REVIEW

Frontiers in cardiovascular medicine

The future of transcatheter aortic valve implantation

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Since the introduction of transcatheter aortic valve implantation (TAVI) into clinical practice, the treatment of aortic stenosis has changed dramatically. In the past, medical therapy with or without balloon aortic valvuloplasty was the only option for inoperable patients. More recently, TAVI has become the treatment of choice for these patients and the preferred alternative for high-risk operable patients. Surgical aortic valve replacement (SAVR) currently remains the gold standard for patients at low or intermediate operative risk. As randomized trials have demonstrated comparable results between TAVI and SAVR in the high-risk population, there is now a clear trend towards performing TAVI even in intermediate-risk patients while awaiting the results of randomized trials in that population. Nevertheless, there are still questions regarding TAVI involving paravalvular leak (PVL), stroke, pacemaker requirements, and durability that remain to be more definitively answered before TAVI can routinely be performed in a broader, lower risk population. Improvements in patient selection, imaging, and second and third generation devices have decreased the incidence of PVLs and vascular complications that followed the earliest TAVI procedures, but the rates of perioperative stroke and permanent pacemaker implantation must still be addressed. Furthermore, the long-term durability of TAVI devices and a role for post-procedure antithrombotic management remain unanswered. Until these questions are more clearly answered, it is the Heart Team's task to determine the optimal treatment for each patient based on risk scores, frailty metrics, comorbidities, patient preference, and potential for improvement in quality of life.

Keywords   Aortic stenosis • Aortic regurgitation • TAVI • Transcatheter aortic valve implantation • TAVR • Transcatheter aortic valve replacement • Aortic valve surgery

Introduction

Over the last decade, transcatheter aortic valve implantation (TAVI) has emerged to become the treatment of choice for inoperable patients and the preferred alternative for high-risk patients with severe, symptomatic aortic stenosis (AS). Previously medical treatment and balloon aortic valvuloplasty were the only treatment options for inoperable patients with an average survival after the onset of symptoms of 2−3 years.[1,2] Following Cribier's first implantation in 2002, TAVI has evolved to become a standard procedure worldwide and can be performed with only moderate sedation rather than general anaesthesia.[3] In contrast to the adoption of percutaneous coronary intervention which started in a low-risk population, TAVI was initially performed in patients at highest risk and is now gradually being assimilated into intermediate and lower risk patients. That over 100 000 TAVI procedures have now been performed worldwide in the last decade attests to the success and acceptance of TAVI. Nevertheless,

surgical aortic valve replacement (SAVR), first reported in 1960 by Harken, remains the gold standard for patients at low or intermediate operative risk because this technique is associated with excellent long-term outcomes and low perioperative risk.[4−6] Recently published short- and mid-term outcomes to 5 years of randomized control trials of TAVI in inoperable and high-risk patients continue to confirm the early results and we await results of randomized trials of TAVI in intermediate-risk patients. In this review, we highlight the current status of TAVI, present questions that remain to be answered, and offer a prediction for what TAVI may hold in the future.

Current status

Guidelines

The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology and the European

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Association for Cardio-Thoracic Surgery defined indications for TAVI in the 2012 Guidelines on the Management of Valvular Heart Disease.[5] The corresponding 2014 U.S. Guidelines define similar indications.[6] Both recommend TAVI in patients with severe symptomatic AS who are not suitable to undergo conventional AVR as assessed by a heart team, if they are likely to gain improvement in their quality of life (QoL) and if they have a life expectancy >1 year given their comorbidities [Class of Recommendation (COR) I, Level of Evidence (LOE) B]. Transcatheter aortic valve implantation should also be considered in high-risk patients with severe symptomatic AS who are suitable for surgery but in whom TAVI is favoured by a Heart Team as a COR IIa LOE B recommendation. Under these current treatment indications, a significant clinical unmet need still exists worldwide (*Figure 1*).[7]

Appropriate patient selection is a key to good outcomes. Especially in the absence of an established, accurate predictive risk score, optimal patient selection is best accomplished by a Heart Team, who must consider all of the patient's comorbidities (COR 1, LOE C) (*Figure 2*). Furthermore, the role of the Heart Team cannot be limited to pre-operative assessment and choices regarding valve type and access route; the Heart Team is essential to the management of intraoperative complications as well as postoperative care. This includes cross-training—that is a cardiologist performing TA-TAVI (after exposure of the apex by the surgeon) or a cardiac surgeon performing TF-TAVI (assisted by an interventional cardiologist)—further promotes the ideal cooperation and collaboration of the Heart Team.

Impact of transcatheter aortic valve implantation on surgical aortic valve replacement volume

