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Transcatheter aortic-valve implantation in high-risk patients: a comparison of UK and European registries

Confluence spoke with Mr Neil Moat, Consultant Cardiac Surgeon and Director of the Transcatheter Valve Programme at the Royal Brompton Hospital in London, UK, and Dr Peter Wenaweser, Director of the Transcatheter Valve Programme, Bern University Hospital, Switzerland. We asked how the UK and Swiss TAVI registries were set up, what insights have been gained from them so far and what we can hope to learn from them in the future…

What is TAVI and what are the benefits and limitations associated with it?

Neil Moat (NM): Transcatheter aortic valve implantation (TAVI) is a technique that was developed for treating very high-risk patients with aortic stenosis. Conventionally, these patients would have undergone surgical aortic valve replacement (SAVR). Using standard open-heart surgical techniques, the old valve is excised and a new valve is sutured into place. With the catheter-based approach, the TAVI, the old valve is left *in situ* and a valve mounted within a stent is inserted into the new valve. The stent then either expands itself – a so-called self-expanding device – or the stent is expanded with a balloon ('balloon-expandable') to open up and relieve the obstruction caused by the diseased valve. The other alternatives are conservative management, which we know has a very poor outcome in this group of patients; or an interim measure, balloon aortic valvuloplasty, which evidence suggests only provides temporary relief.

Peter Wenaweser (PW): The technique is now approximately 10 years old and we have seen considerable progress with the technology and the technique. More than 50,000 patients have now been treated worldwide using this technology with good clinical results. We have seen the clinical benefits of this technology: within 30 days the patient experiences an improved New York Heart Association (NYHA) functional class, I would say at least one or two classes better than at baseline, a normalization of haemodynamics, and an improvement of a reduced ejection fraction of the left ventricle if the procedure is successful. They also have an increase in their quality of life.

Bleeding and vascular access complications are the most frequently observed complications associated with TAVI and for both transfemoral and transapical approaches (the most frequently used approaches), sheath size plays an important role in this regard.

NM: Benefits of catheter-based approaches are that they tend to be less invasive than surgery, with a faster and more rapid recovery and often a shorter hospital stay. The limitations of TAVI are that, with this first generation technology, there are a number of procedural issues which still need to be resolved or improved upon, such as the requirement for pacemaker implantation, paravalvular aortic regurgitation (AR), etc. Then there is the important question of the durability of these biological valves; i.e., how long will it be before they, like all bioprostheses, degenerate and fail?

What is the decision-making process in deciding which patients should receive TAVI? Who is involved? Are there published guidelines to which we should adhere for this treatment?

PW: The Heart Team, consisting of a heart surgeon and an interventional cardiologist, imaging specialist and perhaps other specialists such as a geriatrician and an anaesthetist, should decide the best option for each individual patient.

NM: At present, the patient population is those who are considered to be at high risk from conventional cardiac surgery. Unfortunately, there is no good system or scoring system that allows us to select these patients and therefore the choice of treatment really lies with the Heart Team. It relies on the clinical experience of that team and the people within it, in

judging two main factors: firstly, what would the associated risks be for the patient in question if they were to undergo conventional cardiac surgery? Secondly, at the other end of the spectrum, does the patient in question have so many comorbidities, or are they so frail, that doing anything would be futile? There is an increasing realization that, at this end of the spectrum, there is a group of patients where there is a degree of futility in undertaking TAVI.

PW: Due to the positive results from TAVI registries and trials such as the PARTNER study,[1] TAVI now also has a place in the guidelines. The ESC Guidelines,[2] which were launched during the ESC meeting in Munich this year, stated that after discussion in the Heart Team, TAVI is a valuable alternative to surgical aortic valve replacement for high-risk patients.

What is meant by high-risk patients and how can that be assessed?

