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## Is paravalvular leakage the single most important complication of TAVI?

While there are a number of potential complications involved with transcatheter aortic valve implantation (TAVI), paravalvular leakage is a complication that can be easily avoided with careful preparation. *Confluence* spoke to Nicolas M. Van Mieghem, Interventional Cardiologist at the Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands to find out more.

### What are the major complications associated with TAVI?

In my opinion, stroke is the most severe complication related to TAVI. The second most important issue is aortic regurgitation (AR) due to paravalvular leakage. Other complications include bleeding and conduction disturbances.

The problem of stroke was first highlighted in the PARTNER trial, which compared surgical aortic valve replacement with TAVI.<sup>1,2</sup> It turned out that when they looked at all kinds of neurological events, i.e., transient ischaemic attacks, or minor or major stroke, there was a higher incidence of events in the TAVI group. That is, of course, an important signal because stroke can result in death or severe impairment to quality of life. However, a recent study from the US, the CoreValve US Pivotal High Risk Study, has demonstrated that the rates of stroke were not statistically different in patients undergoing valve replacement with TAVI or surgery. At 30 days post-surgery, rates of stroke were 4.9% in patients treated with Medtronic's CoreValve (Medtronic, Inc.) and 6.2% in the surgical group ( $P=0.46$ ); at 1 year, these rates were 8.8% and 12.6%, respectively ( $P=0.10$ ).<sup>3</sup> The study also demonstrated that stroke rate with the CoreValve System is low, stable and, in contrast to other TAVR studies<sup>1</sup>, comparable to surgical valve replacement in high-risk patients. The study showed that at 1 year, the all-cause mortality rate for CoreValve was superior to surgical valve replacement (14.2% vs. 19.1%, non-inferiority  $P<0.001$ ; superiority  $P=0.04$ ).<sup>3</sup>

Paravalvular leakage, and associated AR, is also a significant issue. Moderate or moderate to severe ARs have been shown to have a clear impact on long-term survival.<sup>4-6</sup> There has, however, been some discussion on the importance of mild or even trivial AR. Analysis of the 2-year results from the PARTNER trial suggested that there was a

correlation between even mild paravalvular AR and mortality.<sup>7</sup> However, this was, in my opinion, overstated because that data stems from univariate analysis, not multivariate analysis. That is a big difference. I am not convinced that mild AR is directly correlated with mortality *per se*.

In a study of 795 patients, change in the mean aortic-valve gradient from baseline to 1 year in the TAVI group was non-inferior to that in the surgical group ( $P<0.001$ ).<sup>3</sup> Furthermore, the rate of moderate or severe paravalvular regurgitation at 1 year was 6.1% in this study, which is favourable compared with rates of 7–16% in other multicentre series.<sup>6,8-12</sup> Although the rates of moderate or severe paravalvular regurgitation were higher after TAVI than after surgical valve replacement, they did not appear to have a negative impact on survival.<sup>3</sup>

Other relatively common procedure-related events are bleeding and vascular complications. These problems impact the patient from the start and may or may not be correlated with late mortality.<sup>13</sup> That is still controversial, but there are some indications and studies that suggest that there is a correlation between the use of packed cells and bleeding and late mortality. Moreover, these bleeding and vascular complications are also associated with longer in-hospital stay and a slower recovery. This potentially jeopardises one of the big advantages of TAVI, namely the increased quality of life compared with surgery.

Conduction disturbances and need for a permanent pacemaker are the final complications. In general, this involves left bundle branch block and permanent pacemaker implantations. While this might not impact the patient in the short-term, they can have a major impact on patients' wellbeing over time. However, the outcomes associated with conduction disturbances are again controversial. There are

the Italian data that say there is no correlation with 1-year mortality and the occurrence of new bundle branch block, whereas data from The Netherlands suggest the opposite.<sup>14,15</sup>

**Do you find that the complications that you have just described vary by the population you are treating? Are some more common in more serious cases than others?**

Some subgroups of patients have a higher risk for stroke or vascular complications, but if there is no alternative, you have to act. For instance, patients with a history of stroke or peripheral arterial disease have a higher risk of stroke after TAVI and they also have a higher risk of vascular and bleeding complications, but you are not going to exclude them from therapy just because they had a stroke or have peripheral arterial disease.

Furthermore, while we are learning more about this all the time, experience tells us that the more calcium we see in the valves and aortic roots, the higher the risk for significant post-procedural AR. Therefore, procedural planning is becoming more and more important. This is illustrated by a clear move away from 2D transoesophageal and transthoracic echocardiography for pre-procedural planning to 3D modalities, especially of course multi-slice CT (MSCT) scans, but also 3D transoesophageal echo.