The number of TAVI procedures performed has increased annually worldwide over the last decade with significant variation from country to country. Mylotte *et al.*[8] demonstrated that reimbursement systems influenced TAVI penetration (*Figure 3*). Owing to the early introduction of a TAVI-specific Diagnosis-Related Group in January 2008 and the country's compulsory health insurance, 46% of all TAVI procedures completed in Western Europe in 2011 were performed in Germany. Although more than 40% of all isolated aortic valve replacement in Germany were performed by TAVI, this did not result in a decrease in the volume of SAVR from prior years
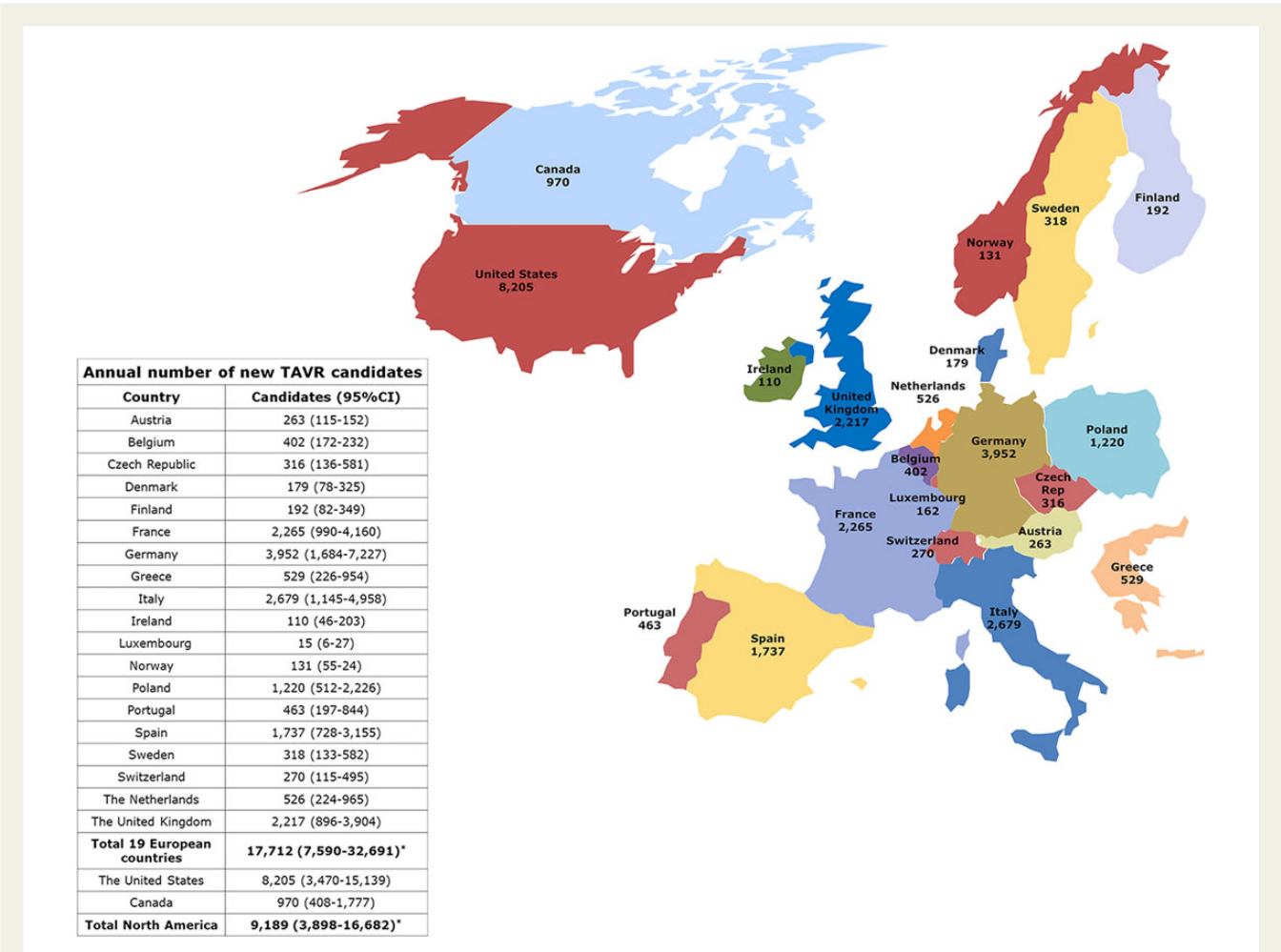
Annual number of new TAVR candidates	
Country	**Candidates (95%CI)**
Austria	263 (115-152)
Belgium	402 (172-232)
Czech Republic	316 (136-581)
Denmark	179 (78-325)
Finland	192 (82-349)
France	2,265 (990-4,160)
Germany	3,952 (1,684-7,227)
Greece	529 (226-954)
Italy	2,679 (1,145-4,958)
Ireland	110 (46-203)
Luxembourg	15 (6-27)
Norway	131 (55-24)
Poland	1,220 (512-2,226)
Portugal	463 (197-844)
Spain	1,737 (728-3,155)
Sweden	318 (133-582)
Switzerland	270 (115-495)
The Netherlands	526 (224-965)
The United Kingdom	2,217 (896-3,904)
Total 19 European countries	**17,712 (7,590-32,691)***
The United States	8,205 (3,470-15,139)
Canada	970 (408-1,777)
Total North America	**9,189 (3,898-16,682)***

