The Year in Cardiology

The Year in Cardiology 2013: valvular heart disease (focus on catheter-based interventions)

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2013 was the year of transcatheter heart valve interventions. Not least because of the 2012 European guidelines on the management of valvular heart disease (VHD), the multidisciplinary heart team approach became an established concept. Decision-making, when a patient is too ‘sick’ for surgery and too ‘healthy’ for catheter-based interventions, is complex, since VHD is often seen at an older age and, as a consequence, there is a higher frequency of co-morbidity and frailty. However, before TAVI and other transcatheter heart valve interventions can be expanded to intermediate-risk patients, evidence in favour of this less invasive treatment has to be provided by upcoming randomized clinical trials.

Keywords
Aortic stenosis • Aortic regurgitation • Mitral stenosis • Mitral regurgitation • TAVI • TAVR • TMVR
PMC • MitraClip • CoreValve • Edwards-SAPIEN • Direct Flow Medical Valve • Boston Lotus Valve • Paravalvular aortic regurgitation • Paravalvular leakage • Stroke • Annular rupture • Durability • Intermediate risk • Risk • Outcome • Co-morbidities • Frailty • GARY • Valve-in-valve • VIV • New oral anticoagulants • NOAC • Anticoagulation • Valvular heart disease

Introduction

Not least because of the revised European guidelines on the management of valvular heart disease (VHD), the multidisciplinary heart team approach with close collaboration of cardiologists and cardiac surgeons became an established concept in 2013.1 Decision-making, when a patient is too ‘sick’ for surgery and too ‘healthy’ for catheter-based interventions, is complex, since VHD is often seen at an older age and, as a consequence, there is a higher frequency of co-morbidity and frailty, contributing to an increased risk of the procedure (Figure 1).

Aortic stenosis

Aortic stenosis (AS) remains the most frequent type of VHD in Europe and often requires hospitalization and intervention.2 In the last decade, transcatheter aortic valve implantation (TAVI) has emerged as an alternative treatment strategy to surgical aortic valve replacement (SAVR) in high-risk patients and is superior to conservative management in inoperable patients.1

The evaluation of the severity of AS remains challenging, especially in patients with low-gradient AS with preserved left ventricular ejection fraction (LVEF). In such cases, it is necessary to assess the transvalvular flow. Intervention should be considered in symptomatic patients with low-flow, low-gradient (LFLG) severe AS, who have a poor prognosis without AVR.3 Transcatheter aortic valve implantation in patients with LFLG severe AS (independent from the LVEF) is associated with mortality rates similar to high-gradient AS, and patients profit symptomatically to a similar extent regardless of AS subtype.4 Furthermore, a sub-analysis from the Placement of Aortic Transcatheter Valves (PARTNER) cohort showed that survival of low-flow AS patients is improved with TAVI compared with medical management in inoperable patients and is similar to TAVI and SAVR in surgical high-risk patients.5

The German Aortic Valve Registry (GARY) represents the largest registry on the outcome of aortic valve procedures comparing SAVR and TAVI so far with >50,000 patients included until September 2013. In the first report from GARY on the acute in-hospital outcome of 13,860 patients recruited in 2011, conventional SAVR yields excellent results in all risk groups: in-hospital mortality was 2.1% without coronary artery bypass grafting (CABG) and 4.5% with CABG. In this real-life registry, TAVI is an alternative to SAVR in high-risk and elderly patients: hospital mortality was 5.1% for transvascular TAVI and 7.7% for transapical TAVI, and stroke risk is comparable with surgery (Table 1).6 For a better comparison, the German
Aortic Valve Score was calculated but overestimated the risk especially in higher risk patients undergoing transvascular TAVI.