Transcatheter valve selection, either using a Medtronic CoreValve or an Edwards Sapien valve (Edwards Lifesciences Corporation) may also affect the incidence of paravalvular AR. For instance, if there is a big piece of calcium in the left ventricular outflow (LVOT) tract there may be an argument to move away from an Edwards valve, preferring instead another device because there is a clear correlation between left ventricular outflow tract calcium and aortic root ruptures with the Sapien device. This is due to the valves' mechanical concepts: the Edwards valve is balloon expandable while the Medtronic CoreValve is self-expanding. When it comes to expanding the non-compliant balloon, you will crush the calcium and you can cause perforations and ruptures by doing that. This does not mean that I have a preference for a particular device in general, but in certain anatomies it may be more sensible to use one valve over the other.

Another issue is the height of the coronary arteries. If the coronaries are implanted rather low down,

I would refrain again from an Edwards valve. However, if there is relative low calcium score in the aortic root, I would be more in favour for an Edwards valve because there is a potential for valve pop-outs with CoreValve in aortic roots with low calcium score.<sup>16</sup>

In terms of outcomes, however, I believe that, at present, there are no clear differences between the two valves, as was recently demonstrated by the PRAGMATIC collaboration.<sup>17</sup> The Comparison of Balloon-Expandable vs Self-expandable Valves in Patients Undergoing Transcatheter Aortic Valve Replacement (CHOICE) clinical trial showed a significantly lower frequency of residual more-than-mild aortic regurgitation and permanent pacemaker implantation when using balloon expandable versus self-expanding valves.<sup>18</sup> However, the small sample size may have been responsible for some sex-based bias in this study, and the results of this study was not designed to demonstrate any long-term difference in critical outcomes such as death or stroke; indeed, there was no difference in 30-day mortality between the two treatments.<sup>18</sup>

**What measures can be employed to help prevent such complications from occurring?**

In order to prevent bleeding and vascular complications the choice of vascular access is critical. John Webb's group in Vancouver, consistently present very low vascular complication rates of 1% and less, through optimized access site selection and procedural technique.<sup>19</sup> For example, if you see that there is significant calcium in the iliofemoral tree, despite the fact that the vessels might be of a decent calibre, it may be an argument to move to an alternative access, either transapical, direct aortic or trans-subclavian.

In principle in TAVI you carry out pre-dilatation with a balloon and then you implant the valve in the aortic root. However, if there is a lot of calcium in the aortic root you may choose not to employ pre-dilatation. There is a very small study that suggests avoiding pre-dilatation in such patients will result in fewer strokes.<sup>20</sup> This may be due to a correlation between manipulation and instrumentation in the aortic root and embolization of debris into the brain. In Rotterdam, we are selective with pre-dilatation and do not use it in all of our patients.

We also have a low threshold for the use of embolic protection devices. The reason being that we have documented that in 75% of patients there was macroscopic debris in the filters.<sup>21</sup> However, we have not yet shown that the use of such protection devices is associated with reduced risk of neurological complications. This is because the risk of stroke is 5% or less, so the number of events is not that large.

Stroke-related TAVI is due not only to tissue embolization, but can also be caused by thromboembolism or bleeding associated with inefficient anticoagulant therapy. The patients undergoing TAVI are often elderly, with pre-existent cerebral vascular disease and atrial fibrillation. Up to one third of all patients treated with TAVI will develop atrial fibrillation or paroxysmal atrial fibrillation, and that alone is a risk for stroke.

### Why does paravalvular leakage occur and what does it involve?

Proper sizing of the aortic valve is important; if you undersize you risk a paravalvular leak. Since we have moved to 3D imaging modalities, we see that our sizing is becoming more accurate. The second reason is the appearance of calcium; when there is a high aortic root calcium score there is a higher risk of paravalvular leakage. Calcium causes suboptimal deployment of the valve and suboptimal apposition of the devices to the aortic wall. The third issue is, of course, if the position of the valve is not optimal. If you position it too high or too low then you can have paravalvular leakage. This is due to the skirts surrounding the transcatheter valves. The skirts are meant to prevent paravalvular leak, but if you put the bioprosthesis too low, the skirt will be in the LVOT and not at the proper location in the root to express its sealing design.