Figure 1 Annual number of elderly patients with severe aortic stenosis who are potential transcatheter aortic valve replacement candidates in different countries under current treatment indications; from Osnabrugge *et al.*[7]
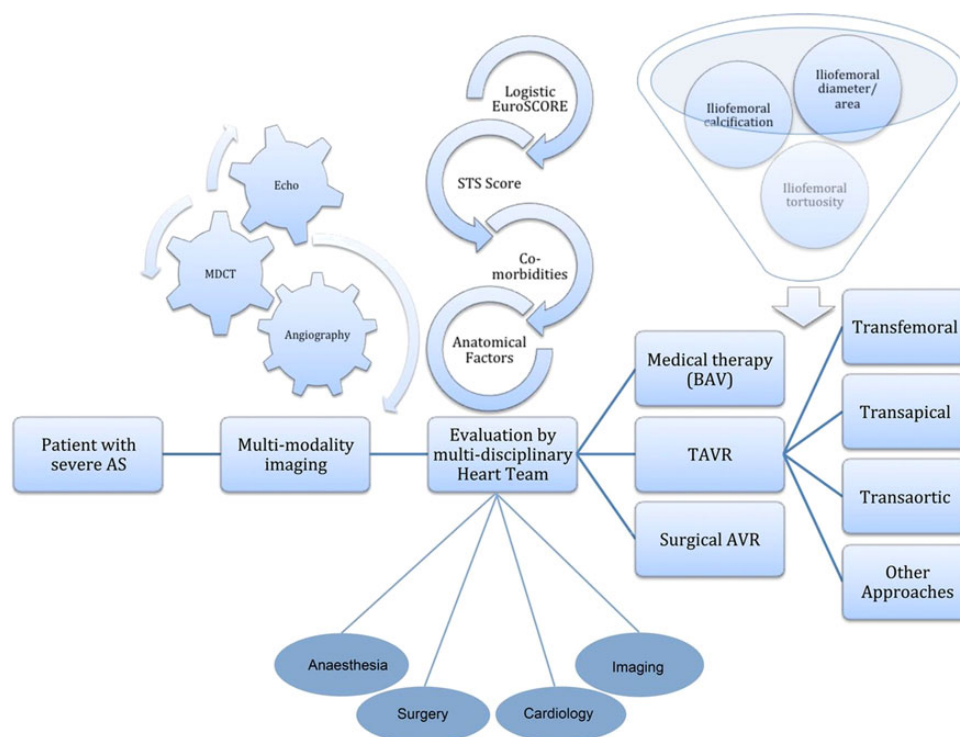
Figure 2 Workflow process involved in the evaluation and management of a patient presenting with severe symptomatic aortic stenosis; from Agarwal et al.[101]

(*Figure 4*).[9] This may be interpreted as most of the patients currently treated with TAVI previously had not been referred for SAVR in the pre-TAVI era. When looking forward it may be predicted, however, that the number of TAVI procedures will surpass the number of SAVR, ultimately decreasing SAVR volume. The rapidity of this paradigm shift will be influenced by the adoption of acceptable reimbursement rates worldwide and the expansion of TAVI indications into the intermediate-risk cohorts and long-term durability data. Until then, several issues remain to be solved.

Open issues

Paravalvular leaks

As compared with SAVR, calcified aortic leaflets are not removed during TAVI, so incomplete sealing between the prosthesis and the native annulus results, leading to paravalvular leaks (PVL). At least mild PVL is reported be present in up to 61% of patients after TAVI.[10] Following SAVR even mild PVL has not traditionally been tolerated, but trace and mild PVL after TAVI is often considered to be acceptable and benign. Studies have shown that moderate and severe PVL are associated with a worse outcome, and some studies even reveal a higher mortality rate in cases of even mild PVL.[11–14] The conflicting results regarding the potential impact of mild PVL may be explained by the variation in grading of PVL severity after TAVI, between devices and studies despite the existing Valve Academic Research Consortium-2 (VARC-2) recommendations and the characteristics of PVL with different devices.[15,16]

In cases of more than mild PVL, post-dilatation (one or more additional dilatations within valve following stent deployment) or valve-in-valve (ViV) implantation (a second TAVI valve) should be considered at the time of the procedure.[17,18] Another option in selected patients is percutaneous PVL closure using an Amplatzer vascular plug.[19]

The incidence of moderate and severe PVL has been decreasing in recent experience. This is a result of several factors: (i) the use of 3D computerized tomographic (CT) reconstruction for measurement of the annulus, which is more accurate than echocardiography and results in better pre-interventional choice of valve size[20]; (ii) the knowledge that most TAVI valves should be modestly oversized relative to the annulus (when measured by CT)[21]; (iii) improved delivery devices that allow repositioning of the valve, leading to optimized valve deployment; and (iv) new TAVI valves that are designed to minimize the risk of PVL (e.g. with special sealing cuffs, skirts, or inflatable cuffs)[18]; and (v) the increasing experience of the operators regarding all technical aspects of valve deployment and the choice of valves contribute definitely to better functional results with less PVLs.[22]