The positive GARY in-hospital outcomes of TAVI patients were confirmed by the first publication of the US transcatheter valve therapy (TVT) registry: 7710 patients with a median Society of Thoracic Surgeons (STS) score of 7% underwent TAVI at 224 US centres with an in-hospital mortality rate of 5.5% and a stroke rate of 2.0%. However, in the future, on-going registries still have to address the durability of existing transcatheter heart valve (THVs) during long-term follow-up. Recently, the first 5-year report on the outcome after TAVI with the balloon-expandable Edwards-SAPIEN prosthesis showed good durability with only 3.4% moderate prosthesis dysfunction.

In the current TAVI patient population, which is characterized by severe comorbidities, the overall prognosis is significantly influenced by peri-procedural complications, such as stroke and paravalvular aortic regurgitation (AR).

Stroke after TAVI still represents a peri-procedural complication, which is feared by most of the patients more than death. Although several studies were able to show that the rate of silent cerebral embolism may be as high as 80% of patients after TAVI, fortunately, there is only a low incidence of manifest stroke affecting < 3% of patients. However, Van Mieghem et al. corroborated the hypothesis of procedure-related embolism, as they were able to capture embolic debris travelling to the brain in 75% of TAVI procedures when using a filter-based embolic protection device.

Whether capturing this debris translates into a clinical benefit has to be shown in larger studies, but again raises the question of the embolization source during TAVI, since only half of the debris could be identified as parts of the aortic valve and wall. Therefore, it is our opinion that embolic protection devices should be used in all patients undergoing TAVI until we have identified a patient group at particular risk for stroke.

One of the most important steps of each TAVI procedure is to choose the appropriate size of the valve prosthesis. Like Ulysses, we are caught between Scylla and Charybdis, as incorrect pre-procedural sizing of the aortic annulus may lead to prosthetic undersizing, which can cause significant paravalvular AR or valve embolization, while oversizing carries the devastating risk of annular rupture.

As precise echocardiographic quantification of paravalvular AR in TAVI patients remains challenging, a multimodal approach is recommended for the evaluation of AR with the use of multiple imaging modalities and haemodynamic measurements to precisely quantify the severity of AR immediately after valve implantation and to identify
patients, who will benefit from corrective measures such as post-dilatation or valve-in-valve (VIV) implantation.\textsuperscript{10}

Whether already mild paravalvular AR has a negative impact on outcome remains to be elucidated, as this raises the question as to whether we tend to systematically underestimate the degree of AR with current imaging modalities or whether other factors such as haemodynamics contribute to the worse outcome in patients with significant paravalvular leakage. Interestingly and in contrast to the PARTNER Trial data, the first analysis of the CoreValve US Pivotal Trial Extreme Risk Cohort suggested that 80% of the patients with moderate paravalvular AR at 1 month, who survived to 1 year, experienced a reduction in AR severity. Furthermore, only severe but neither mild nor moderate AR had a negative impact on mortality.\textsuperscript{12}

If these findings can be explained by the low prevalence of AR, the echocardiographic grading of AR, or are a prerequisite of self-expanding THV prostheses to has to be clarified in larger future studies such as the SURTAVI Trial.

Aortic root rupture, albeit infrequently observed, remains a significant concern especially with the deployment of balloon-expandable THV prostheses and post-dilatation in general. A multicentre study showed that calcification of the LV outflow tract and aggressive annular oversizing (≥20% area oversizing) are associated with an increased risk of aortic root rupture in patients undergoing TAVI with use of the balloon-expandable Edwards-SAPIEN prostheses.\textsuperscript{11} In addition, the in-hospital mortality rate of 48% emphasizes the need for a functioning heart team on-site.

Two registry studies addressed the impact of procedure-related conduction disturbances and showed that a persistent, new-onset left bundle branch block was not associated with death or repeat hospitalization, but a higher rate of permanent pacemaker implantation and less improvement of the LVEF after TAVI.\textsuperscript{13,14}

So-called ‘next-generation’ THVs are eagerly awaited to further improve our results and to overcome remaining procedure-related issues such as paravalvular AR by device modifications (e.g. paravalvular space-fillers, full repositionability). The early published data of the DISCOVER Trial (Direct Flow Medical Valve)\textsuperscript{15} and the REPRISE II Trial (Boston Lotus Valve)\textsuperscript{16} showed very promising first results in the reduction of paravalvular leakage.