NM: There is not a precise definition of what high-risk is; high-risk, very high-risk, and intermediate-risk are all subjective terms. Clearly, if one looks at a population of patients with severe symptomatic aortic stenosis, there is a spectrum. This would range from a patient who is relatively young with no other comorbidities; here, the risk of dying within the first 30 days after surgery, or of having any significant complications, is extremely low. At the opposite end of the spectrum are patients who tend to be very elderly, have many comorbidities and may be very frail. In these patients, there is a risk of either dying early following conventional surgery or, perhaps even more importantly, of having very long stays in the intensive care unit or in hospital and never returning to a full active, independent life.

At the moment, TAVI is being considered in the high to very high-risk patient population. These patients would tend to have Society of Thoracic Surgeons' (STS) scores ≥8 and a logistic EuroSCORE of >18–20 (accepting the very marked limitations of these scoring systems).

Were patients included in the TAVI registries based on the decision made by the respective Heart Teams in each centre, then, rather than on specific inclusion criteria?

NM: Established in 2007, the UK registry[3] is an all-comers registry that has captured every consecutive implant that has occured in the mainland UK. Initially, the Heart Team must decide that the patient in question would benefit from TAVI. Once this has been established, a detailed dataset is recorded for each patient, including their demographics, the procedure they underwent and early and late post-operative recovery. In addition to these records, there is an NHS central register in the UK which records all deaths. So perhaps the two biggest strengths of the UK registry are that all patients are included and that we are able to record when those patients died. So we have a very accurate record of survival following TAVI.

PW: We designed the Swiss TAVI Registry to help us in assessing which patients are treated with TAVI and what their outcomes are. Like the UK registry, the aim of the Swiss TAVI Registry is to include every patient who is treated with TAVI, irrespective of any risk score. We really want to have a consecutive patient population treated with TAVI and we would like to see a true reflection of how interventional cardiologists and heart surgeons in Switzerland decide on treatment.

To date, the registry includes approximately 90% of the TAVI procedures performed in Switzerland since the registry began. At the moment, there are 9 centres involved out of 13 centres performing TAVI. We hope that all of the remaining centres will participate eventually.

What do you consider to be the key clinical outcomes that are recorded in the TAVI registry? Do these differ between the European registries?

NM: We have to distinguish between what the key outcomes are, but also what outcomes can be captured in the registry. Clearly, important outcomes are death and stroke but also, particularly in the elderly population, quality of life and functional recovery.

There are subtle differences between most of the European registries, with each having their strengths and weaknesses. All are of value in creating a picture of the clinical course of patients receiving TAVI. A particular strength of the UK registry is its very good mortality follow-up. It is also very robust in recording the duration of patients' hospital stay and where patients go on to afterwards (e.g., what proportion of patients go back home, and after how many days? How many patients move into other types of care facility?). However, patients' long-term functional outcome is not well recorded

in the UK registry because that requires detailed clinical follow-up, which the registry is not set up to capture. On the other hand, for example, the French registry has very robust data on myocardial infarction (MI) and functional class at one year, so contains more data about functional outcome than in the UK registry.

PW: We decided to use the Valve Academic Research Consortium (VARC) criteria for safety and major adverse cardiac events (MACE) as an efficacy endpoint, to have a comparable dataset with other registries. We will try to incorporate the VARC-2 criteria once they have been published. One concern across different registries is consistency in reporting, for example about MI or stroke: would a stroke in this registry not be classified as a stroke in another? By using the standardized criteria, such as VARC, this is something we will now be able to overcome.

What differentiates the Swiss registry is that we have an independent clinical event committee which looks in great detail into the complications reported. This may not be present in all other registries. This means we are not relying on the self-reporting from each centre, but we are looking into each complication in detail; I think we have high-quality data with respect to complications and outcome reporting. This may be the main strength of the Swiss TAVI Registry. It involves a great deal of work to do this but I think it is worthwhile.

Overall, which patients are being included in the registries?

NM: The patient populations are remarkably similar across all of the registries. The mean age is between 71 and 81 years. Although the precise numbers will vary between registries, the proportion of patients receiving TAVI who have comorbidities is much greater than in the patient populations that are undergoing aortic valve replacement. There are often quite a high number of patients who have had previous cardiac surgery, or have peripheral vascular disease, diabetes or renal dysfunction. These are generally much more prevalent in the TAVI population than in patients who are having conventional cardiac surgery.