Vascular complications

Vascular complications (VCs) are most commonly a consequence of arterial sheath insertion during TF-TAVI. Reported rates of major VC range from 5.5 to 20%.[23,24] This wide range may be the result of studies using definitions of VC other than the established VARC definitions as well as the experience of the reporting centre
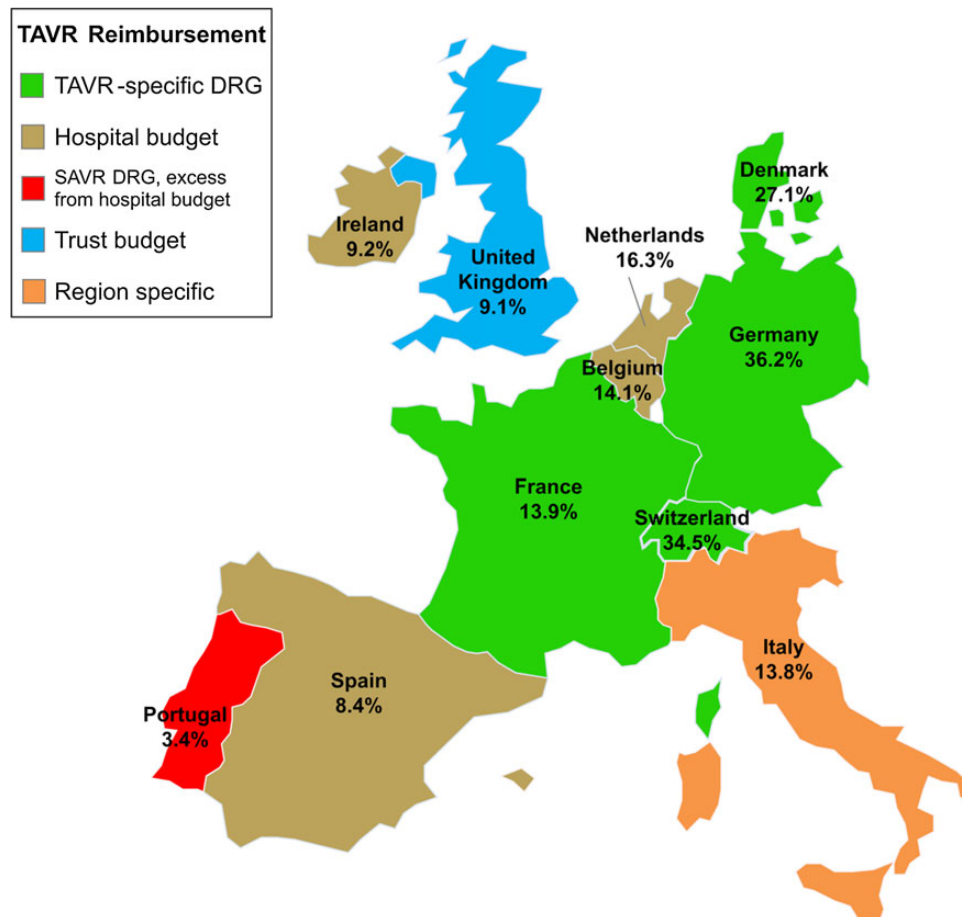
Figure 3 Reimbursement systems and transcatheter aortic valve replacement penetration across Europe: map of the 11 study nations depicting estimated transcatheter aortic valve replacement penetration rate (the use of transcatheter aortic valve implantation among eligible patients) and the 2011 transcatheter aortic valve replacement reimbursement systems; from Mylotte *et al.*[8]

and the availability of newer, smaller delivery systems.[15,25] The size of TF-TAVI delivery sheaths has decreased significantly compared with the first generation systems. The Edwards Sapien 3 (Edwards Lifesciences, Inc., Irvine, CA, USA), for example, has reduced sheath size from 22 to 14 Fr for a 23 mm valve compared with the original Sapien valve (*Figure 5*). Although, together with the use of percutaneous closure devices, these technical improvements have led to a lower incidence of VC than in initial trials, recently published studies still report some VC rates up to 20%.[23,26] However, the continued efforts towards smaller sheaths should in the future reduce the risk of VC.

Long-term durability

The long-term durability of TAVI valves is a question that was especially prominent early in the history of TAVI. This question remains an important one if TAVI is to be considered for use in lower risk and younger patients. As the designs of the valves differ considerably, the long-term data for one valve may not necessarily equate to others. Not removing valve calcification may influence valve stent geometry causing distortion or incomplete expansion and lead to mechanical stress on implants. These factors, as well as valve

crimping, may affect valve durability.[27] Stent fractures, as seen in the Melody valve (Medtronic, Inc., Minneapolis, MN, USA), have not been observed in TAVI devices.[28–30] The longest reported outcomes are currently at 5 years with smaller experience reported up to 9 years with as yet no significant signal of structural valve deterioration. In the PARTNER trial, no structural valve deterioration requiring SAVR was detected after 5 years and the valve area as well as the mean transvalvular gradient remained stable.[31,32] Another group has reported that after 5 years, 9.7% of living patients have moderate prosthetic valve failure without the need for reoperation or reintervention.[33] Of note, no valve deterioration was detected at the 4-year follow-up in the same cohort. Most reports have shown only prosthesis dysfunction that have no need for intervention.[34] In the longest reported experience, >1000 valve implantations, with a small number of the valves at over 9 years in Vancouver, only five failed valves could be identified.

