who were treated with the Edwards SAPIEN valve (Edwards Lifesciences Inc., Irvine, CA, USA), Binder et al<sup>12</sup> showed that the group of patients in whom the prosthesis size was selected based on MDCT-derived aortic annulus measurements less frequently had significant paravalvular AR than the controls in whom the device size was selected based on echocardiography or angiography (5.3% vs. 12.8%,  $p=0.032$ )<sup>12</sup>. However, it remains unknown whether such an approach would have resulted in similar results if self-expandable prostheses had been implanted. Furthermore, the role of the amount and location of aortic valve and root calcifications assessed with MDCT on the selection of prosthesis design and size was not analysed and remains a source of debate. The new-generation valves with paravalvular sealing systems (Edwards SAPIEN 3 [Edwards Lifesciences] and Sadra Medical Lotus [Boston Scientific, Natick, MA, USA]) may overcome the challenges that severe calcification of the aortic root poses to TAVI.

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