Once the Heart Team has identified the patients should undergo TAVI, which intervention was used in the registries?

PW: In the Swiss registry, all devices with CE approval in clinical use are included and monitored. This fact clearly provides another important advantage over studies including only one single device. A comparison of outcome and valvular performance between the patients treated with different devices will therefore be possible in the future. Furthermore, a deeper insight into the device selection process will be facilitated.

NM: Until the end of 2011, there were only two commercially available devices – the SAPIEN (Edwards) and the CoreValve (Medtronic, Inc.). Essentially, what happened in the UK was that centres adopted one or other of those technologies. The technologies are different and the implantation techniques and skills are different, so it was important that centres could complete the learning curve using one technology rather than trying to use two different devices. The UK Registry has shown consistently that there has been no difference in clinical outcome, in terms of mortality, between the two devices. Furthermore, the patient demographics of the patients being implanted with SAPIEN (Edwards) are pretty much identical to those being implanted with CoreValve (Medtronic, Inc.).

What do you expect to learn from the registry data – how will those learnings affect clinical practice?

PW: We hope to determine the extent to which clinical outcomes are favourable for those patients selected for TAVI by the Heart Team. We need to show that this technology is a viable option for the replacement of stenotic aortic valves.

I also think that the results of the registry will affect decision-making within Heart Teams. Already in Europe, intermediate-risk patients are starting to be treated with TAVI, based on the discussion of the Heart Team. As we know, the risk calculations with the STS score and the EuroSCORE are just one little piece in the puzzle for treatment allocation. A patient might be very frail, with a low EuroSCORE or low STS score, but perhaps the better option for these patients is to treat them with TAVI, despite the low calculated risk score for surgery. This is something we will learn from the registry, whether the outcome of so-called intermediate-risk patients will be favourable as well.

NM: The registries will provide complementary data to randomized trials as they provide real-world data for patients who are undergoing treatment, whereas randomized trials tend to have very strict inclusion and exclusion criteria, which therefore restrict the patient population enrolled.

There are three studies, SURTAVI, PARTNER II and the UK TAVI trial, that have just started or are about to start, that will address the issue of how TAVI will perform in relatively high-risk patients, although not as high-risk as those included in the original PARTNER trials. I think they will provide vital information on how TAVI performs in a slightly lower-risk population, and they will determine very much how the use of TAVI expands. I think everyone agrees that the type of patients who will be enrolled in these trials should not undergo TAVI outside the clinical trials, because we know that there is a very good treatment option (SAVR) available for these patients and at present we do not have the evidence base to offer them a catheter based approach.

It is also important to realize that changes in population demographics in Europe and North America in particular will mean that there will be a dramatic increase in the number of patients over 80 years of age. Even if the selection criteria were to remain as they are now, there would still be a substantial growth in the number of TAVIs being performed, purely based upon these population changes.

It seems that patients being implanted with TAVI often have a number of comorbidities. Were any of those associated with reduced survival after TAVI?

NM: In the UK Registry, data analysis using a univariate model showed that survival was adversely affected by renal dysfunction, the presence of coronary artery disease and a transapical approach. However, in a multivariate model, the only factors that were independent predictors of mortality were poor left ventricular function, significant respiratory dysfunction, and the presence of moderate or severe paravalvular AR after the implant.

Across the various registries, these generally tend to be fairly similar, although there are some subtle differences. The French registry, which was published recently, again found that a transapical approach and AR were significant independent predictors of mortality, but it also found NYHA Class and the logistic EuroSCORE were independent predictors of mortality. One could summarize by saying that clearly those patients who are in a poorer functional class, have poorer left ventricular function and have more severe comorbidities tend to do worse.

Can you explain why the different implantation route makes such a difference?

NM: There has been a good deal of discussion in relation to this. There are probably five implantation routes that are now practised. The most common is transfemoral and the next most common is transapical. There is also implantation via the subclavian artery, a direct approach to the ascending aorta and, more recently in a small number of patients, through a carotid approach.