However, the remaining challenge is patient selection itself. The key question is to know how the individual ‘surgical’ and ‘interventional’ risk can be reliably, consistently, and reproducibly estimated. Therefore, we are in need of a dedicated TAVI score to assess whether a patient should undergo SAVR or TAVR. The development of better scores for the assessment of surgical risk and that of TAVI will improve patient selection and foster the efforts for continuous improvement of quality in aortic valve procedures.

At one end of the spectrum, we can ask: when is a patient too sick for TAVI? At present, the heart team has to be the gatekeeper, since existing surgical risk scores such as the EuroSCORE or the STS mortality score insufficiently assess the risk of patients undergoing TAVI, who are characterized by advanced age and multiple co-morbidities (Figure 1). A dedicated frailty index, based on cognition, mobility, nutrition, instrumental, and basic activities of daily living, has been shown to predict functional outcome in elderly patients undergoing TAVI and might be one tool to identify patients, who would potentially benefit from additional geriatric interventions after TAVI or should not undergo any intervention at all.\textsuperscript{17}

At the other end of the spectrum, and even more subject of debate in common practice, is the treatment of so-called ‘intermediate-risk’ patients (Figure 1). In a recent observational study, Wenaweser et al.\textsuperscript{18} demonstrated that, in well-selected low- and intermediate-risk patients (defined by an STS score of ≤3% and 3–8%, respectively), TAVI has a very favourable outcome with a 30-day mortality rate of 2.4 and 3.9%, respectively, compared with 14.9% in high-risk patients (STS score of >8%). As a consequence of the present insufficient scoring systems for the definition of the individual risk associated with AVR, we already observed a shift of TAVI towards the so-called intermediate-risk patient population in Europe. This fact is already reflected by promising results in the intermediate-risk population of registries such as GARY with a comparable mortality risk for SAVR and TAVI (3.5 vs. 3.9% in patients with the German Aortic Valve Score of 3–6%).

These data strongly encourage the on-going randomized controlled SURTAVI trial (patients with an STS score between 4 and 10%) and the PARTNER IIA trial (patients with an STS score of >4%) comparing the outcomes of TAVI and SAVR, respectively, in

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**Table 1**  
Update on clinical outcomes of ongoing European TAVI multicentre registries

<table>
<thead>
<tr>
<th></th>
<th>GARY (N = 3876)\textsuperscript{b}</th>
<th>FRANCE 2 (N = 3933)\textsuperscript{a}</th>
<th>UK TAVI (N = 3981)\textsuperscript{c}</th>
<th>Italian CV (N = 663)\textsuperscript{d}</th>
<th>SOURCE XT (N = 2706)\textsuperscript{e}</th>
<th>ADVANCE (N = 1015)\textsuperscript{f}</th>
</tr>
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<tr>
<td>Transvascular approach (%)</td>
<td>69.5</td>
<td>82.0</td>
<td>N/A</td>
<td>100.0</td>
<td>66.6</td>
<td>100.0</td>
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<tr>
<td>CoreValve/Edwards-SAPIEN (%)</td>
<td>53.2/41.6</td>
<td>33.0/67.0</td>
<td>48.5/51.5</td>
<td>100.0/0.0</td>
<td>0.0/100.0</td>
<td>100.0/0.0</td>
</tr>
<tr>
<td>Mean logistic EuroSCORE (%)</td>
<td>N/A</td>
<td>21.8</td>
<td>N/A</td>
<td>23.0</td>
<td>20.5</td>
<td>19.4</td>
</tr>
<tr>
<td>30-day mortality (%)</td>
<td>5.1\textsuperscript{TV}/7.7\textsuperscript{TA}</td>
<td>9.5</td>
<td>6.1</td>
<td>5.4</td>
<td>6.3</td>
<td>4.5</td>
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<tr>
<td>1-year mortality (%)</td>
<td>N/A</td>
<td>24.1</td>
<td>N/A</td>
<td>15.0</td>
<td>19.5</td>
<td>17.9</td>
</tr>
<tr>
<td>Paravalvular AR ≥2 (%)</td>
<td>7.0\textsuperscript{TV}/3.4\textsuperscript{TA}</td>
<td>N/A</td>
<td>N/A</td>
<td>21.0</td>
<td>4.4</td>
<td>16.0</td>
</tr>
<tr>
<td>Cerebrovascular event (%)</td>
<td>3.7\textsuperscript{TV}/3.5\textsuperscript{TA}</td>
<td>4.6</td>
<td>2.7</td>
<td>2.5</td>
<td>6.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Vascular complication (%)</td>
<td>15.9\textsuperscript{TV}/4.1\textsuperscript{TA}</td>
<td>11.8</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>20.7</td>
</tr>
<tr>
<td>Permanent pacemaker (%)</td>
<td>23.7\textsuperscript{TV}/9.9\textsuperscript{TA}</td>
<td>15.8</td>
<td>N/A</td>
<td>19.1</td>
<td>10.5</td>
<td>26.3</td>
</tr>
</tbody>
</table>

