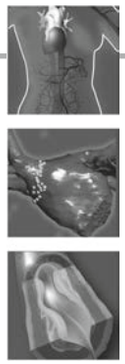

Reducing mortality rates in patients undergoing transcatheter aortic valve implantation

"Reading and understanding the anatomy of the patient, imagining how the valve will behave during implantation, anticipating potential complications and preparing the equipment and the team to resolve them is the key to success."

KEYWORDS: aortic valve stenosis ■ Edwards SAPIEN transcatheter heart valve ■ Medtronic CoreValve® System ■ surgical aortic valve replacement

Our society is rapidly aging, and this is associated with an increase in the number of patients with cardiovascular disease, such as aortic valve stenosis. In the western world, aortic valve stenosis is predominantly the consequence of valve degeneration, which shares some pathophysiological pathways with atherosclerosis, finally leading to leaflet calcification [1]. With the occurrence of symptoms, current guidelines recommend aortic valve replacement (AVR) [2]; however, numerous people do not undergo surgical valve replacement [3]. There are three main reasons for this: they are considered too 'old' or too 'frail' and, therefore, are not referred to the cardiac surgeon; the surgeons turn down the operation, predominantly because of the patients higher age or their poor ejection fraction; or the patients refuse surgery because they are afraid or think it is not worth undergoing a cardiosurgical procedure at a higher age [3].

For low-risk patients, which is the vast majority, surgical AVR is still the first-line therapy in patients with severe, symptomatic aortic stenosis [2]. This recommendation is based on the life-saving and symptom-improving effect of valve replacement in the presence of low mortality rates of surgical AVR. Based on health economic data, for example from Germany, mortality rates are approximately of 3% at 30 days after surgical AVR and are, therefore, considerably lower compared with those in early and recent transcatheter valve studies and registries [4]. This is not surprising given the lower risk profile of patients treated with surgical AVR.

For those that do not qualify for conventional AVR, transcatheter aortic valve implantation (TAVI) represents an alternative treatment option. It can be carried out through the femoral, iliac, carotid or subclavian/axillary artery, through a transapical or direct aortic approach [5–15]. The Edwards SAPIEN XT transcatheter heart valve (Edwards Lifesciences Corporation, CA, USA) and the Medtronic CoreValve® System (Medtronic Inc., MN, USA) have been used in thousands of high-risk and inoperable patients to treat aortic stenosis. In addition, the Accurate™ Aortic Valve (Symetis Inc., Ecublens, Switzerland) and the JenaValve (JenaValve, Munich, Germany) received CE approval for transpical treatment, whereas the recapturable and retrievable Portico™ Valve (St Jude Medical, MN, USA) has been available to transvascular therapy of aortic stenosis since 2012. However, especially in the early TAVI days, mortality was high [5–7]. This was due to many reasons: the patients were extremely sick and frail; the systems were bulky and difficult to operate and position, which made the procedure complex and time consuming; and the operators had little experience regarding patient selection, recognition and treatment of complications, which include vascular injury at the access site; access vessel rupture or perforations; aortic rupture, perforation or dissection; ventricular perforation by the stiff wire that is required to guide the TAVI system; coronary occlusions either by the leaftlet itself or embolized calcified material; annular rupture; strokes; conduction abnormalities; or infections. Thus, what has been achieved with regard to the prevention and treatment of complications that are known to impact on mortality? During recent years, numerous single-center studies and national TAVI registries have been published addressing this topic [5–15]. However, their impact is hampered by the subjective definition of inoperability as an inclusion criterion, the selection bias regarding the access site, the absence of uniform definitions with respect to valve performance or clinical end points and

Norman Mangner

Department of Internal Medicine/Cardiology, Heart Center, University of Leipzig, Strümpellstrasse 39, 04289 Leipzig, Germany

Axel Linke

Author for correspondence: Department of Internal Medicine/Cardiology, Heart Center, University of Leipzig, Strümpellstrasse 39, 04289 Leipzig, Germany
Tel.: +49 341 865 1427
Fax: +49 341 865 1461
linkea@medizin.uni-leipzig.de