For comparison, the reported mid-term failure rates in surgical bioprostheses are very low, <1% before 5 years and 10% at 10 years for patients over 65 years old.[35] As studies showed that structural valve deterioration is age-related, detecting prosthesis failure in an elderly cohort, like TAVI patients, is very unlikely due to slower
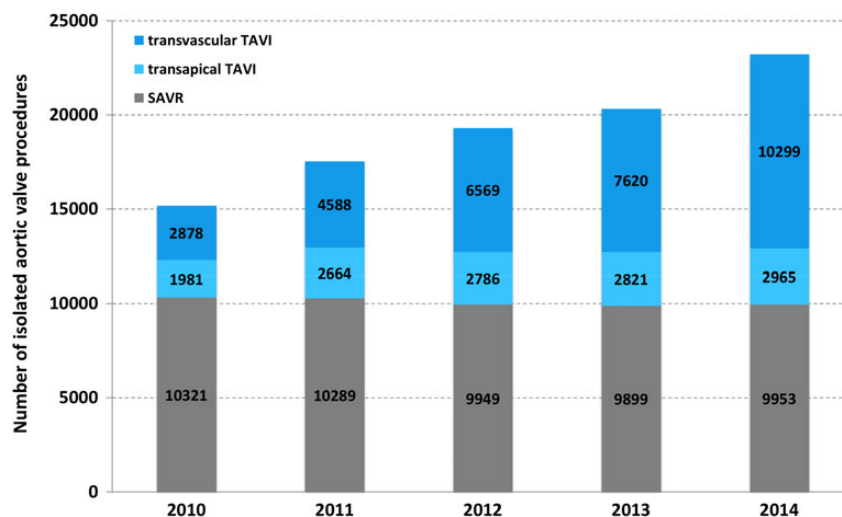
Figure 4 Isolated SAVR and transapical or transvascular aortic valve implantation (TAVI) in Germany. The figure shows almost unvaried quantity of SAVR and the increase of TAVI. Modified after AQUA Qualitätsreport 2014.[9]
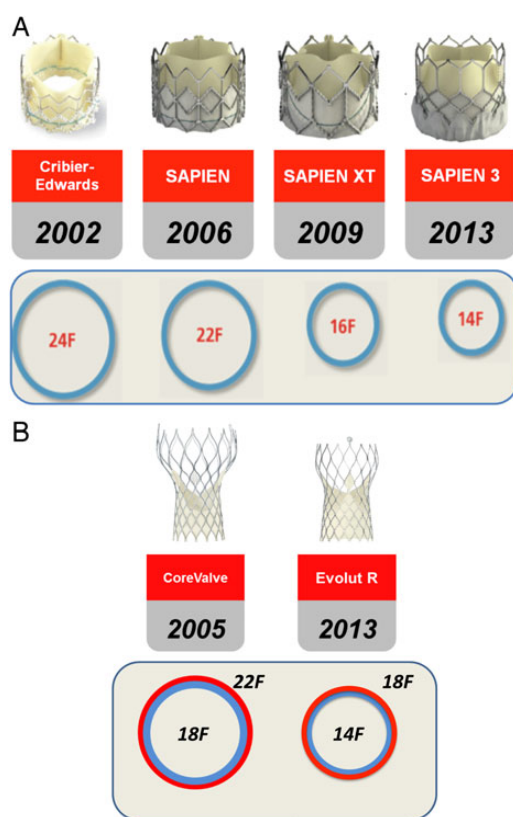

Figure 5 Evolution of the Edwards balloon-expandable transcatheter valves (A) and Medtronic self-expandable valves (B) (sheath compatibility for a 23 mm valve).

deterioration and shorter term survival. The fact that even single-centre reports about the long-term outcome of surgical bioprosthesis, analyse a total follow-up of more than 18 000 valve-years implanted, demonstrates the difficulty in obtaining reliable durability data for TAVI at this still early stage.[36]

In conclusion, the reported durability of TAVI devices appears at the current state of knowledge sufficient for an elderly, high-risk cohort, but long-term studies, much longer than 5 years in duration, are necessary to prove comparable durability to SAVR valves, which will allow for implantation in younger patients.

Pacemaker rates

The onset of new atrioventricular conduction disturbance after TAVI, requiring permanent pacemaker implantation (PPI), is one of the most frequent complications after TAVI and higher than in SAVR.[37] This complication is due to the anatomical proximity of the aortic valve to the AV node, bundle of His, and major conduction branches. Of note, some studies calculated PPI rate as the incidence of new PPI in the total study cohort. Such a definition underestimates the true PPI rate because patients with pacemaker in place prior to TAVI, usually ~20%, are included in the total cohort. To determine the true risk of new PPI in TAVI patients, patients with prior pacemaker implantation should be excluded from the analysis to determine the new PPI rate of only the patients at-risk. Nazif et al.,[38] for example, correctly calculated an 8.8% new PPI rate for at-risk patients in the PARTNER trial.

The rate of PPI varies between studies and implanted valves. While the rate is 5–12%[39–42] after implantation of an Edwards Sapien valve, it is considerably higher with 24–33%,[43,44] with Medtronic CoreValve (Medtronic, Inc.). Siontis et al. published a meta-analysis that included 11 210 patients undergoing TAVI with a

median PPI rate of 6% after Edwards Sapien and 28% after Medtronic CoreValve implantation consistent with earlier reports.[45,46] Some reports compare these PPI rates of the Edwards Sapien and Medtronic CoreValve and conclude that, due to their design, self-expandable valves are associated with a higher incidence of PPI. However, several second generation self-expanding devices appear to have a PPI rate more comparable with the Edwards Sapien valve.[47,48] Additionally, higher rates of PPI have been reported when using the Edwards Sapien 3 valve, which seems to be related to a longer length of stent below the annulus with impingement on the conduction system.[49,50]

Whether PPI is to be considered a major complication and/or significantly influences patients' functional outcomes and QoL is controversial. Weber *et al.*[51] have reported that left ventricular conduction disturbances with permanent right ventricular pacing are associated with worse recovery of left ventricular ejection fraction and increased heart failure-related symptoms (20.4% of patients with PPI remained in NYHA III or IV after 3 months). In the PARTNER trial, new PPI was associated with a longer duration of hospitalization and higher rates of repeat hospitalization, mortality, and repeat hospitalization at 1 year.[38]