### How do patients with that leakage present? How does it affect them?

When there is a massive AR then there is an immediate haemodynamic compromise and the operator will notice subsequent haemodynamic compromise right away. If there is moderate AR, then these patients will typically show less improvement, as compared to a patient with no leakage. We typically see our patients after 30 days for the first time after discharge. We see that patients who have moderate to severe AR tend to have a higher New York Heart Association class after the intervention. Not only does it appear that

patients with moderate to severe AR have higher mortality, but according to the literature and our own dataset, it also appears that their quality of life may be reserved.

### Can you always treat AR?

You cannot always treat the paravalvular AR and that is the problem. Sometimes, for instance, if you undersized the valve then what do you do? The only option is surgery and to expose the patient to risks which were the reason why the patient was treated with TAVI in the first place! Alternatively, you can try to do aggressive post-dilatation with a balloon, but you risk overstretching the valve leaflets and with that affecting the integrity of the transcatheter valve.

If you position the valve too high or too low you can do a valve-in-valve procedure. The results of valve-in-valve procedures are quite good. There are no reports suggesting that valve-in-valve procedures are associated with worse outcomes. That being said, in concordance with other groups, our data from Rotterdam, suggests that increasing the number of manipulations in the aortic root is correlated to stroke risk.<sup>22</sup> It is important to remember that such salvage procedures to treat paravalvular AR are not without risk. The experience with plug closure of paravalvular leakage is, as far as I know, relatively limited.

So, in conclusion, the best way to manage paravalvular AR is to prevent it in the first place! That is why most centres are now very meticulous in their pre-procedural planning, relying on multi-modality imaging protocols.

### How do you work with other members of the Heart Team to manage paravalvular AR?

Again, the MSCT scan is key. In Rotterdam, experienced radiologists report the pre-procedural MSCT scans first. They are responsible for the overall scan interpretation including the evaluation of non-vascular structures. The interventionalist will subsequently and independently assess the scan zooming in on the anatomy that is relevant to the TAVI procedure itself, using a dedicated software program. Both parties will assess the peripheral arterial tree and the aortic root. This parallel evaluation warrants optimal sizing and may improve access site selection. In case of significant discordance, both the radiologist and the interventionalist gather to discuss the scan in more detail together.

## What improvements in technology are we likely to see in the next couple of years that are potentially going to reduce paravalvular leakage associated with TAVI?

The second generation of valves, the repositionable and retrievable devices, may provide a breakthrough. I am a believer that by using these repositionable systems you may have a considerable impact on the incidence of AR. However, when you have a repositionable system, repositioning of the device still means additional manipulation in the aortic root with all the potential sequelae, such as embolization. At the end of the day, the question is whether the second-generation devices will reduce the overall incidence of complications? That remains to be seen.

Refinements to software tools will help predict how a transcatheter valve will behave in the aortic root. That means that given a certain anatomy, with a certain amount of calcium, you could predict how a bioprosthesis would be deployed in that particular anatomy. For example, it may be that you could predict malapposition or underexpansion, and this may eventually help with the selection of devices.

## Looking even further forward, what does an ideal valve look like?

An ideal valve would have a harness that is very compliant and able to accommodate different

anatomies. In case of excessive and protruding aortic root calcifications, the bioprosthesis could then accommodate and wrap around protrusions without leaving lacunes that could create paravalvular leaks. Furthermore, I do believe that repositionable and retrievable valves are the way to go; I believe this is an essential feature in the immediate future.

Of course, durability is an important issue; the ideal valve should last for life. At present, we only have data for about 5 years; so far we have no indication that there is accelerated degeneration of the bioprosthesis as compared with surgical valves. However, we must continue to monitor this.

## What do you see as being the crucial studies that need to be carried out in this field?

Long-term data are vital. The initial wave of data showed us that the short-term and 1-year outcomes are positive, but now we need more information on how the valve will behave after 10 years. That is the goal of all the registries looking at TAVI and I hope that these efforts will continue. For instance, data from SOURCE or ADVANCE, as well as long-term follow-up of national registries will be very relevant.<sup>23</sup> This will demand not only continued effort, but also continued investments in long-term research.

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DISCLOSURES: NMM is Consultant for Medtronic and Boston Scientific.

## EuroPCR 2014, Paris, France 20–23 May

If you are attending EuroPCR 2014, be sure not to miss Dr Jeffrey Popma's presentation of the CoreValve US IDE clinical study.

These unique data of the randomized clinical trial comparing TAVI to surgical replacement in high-risk surgical patients will be presented during the TAVI symposium sponsored by Medtronic on **Thursday 22 May** in the Theatre Havane, **12:30–14:00**