Future Medicine part of fsg

the use of the different TAVI systems. The publication of the Valve Academic Research Consortium criteria in 2011 and its revision in 2012 resolved the issue of nonstandardized end point definitions, since it describes uniform standards for the assessment of TAVI success and transcatheter valve performance [16,17]. This will allow us to better compare the results of ongoing TAVI trials in the future. Nevertheless, the short-term mortality rates after TAVI have dropped since the first-in-men studies in 2002 until today, and these data are valid since 'all-cause mortality' is clearly defined [5–15]. These data already reflect the increasing knowledge and skills regarding patient selection and procedural performance. However, the rapidly growing number of TAVI procedures in some countries is raising the suspicion that not all of the patients are really 'high risk' or 'inoperable'. This notion is supported by the decline in the risk profile of patients in recent TAVI reports. In addition, the definitions of the words 'inoperable' or 'high risk', which are prerequisites to consider TAVI, is subjective in nature. In the PARTNER trial, the patient was considered inoperable if the risk of death or serious irreversible morbidity, as assessed by one cardiologist and two cardiac surgeons, was believed to exceed 50% [18,19]. However, this is difficult to measure. Traditional scores, such as the Society of Thoracic Surgeons score and the European System for Cardiac Operative Risk Evaluation (EuroSCORE), are of little help since they fail to assess frailty, which appears to predict long-term survival. Cohort B of the PARTNER study, which assessed the impact of transfemoral Edwards SAPIEN implantation compared with medical treatment on prognosis, revealed a mortality rate of 5.0 and 2.8% at 30 and 30.7 days versus 50.7% ($p < 0.001$) at 1 year in the TAVI and standard medical treatment group, respectively [18,19]. The 30-day mortality in the TAVI group was low and predominantly driven by procedural complication. [18,19] However, despite the low 30-day mortality, one out of four patients died during the first year after successful TAVI, predominantly owing to comorbidities [18,19]. Why was the 30-day mortality lower compared with many national registries in which the patients appeared to have fewer comorbidities? Patients treated within a clinical study represent a selected population; those with suboptimal anatomy are usually turned down, which definitively reduces procedural complications and short-term mortality. In addition, the presence of a highly experienced proctor ensures that procedural mistakes are avoided and complications are immediately recognized and treated. Furthermore, patients are closely followed, which enables the immediate recognition of health state deterioration that would otherwise impact on prognosis. In this context, it would be interesting to have information on the prognosis of patients who were evaluated in the PARTNER trial, but were turned down due to anatomical or other reasons. Unfortunately, these data are not available yet. By contrast, national registries contain the learning curve of the operators with regard to patient selection and the TAVI procedure itself, which may be one explanation for the higher mortality compared with the randomized controlled PARTNER trial. In addition, in clinical reality, operators are sometimes forced to treat patients with a complex anatomy, taking a higher complication rate into account, if an alternative treatment option for the patient does not exist.

> *"For low-risk patients, which is the vast majority, surgical aortic valve replacement is still the first-line therapy in patients with severe, symptomatic aortic stenosis."*

Today, TAVI is a safe procedure with a low short-term risk. Nevertheless, there is still room for improvement, especially before indications can be expanded. The patient's anatomy should be thoroughly investigated using cardiac catheterization, peripheral angiography, transesophageal echocardiogram (preferably 3D), transthoracic echocardiogram and computed tomography. Understanding the anatomy allows the operator to select the right approach and the right valve for each patient [20]. There should be a clear commitment of the patient to the TAVI procedure, which disqualifies patients that are not oriented with regard to the own person and time. In addition, patients that have spent weeks or months in referring hospitals and are, therefore, completely immobilized, are often reluctant to undergo TAVI. In many cases, these patients have subclinical infections, which increase the risk of death even after successful TAVI. In this cohort, valvuloplasty may be considered to improve the hemodynamic situation and to achieve a situation enabling mobilization and ambulation of the patient, before a reassessment is performed at 6–8 weeks. At the beginning, centers, especially those with a low case volume, should consider starting their program with a small team of dedicated operators using one transcatheter valve only, until they are

experienced with this system. Studies suggest that center case volume affects percutaneous coronary intervention outcome, and there is reason to believe that a similar association exists for TAVI. Reading and understanding the anatomy of the patient, imagining how the valve will behave during implantation, anticipating potential complications and preparing the equipment and the team to resolve them is the key to success. Pushing the limits too far is most often deleterious for the patients. If the procedure does not progress for whatever reason, the heart team should not hesitate to abort the TAVI at a time when the patient is still stable, reconvene and look for alternative treatment options. In addition, the patients should not leave the hybrid suite with hemodynamically suboptimal results, for example, with a higher grade aortic regurgitation. Some of the procedural problems operators are facing today may disappear with the newer generation of TAVI devices: the guiding catheters will become smaller, will be steerable, which allows for better valve positioning, the valves will better adapt to the anatomy, will have a sealing to reduce paravalvular leaks and will be recapturable to reposition the device in case of unexpected movements during deployment. New access-site closure devices will provide a better hemostasis and reduce bleeding events. It is believed that these features have the potential to increase the speed of implantation and improve the overall safety of the procedure. Devices, capturing or deflecting calcific/atherosclerotic material eroded from the valve and the aorta, which were developed to reduce the stroke risk, are currently under investigation. However, to elucidate which patient is going to benefit over the long term and which patient does not, will remain the challenging task [20]. This requires further studies establishing frailty measures, which appear to be better predictors of long-term prognosis compared with the risk score we are currently using to estimate outcome.