AR, aortic regurgitation; CV, CoreValve; FRANCE, French Aortic National CoreValve and Edwards Registry; GARY, German Aortic Valve Registry; STS, Society of Thoracic Surgeons; TA, transapical; TAVI, transcatheter aortic valve implantation; TV, transvascular (including transfemoral, transsubclavian, and transaortic); TVT, transcatheter valve therapeutics.
intermediate-risk patients. The results of these trials will further clarify how to define risk in patients undergoing AVR (Figure 1) and will potentially lead to the adaption of our ESC guidelines expanding the indication of TAVI to intermediate-risk patients.

Among the other most challenging clinical situations is the management of coronary artery disease (CAD) in AS patients referred for TAVI. A comprehensive review of the literature showed that significant CAD is present in up to 75% of patients, but complete recanalization seems not to be a prerequisite for successful TAVI. On-going studies randomizing patients to surgical or percutaneous management strategies for severe AS will help provide valuable information regarding the impact of CAD on TAVI outcomes, the role of PCI, and its timing in relation to TAVI.

The impact of pre-interventional mitral regurgitation (MR) on the clinical outcomes of patients undergoing TAVI also remains controversial. A sub-analysis from the PARTNER trial found that both TAVI and SAVR were associated with a significant improvement in the severity of MR in survivors. However, moderate or severe MR at baseline was associated with increased 2-year mortality after SAVR but not after TAVI. These findings could be confirmed in a sub-analysis of the Italian CoreValve registry, which added that a significant improvement in MR was more likely in patients with functional MR without pulmonary hypertension and atrial fibrillation.

### Aortic regurgitation

Patients with severe AR developing symptoms have a poor prognosis. Treatment of isolated AR has traditionally been SAVR with an increasing amount of repair strategies in expert centres. However, selected patients at high surgical risk might benefit from a transcatheter therapeutic approach.

A preliminary report in high-risk patients with pure native aortic valve regurgitation, who underwent TAVI with use of the self-expanding Medtronic CoreValve, showed a 30-day mortality rate of 9.3%, but two important limitations became obvious: 18.6% of the patients needed a second valve as a consequence of incomplete anchoring resulting in malposition and/or migration, and 20.9% had non-existent calcified landing zone due to suboptimal prosthesis sizing. The final role of TAVI in this patient group needs further determination in future trials, since a large proportion of patients with AS will potentially lead to the adaption of our ESC guidelines expanding the indication of TAVI to intermediate-risk patients.

The current guidelines state that the percutaneous MitraClip procedure may be considered in symptomatic patients with severe primary or secondary MR despite optimal medical therapy, who fulfil the echo criteria of eligibility, are judged inoperable or at high risk for surgery by a heart team, and who have a life expectancy of >1 year.