Reduction of risk for stroke

The risk of cerebrovascular events was one of the primary concerns associated with TAVI. New ischaemic lesions can be detected by magnetic resonance imaging (MRI) in 68−84% of patients after TAVI.[52] However, in these studies, only up to 4% of the lesions by imaging were associated with clinical stroke. About half of perioperative strokes occur intraprocedurally or within the first 24 h after TAVI. The degree of device manipulation performed during the procedure, including multiple valve positioning manoeuvres or post-balloon dilatation, is associated with a higher rate of early stroke. Delayed strokes may be related to post-operative atrial fibrillation or other factors. Two meta-analyses, each including more than 6000 patients, report a mean 30 days clinically significant stroke rate of 3−4%.[53,54] In the PARTNER trial, TAVI showed a statistically significant higher rate of stroke and transient ischaemic attack at 30 days (2.4 vs. 5.5%, $P = 0.04$) and 1 year compared with SAVR, but no difference was appreciable after 5 years.[55,31] The rate of major stroke was similar after TAVI and SAVR. In an more recent trial no increased risk in stroke was noted for TAVI.[56]

New embolic protection devices aim to reduce the number of neurological events caused by intraoperative embolization of debris. These devices can be categorized in two groups: (i) filters that capture debris liberated into the cerebral circulation and (ii) devices deflecting such debris away from the cerebral circulation. Several small trials have studied their ability to reduce neurological events. In the CLEAN-TAVI trial, a 100 patient single-centre study, patients were randomized to either TAVI without emboli protection or TAVI with the Claret Montage™ dual-filter Cerebral Protection System.[56] In patients for whom the device was implemented, the number and volume of cerebral lesions, as determined by MRI at 2 and 7 days, were significantly reduced. The rate of post-operative ataxia was also reduced at 2 days, but not at 7 days or 30 days. Another study found that the Edwards Embrella Embolic Deflector (EED) also reduced lesion volume compared with TAVI without embolic protection device.[57] However, a recently published study confirmed this reduced lesion volume, but an increased number of cerebral ischaemic lesions after EED use were discovered.[58] The TriGuard™ HDH Embolic Deflection Device (TriGuard) achieved complete coverage of the cerebral vessels in 89% of the patients in an initial trial. This small study suggested a trend to less new neurologic deficits following TAVI (15.4 vs. 3.1%) but was unable to reach significance ($P = 0.16$).[59]

Currently all published studies employ very small cohorts, so larger studies must be completed to determine whether using an embolic protection device truly improves neurological outcomes after TAVI. Nevertheless, these devices only reduce neurological lesions occurring *during* the procedure. Because up to half of cerebral ischaemic lesions are delayed, proper yet not determined antithrombotic management of patients is, and will remain to be of tremendous importance.

Antithrombotic therapy

The main rationale for antithrombotic therapy post-TAVI is to prevent cerebral ischaemic events and is based on the experience of SAVR: with post-procedural sinus rhythm, dual antiplatelet therapy with clopidogrel and aspirin for 3−6 months followed by lifelong aspirin therapy is recommended (COR IIb, LOE C). Clopidogrel should not be used if a vitamin K antagonist is used.[5,6]

Another indication for anticoagulation is early valve thrombosis. Latib *et al.*[60] reported an incidence of 0.61% in a large study with 4266 patients undergoing TAVI. However, Leetmaa *et al.*[61] showed in a study employing CT imaging that, within 1−3 months after TAVI valve thrombosis was more common than anticipated but was asymptomatic in the majority of cases (4% after 1−3 months). Several case reports suggest that thrombosis occurs during the first 2 years after TAVI (with the majority occurring by 1 year) and can lead to valve dysfunction with rapid increases in transvalvular aortic gradients.[60,62−64] Treatment options include either anticoagulation with heparin when discovered or warfarin or SAVR if severe and not resolving on anticoagulation.[64] Different mechanisms for early valve thrombosis, such as suboptimal positioning leading to turbulent flow or coagulation disorders, have been proposed. Thus, until recently, valve thrombosis was thought to be a very rare and treatable complication after TAVI. However, due to new findings using 4D CT imaging, valve thrombosis for TAVI devices has become an issue of some concern. This issue was first noted in the early Portico IDE study, showing reduced leaflet motion and thrombosis. In the 2015 EuroPCR and TVT meetings, incidences of up to 10−40% were reported. Among these reports, the Portico IDE study showed the highest rates of reduced leaflet motion with 43.2% after Portico (St Jude Medical Inc., St Paul, MN, USA) and 42.9% after Sapien XT implantation. The SAVORY study performed 4D CT 3 months after AVR and observed reduced leaflet motion in all types of aortic bioprostheses including SAVR (TAVI 18.5% vs. SAVR 6.7%; $P = 0.43$). The RESOLVE registry at the Cedars-Sinai Heart Institute showed a similar valve thrombosis rate of 10% after TAVI and 8% after SAVR. Reduced leaflet motion was not associated with symptoms, clinical events, or increased transvalvular gradients. Based on these findings, several issues need to be addressed: (i) Is this an imaging finding only or is it associated with significant clinical events? (ii) Is it device specific or class specific? (iii) Can it be prevented and if so by what means, e.g. antiplatelet therapy or anticoagulation?