The studies that look at the transfemoral versus transapical approaches show that the patients treated by the transapical approach are different from those who undergo a transfemoral approach. By nature of not being suitable for a transfemoral approach, you tend to have some of the risk factors, in particular the presence of peripheral vascular disease, which puts the patient into a higher risk category. What is not clear at the moment, however, is how much of the excess risk induced by a transapical approach is due to the different patients or whether there is also an increased risk directly associated with this access route.

PW: In our own registry in Bern, we have seen that the transapical approach has a less favourable outcome compared with patients treated transfemorally. I remain convinced that a transfemoral approach is the most minimally invasive and, therefore, associated with a better outcome than the transapical approach. This is a great debate and it is important to remember that, for any access site, you need to have an experienced operator: an experienced team or operator will of course have a better outcome than an inexperienced team in respect of the access site. For me, it is quite clear that the transfemoral approach will stay as the main access site for the TAVI procedure. The subclavian and direct aortic approaches seem to have many of the advantages of the transapical approach (such as enhanced control of device delivery) without many of the recognised disadvantages.

What are the next steps for the UK and Swiss registries?

NM: In the UK, the plan is to continue the enrolment of patients in the registry. Indeed, funding for TAVI will only be provided to centres who enter their patients into the registry. Every patient who has an aortic valve replacement and every patient who has had a TAVI are captured within national registries.

This will continue, as will long term follow-up. Again, going back to the NHS central register, we will be able to track these patients *ad infinitum*.

We now have over 3,000 patients in the registry. The dataset up to the end of 2011 contains approximately 2,600 patients and this has just been cleaned and validated. The first series of analyses on those data are underway. Obviously, year-on-year, because we have more numbers and longer follow-up of the earlier patients, it will provide more interesting and useful information.

PW: Despite having two or three centres that we would like to motivate to participate, more than 500 patients have been included in the Swiss TAVI Registry since its inception. At present, typical patient follow-up occurs at one month, at one year, and then yearly for five years. We have had recently held the second Clinical Event Committee meeting and we are aiming to publish the first results from these 500 patients soon.

Of course, there is also interest in having more detailed research projects included in this registry, rather than just collecting outcome data, and we will be running specific research programmes around the registry. For example, we need to define the best peri-procedural medication, because we know that there is the risk of stroke or transient ischaemic attack. Indeed, we know very little about the optimal anticoagulation regimen that might be required to reduce the risk of stroke in a specific target population. That is perhaps a focus that could be integrated into the registry.

With respect to the Swiss TAVI Registry, I would like to encourage every country to set up a registry like this for new technologies which are often introduced rapidly into clinical practice as soon as there is CE approval. In Europe, there are fewer obstacles to implanting a new device in patients but it is very important to have reliable outcome data to show the community that this is not just a new fad, but a viable and effective technology from which patients can benefit. I would just like to encourage every centre to show, by participating in a registry, that the data are good and that patients can benefit from it.

How do you see these devices progressing in the future?

NM: As you might imagine, owing to the early, very good results with this first-generation technology, there are a large number of new devices being developed. The companies that already have a device are improving their devices. Both established and start-up companies are designing new devices. Many of them are trying to reduce the procedural complications associated with first-generation devices: they are trying to be able to position the device more accurately, to minimize injury to access route vessels by bringing sheath sizes down, and to bring the size of the delivery systems down. Devices are being made to be re-capturable and re-positionable. An enormous amount of work is being done in order to improve the technical features of the devices.

PW: I think there are three important issues to be addressed by the new technology. First, there is the issue of paravalvular leakage. Further technology development will address this and will lead to a further reduction in paravalvular leakage, which is important for a good long-term clinical outcome. Another point is reducing the need for permanent pacemaker implantation, which requires an additional procedure. Clearly, it is not desirable for patients to undergo further surgery two or three days after TAVI. While we could also do better with regard to this outcome during implantation, I think approximately 50% of these AV conduction disturbances are mainly induced by the disease itself and not by the procedure. Last but not least, and this is already more or less in use, the reduction of the sheath size will also lead to a reduction in bleeding and access site complications. This will further reduce the rates of periprocedural complications and improve clinical outcomes.

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