The 4-year data from the Endovascular Valve Edge-to-Edge REpair Study (EVEREST) trial showed that although MitraClip patients more commonly required surgery to treat residual MR (24.8 vs. 5.5%), there was no difference between the groups with regard to mortality (17.4 vs. 17.8%) and functional improvement (moderate/severe MR: 21.4 vs. 24.7%).

The real-world ACCESS-EU (A Two-Phase Observational Study of the MitraClip System in Europe) registry, where most of the patients were treated for secondary MR, confirmed that the MitraClip procedure is effective with low rates of hospital mortality and adverse events, and functional improvement up to 1 year in elderly, high-risk patients.

Randomized trials comparing medical therapy and MitraClip in secondary MR are ongoing in Europe and the USA to further define the indications of this technique in a patient group where surgical results are suboptimal.

### Mitral stenosis

Although rheumatic fever, which is the predominant aetiology of mitral stenosis (MS), has greatly decreased in western countries, percutaneous mitral commissurotomy (PMC) is still the reference treatment for MS in patients with favourable valvular anatomy and is able to prevent mitral valve replacement with the inherent operative mortality and long-term risks of prosthesis-related complications. The long-term follow-up analysis over 20 years demonstrated that, after successful PMC (valve area of \( \geq 1.5 \text{ cm}^2 \)) and/or surgery, 60% remained free from surgery after 10 years, with few or no symptoms in most cases. Thus, this study elegantly emphasized the role of repeat PMC in delaying mitral surgery.

Nonetheless, dedicated devices for transcatheter mitral valve replacement (TMVR) are eagerly awaited for patients, in whom PMC and/or surgery is contraindicated. The first-in-man TMVR using the commercially available balloon-expandable Edwards-SAPIEN prosthesis suggested feasibility in selected patients with calcified native mitral valve stenosis at prohibitive surgical risk.

### Degenerated bioprosthetic valves

With >200 000 SAVR procedures globally, transcatheter VIV implantation has an important potential role as a new treatment option for degenerated bioprosthetic surgical valves. The global VIV registry with 202 patients from 38 centres demonstrated that the VIV procedure was successful in the vast majority of patients (93.1%) with acceptable 30-day mortality (8.4%). Safety and efficacy
concerns include device malpositioning, ostial coronary obstruction, and high gradients after the procedure. 28

Long-term outcomes are needed, before a general recommendation can be given that younger patients could undergo valve replacement with use of a xenograft valve in order to prevent oral anticoagulation and to overcome potential bioprosthetic valve failure with transcatheter VIV implantation. It is our believe, however, that transcatheter VIV implantation will play an increasingly important role in the management of this difficult patient group.

Anticoagulation in mechanical prostheses

RE-ALIGN is the first randomized study comparing a novel oral anticoagulant with warfarin in patients with a mechanical valve. It showed that dabigatran is not as effective as warfarin for the prevention of thromboembolic complications in patients with mechanical heart valves and is associated with more bleeding events. Thus, dabigatran and other new oral anticoagulants (NOAC) should not be used in patients with mechanical heart valves. 29

Conclusion

Our crystal ball prediction for the next decade is that transcatheter-based therapeutic approaches will increasingly gain ground for the management of VHD, complement many ‘open heart’ procedures, and finally, may supersede—at least in part—some conventional surgical techniques. However, before TAVI and other transcatheter heart valve interventions can expand to intermediate-risk patients, evidence in favour of this less invasive treatment has to be provided by upcoming randomized clinical trials.

Conflict of interest: J.-M.S. has received research grants and speaker’s fees/honoraria from Medtronic and Edwards Lifesciences. E.G. has received speaker’s fees/honoraria from and is a proctor physician for Medtronic. A.V. has received speaker’s fees/honoraria from Edwards Lifesciences and Abbott and is consultant to Valtech and Abbott.

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