New valves

Apart from advancements made in the established Edwards Sapien and Medtronic CoreValve devices, other new valve designs may influence the future of TAVI. Some of the next-generation devices, such as the Portico or the DirectFlow (DirectFlow Medical, Santa Rosa, CA, USA) valve, are repositionable and retrievable until fully deployed. Owing to new deployment techniques, like with the DirectFlow or Lotus valve (Boston Scientific, Natick, MA, USA) rapid pacing can be avoided. Next generation, low profile TAVI devices might expand transfemoral access and further reduce VCs. The Colibri device (Colibri Heart Valve, LLC, Broomfield, CO, USA) is a pre-mounted and pre-packaged TAVI valve within a 14 Fr (24 mm-sized valve) introducer and comes ready for insertion into the patient.[65] Tissue engineered heart valves with regenerative potential might overcome the continuous degeneration that plagues bovine or porcine bioprostheses.[66] Tissue engineered heart valves have already been produced by several groups.[67,68] Catheter-based implantation of these valves is currently undergoing testing in the aortic and pulmonary positions in animal studies.[66,67,69]

Other complications

Other complications such as annulus rupture, myocardial perforation, valve dislodgement, and implantation in a suboptimal position are rare, and the incidence of several of them is being reduced over time. A recently published report from the German Aortic Valve Registry (GARY) in 15 064 implantations showed a significant decrease of severe life threatening and technical complications in the last years.[22] Improved imaging and pre-procedural planning resulted in low rates of aortic dissection (0.2%) and aortic annular rupture (0.4%). Improved devices and operator experience lowered the incidence of device embolization (0.3%), need for repositioning of the valve prosthesis (1%), and retrieval of the valve prosthesis (0.9%). In the same registry, renal replacement therapy was needed in 5% of the patients. Acute kidney injury still remains with an incidence, depending on the definition used, between 3.4 and 57%.[70] Newer techniques like pre-procedural assessment of aortic annulus dimensions with a non-contrast 3D FLASH magnetic resonance angiography or intraprocedural single minimal contrast media injection might be able to further reduce this complication.[71,72] The trend towards TAVI under monitored local anaesthesia without endotracheal intubation precludes routine transoesophageal echocardiographic monitoring during the procedure. Whether the loss of this valuable imaging tool is compensated by increased operators experience, better valve technology and improved pre-operative imaging remains an open question.

Improved patient selection

Owing to the lack of a TAVI-specific risk score, risk assessment is currently performed with either the EuroSCORE II or Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score.[73,74] Though both scores are superior to the logistic EuroSCORE, they have only moderate discrimination for predicting 30-day mortality after TAVI.[75] Incorporating patient frailty into the pre-operative risk assessment is essential because many significant comorbidities are not captured by STS-PROM or EuroSCORE II. In order to better predict patients' risk, specific risk scores, like

the German Aortic Valve Score, were developed.[76] Patients should not undergo TAVI if a non-cardiac disease is the main cause of limited QoL or if the estimated life expectancy is <1 year. A procedure should only be performed if an improvement in QoL is reasonably expected. Thus, poor outcome for TAVI is currently defined by measuring QoL at 6 months as defined by the Kansas City Cardiomyopathy Questionnaire score <45, a decrease in score ≥10 compared with baseline, or death.[77] Ultimately, the Heart Team is tasked to consider simultaneously risk scores, patient frailty, medical history, and potential for QoL improvement for each patient individually before making a therapeutic decision. The development of more accurate risk scores for potential TAVI patients will help the Heart Team to increase objectivity in this decision-making process.

Outlook/what happens if we solve these issues?

Valve-in-valve

In the early years of TAVI, ViV implantation was primarily used acutely after malpositioned TAVI devices associated with severe aortic regurgitation (AR). By implanting a second valve with improved positioning during the same procedure, AR could often be reduced acutely.[78] Currently, due to improvements in delivery devices, imaging, and experience, such an acute indication for ViV is no longer the primary focus. Valve-in-valve is, on the other hand, more commonly being used in the treatment of degenerated aortic valve bioprostheses. The perioperative risk of a re-operation due to a degenerated aortic valve bioprosthesis ranges from ~2% in low-risk patients up to 20% in the high-risk cohort.[79–81] As an alternative, implanting a TAVI valve within a failed surgical bioprosthesis can extend the lifespan of the original implant. This new treatment option for degenerated bioprostheses also promotes the trend towards implanting biological surgical valves in younger patients under the age of 60, as is increasingly recommended by society guidelines.[5]

While ViV is increasingly used, the variability in the true inner diameter of various surgical bioprostheses and their radiopaque signature present unique challenges. The inner diameter of a bioprosthesis determinates whether ViV is possible and, if so, which valve can be used. Radiopaque markers are crucial for intraoperative valve positioning. A ViV app designed by Bapat provides the necessary information about each valve to aid decision-making.[82]

Of note, ViV is also being employed in the mitral position to treat patients with deteriorated mitral bioprostheses or for recurrent mitral regurgitation after annuloplasty with a complete annuloplasty ring.[83,84] Transcatheter Mitral Valve Implantation is also currently under investigation, and the first feasibility studies, enrolled in 2014, may ultimately obviate the need for ViV therapy at the mitral position.