Financial & competing interests disclosure

A Linke is a consultant to Medtronic, St Jude Medical and Terumo. He received speaker honoraria from Edwards Lifesciences Corporation, Medtronic and St Jude Medical, and is a proctor for Medtronic, Edwards Lifesciences Corporation and St Jude Medical. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Matsumoto Y, Adams V, Jacob S *et al.* Regular exercise training prevents aortic valve disease in low-density lipoprotein-receptor-deficient mice. *Circulation* 121(6), 759–767 (2010).

2 Bonow RO, Carabello BA, Chatterjee K *et al.* American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J. Am. Coll. Cardiol.* 52, e1–e142 (2008).

3 Iung B, Cachier A, Baron G *et al.* Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur. Heart J.* 26, 2714–2720 (2005).

4 Gummert, JF, Funkat AK, Beckmann A *et al.* Cardiac surgery in Germany during 2010: a report on behalf of the German Society for Thoracic and Cardiovascular Surgery. *Thorac. Cardiovasc. Surg.* 59(5), 259–267 (2011).

5 Grube E, Schuler G, Buellesfeld L *et al.* Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second- and current third-generation self-expanding CoreValve prosthesis: device success and 30-day clinical outcome. *J. Am. Coll. Cardiol.* 50, 69–76 (2007).

6 Walther T, Simon P, Dewey T *et al.* Transapical minimally invasive aortic valve implantation: multicenter experience. *Circulation* 116, I240–I245 (2007).

7 Piazza N, Grube E, Gerckens U *et al.* Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) CoreValve Revalving System: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. *EuroIntervention* 4, 242–249 (2008).

8 Thomas M, Schymik G, Walther T *et al.* Thirty-day results of the SAPIEN aortic Bioprosthesis European Outcome (SOURCE) Registry: a European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation* 122, 62–69 (2010).

9 Rodés-Cabau J, Webb JG, Cheung A *et al.* Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J. Am. Coll. Cardiol.* 55, 1080–1090 (2010).

10 Falk V, Walther T, Schwammenthal E *et al.* Transapical aortic valve implantation with a self-expanding anatomically oriented valve. *Eur. Heart J.* 32, 878–887 (2011).

11 Moat NE, Ludman P, de Belder MA *et al.* Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J. Am. Coll. Cardiol.* 58, 2130–2138 (2011).

12 Kempfert J, Rastan A, Holzhey D *et al.* Transapical aortic valve implantation: analysis of risk factors and learning experience in 299 patients. *Circulation* 124, S124–S129 (2011).

13 Tamburino C, Capodanno D, Ramondo A *et al.* Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation* 123, 299–308 (2011).

14 Zahn R, Gerckens U, Grube E *et al.*; German Transcatheter Aortic Valve Interventions-Registry Investigators. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. *Eur. Heart J.* 32, 198–204 (2011).

15 Gilard M, Eltchaninoff H, Iung B *et al.* FRANCE 2 Investigators. Registry of transcatheter aortic-valve implantation in high-risk patients. *N. Engl. J. Med.* 366, 1705–1715 (2012).

16 Leon MB, Piazza N, Nikolsky E *et al.* Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *J. Am. Coll. Cardiol.* 57, 253–269 (2011).

17 Kappetein AP, Head SJ, Genereux P *et al.* Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur. Heart J.* 33, 2403–2418 (2012).

18 Leon MB, Smith CR, Mack M *et al.* PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N. Engl. J. Med.* 363, 1597–1607 (2010).

19 Kodali SK, Williams MR, Smith CR *et al.* PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N. Engl. J. Med.* 366, 1686–1695 (2012).

20 Lange R, Bleiziffer S, Mazzitelli D *et al.* Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J. Am. Coll. Cardiol.* 59, 280–287 (2012).