Aortic regurgitation

According to the European Heart Survey, AR causes 10.9% of all native valve disease.[85] Because calcification is usually absent in isolated AR, anchoring of a TAVI valve is more challenging. The absence of calcification is a relative contraindication for TAVI, but several devices have been used for successful implantation in patients with AR.[86–90] In a series of Corevalve (Medtronic, Inc.) implantations

for the treatment of isolated AR, Roy *et al.*[86] reported a need for a second valve implantation due to residual AR in 8 of 43 patients (18.6%). The Jenavalve prosthesis (Jenavalve Technology, Inc., Munich, Germany), which clips on to the aortic valve leaflets, was the first device approved for the treatment of isolated AR. In a German multicentre study, 31 high-risk patients with isolated AR were treated with the Jenavalve device.[88] Implantation was successful in 30 of 31 patients, but due to patients' comorbidities, the 30-day mortality was 12.9%. Larger studies must be completed before the expansion of TAVI for the treatment of AR is appropriate.

Bicuspid

The incidence of AS in patients with a bicuspid aortic valve is high (up to 75%), but onset of disease and symptoms is usually at a relatively young age.[91] In addition to the low-risk profiles of these patients, prominent concerns regarding TAVI valve durability and function (a less circular deployment of TAVI valves results in PVL) suggest a relative caution for TAVI in bicuspid aortic valve therapy. Several studies have demonstrated feasibility and acceptable outcomes in this population.[92–94] However, the incidence of relevant PVL was reported to be up to 31%, unacceptably high for patients at low or intermediate risk. The usage of balloon-expandable valves does appear to result in a more circular-shape deployment with reduced rates of PVL, so there may indeed be a future for TAVI in the treatment of bicuspid aortic valves. It should also be remembered that ~25% of patients with true bicuspid disease also have aneurysmal disease of the ascending aorta, which also needs to be addressed. A prospective study specific to this population is warranted.

Percutaneous TA-transcatheter aortic valve implantation

Although most centres favour a TF-TAVI-first strategy and smaller sheath sizes have increased the number of patients that can be treated by a TF approach, there remains a need for alternative access routes for TAVI. TA-transcatheter aortic valve implantation, the second-most employed access route, is characterized by relatively easy surgical access, and the short, straight distance between the incision and the aortic valve allows for accurate valve positioning. The use of vascular closure devices for TF-TAVI is already standard of care, but apical closure devices are still under investigation.[95] With these devices, percutaneous TA-TAVI might become more feasible.

Intermediate risk

A very important question for the future of TAVI is how indications will be expanding in the coming years. Although TAVI was initially used to treat inoperable patients, this procedure has already become standard for high-risk patients. Data demonstrate that patients at intermediate risk are increasingly being treated with TAVI worldwide. A report from the TVT Registry demonstrated a median STS risk score of ~7% in patients treated with TAVI from November 2011 through March 2013.[42] During the same time period, the STS score in the German GARY registry was 5.0 indicative of largely an intermediate-risk profile.[22] Several reports from European centres demonstrate the shift to intermediate-risk patients in clinical practice and reveal low mortality and stroke rates in these patients,[96–98] comparable with SAVR. Large randomized trials are ongoing with the potential to confirm these early findings in intermediate-risk cohorts.[99] The PARTNER IIa trial has enrolled 2000 intermediate-risk patients with an STS score between 4 and 8 undergoing TAVI with the Edwards Sapien device. The SURTAVI trial, with an estimated subject enrolment of 2500, includes patients with an STS score ≥ 3 and ≤ 10 undergoing TAVI with the Medtronic CoreValve system. Both trials have a primary composite endpoint of all-cause mortality and disabling stroke at 2 years post-TAVI randomized against SAVR. The anticipated results of these trials are expected in early 2016 for PARTNER IIa and later for SURTAVI, but the investigators of the NOTION trial have published results from a randomized TAVI vs. SAVR 'all-comers' trial in patients over 70 years.[100] The TAVI-treated group, with mean STS Predicted Risk of Mortality of 2.9 ± 1.6 and ES II of 1.9, failed to demonstrate superiority to SAVR: there was no significant difference in the primary endpoint (composite of stroke, myocardial infarction, or death from any cause at 1 year; 16.3 vs. 13.1%; $P = 0.43$). However, during the study period of 3.5 years, only <20% of the screened patients were enrolled in this study, so the nature of NOTION as a true 'all-comers' trial is debatable. Furthermore, the trial was underpowered, so any firm conclusions cannot be drawn yet.

Conclusion

Whether TAVI will become the standard of care (and SAVR the exception-to-the-rule) after another decade is uncertain, but appears possible. Despite the great success and increasing frequency of TAVI use, the volume of SAVR has so far remained constant. If the trend towards performing TAVI in intermediate-risk patients continues, the stability of SAVR rates will likely change downward in the near future. The results of the upcoming PARTNER IIa and SURTAVI studies will be critical to informing the field and expanding TAVI to intermediate-risk patients. For now, SAVR remains gold standard with excellent results for low- and some intermediate-risk patients, at least until long-term durability of TAVI valves is firmly established, and the rate of PVL, stroke, and PPI is lowered to the level of SAVR. In the meantime, the Heart Team is tasked to determine the optimal treatment for each patient based on risk scores, frailty, comorbidities, patient preference, and potential for improvement in QoL.

Authors' contributions

C.W.H., M.A., M.M.: acquired the data, conceived and designed the research, drafted the manuscript, and made critical revision of the manuscript for key intellectual content.

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