Even in the late 1950s, patients suffering from significant aortic stenosis were confined to death owing to the absence of treatment option for the disease. The invention of extracorporeal circulation revolutionized cardiac surgery. Complex surgical intervention on the diseased heart became available, including replacement of the stenotic aortic valve. Especially in the early days of conventional aortic valve replacement (AVR), however, in-hospital mortality was up to 25% because of cardiac failure, bleeding or thromboembolic complications, infections, or arrhythmias. The design of the first mechanical heart valves left patients with peak gradients of ≥60 mm Hg. Applying the updated standardized end-point definitions for transcatheter aortic valve implantation (TAVI; Valve Academic Research Consortium [VARC] 2) definitions to this patient population would have resulted in a procedural success rate of 0%, and the US Food and Drug Administration probably would have never approved the devices. The world has changed considerably since then. Half a century later, conventional aortic valve surgery (AVR) can be considered a top turnaround story: nowadays, the operation is fast and easy and yields excellent outcomes in a broad patient population. This is the consequence of advances not only in technology but also in surgical experience gained in millions of patients with aortic stenosis. Today, minimally invasive techniques are applied that facilitate postoperative recovery, especially in elderly patients, and reduce the likelihood of wound infections. The flow properties of mechanical heart valves also improved remarkably, which led to less rigid need for anticoagulation and lower bleeding and thromboembolic complications. Stented and stentless bioprosthetic valves have been shown to be long-lasting, which reduces the need of reoperation in case of bioprosthetic valve failure. The hemodynamic results are excellent with low transvalvular gradients, regardless of whether mechanical or bioprosthetic valves are used, usually in the absence of any aortic regurgitation. The stroke rate is <5%, and the likelihood of postoperative permanent conduction abnormalities is <8%. As a result of all these improvements, 30-day mortality declined from up to 30% in 1960 to <3% in 2012, with life expectancy normalized after a successful AVR.

Response by Falk on p 2331

Transcatheter AVR: The New Kid on the Block
In 2002, expectations were high when Dr Alain Cribier clinically introduced the concept of transcatheter AVR (TAVR). Whereas the surgeons developed conventional AVR in a young patient population without comorbidities, Cribier and his team treated the frailest patients to establish a completely new technique. After a few cases in inoperable, frail patients, it became clear that the balloon-expandable devices

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.
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were too bulky and the procedure too complex and lengthy.\textsuperscript{24} This early experience triggered refinements of the Cribier-Edwards valve; the delivery system and concept changed the transfemoral procedure from a transseptal antegrade to a retrograde approach.\textsuperscript{25} In parallel, a self-expanding prosthesis was developed consisting of a porcine pericardial tissue valve sutured into a self-expanding nitinol frame (CoreValve). The beauty of this system was the smaller profile (18F) because the space for the balloon as the valve carrier was saved.\textsuperscript{26} The results of the first studies in humans with both valves appeared to be promising. The delivery of the valves was reliable; the reduction in mean and peak gradients across the stenotic aortic valve was excellent; and the mortality rates for the patients considered inoperable were acceptable.\textsuperscript{24,27} However, the high rate of strokes, bleeding, and vascular complications raised concerns because they were inevitably linked with mortality.\textsuperscript{24,27} Nevertheless, the results were convincing enough to file for CE approval, which was received for both the Edwards SAPIEN and Medtronic CoreValve prostheses in 2007. This allowed treatment of patients with severe aortic stenosis in daily clinical practice. Unfortunately, the data were only partially collected in registries, and most of the events were investigator reported in the absence of independent monitoring.\textsuperscript{24,27} In addition, clear end-point definitions of success and complications were missing, hampering the comparison of publications from different centers and countries. This situation improved with the development of the VARC\textsuperscript{28} and VARC\textsuperscript{210} criteria.

The True Evidence of TAVR: Data From Randomized, Controlled Trials

Our scientific evidence concerning TAVI is derived primarily from cohorts A\textsuperscript{29} and B\textsuperscript{30} of the Placement of Aortic Transcatheter Valve Trial (PARTNER; NCT00530894), a true landmark study. Cohort B of PARTNER aimed to evaluate the impact of TAVR compared with conventional medical therapy, which could include balloon valvuloplasty, on inoperable patients with severe aortic stenosis. Almost 360 patients were randomized, 179 to receive transfemoral TAVR with the Edwards-SAPIEN valve and 179 to medical treatment, which involved aortic balloon valvuloplasty in 84\% of the patients (Figure 1). The mean age was >80 years of age (83.1±8.6 years for TAVR versus 83.2±8.3 years for standard medical therapy); the mean logistic euroSCORE was >25 (26.4±17.2 for TAVR versus 30.4±19.1 for standard medical therapy); and the mean Society of Thoracic Surgeons (STS) score was >11 (11.2±5.8 for TAVR versus 12.1±6.1 for standard medical therapy). The 1-year mortality was 30.7\% in the TAVR group and therefore 20\% lower than for patients treated medically (1-year mortality, 50.7\%).\textsuperscript{31} Therefore, in later clinical studies evaluating other transcatheter valves like the Medtronic CoreValve, it was considered unethical to randomize the patients against medical treatment only (NCT01240902; Figure 2). However, the extreme-risk population in the Medtronic CoreValve pivotal study was similar to that in PARTNER. The mean age was 83.1±8.6 years; the logistic euroSCORE was 22.7±17.4; and the STS score was 10.3±5.6\%. Total mortality was 7.9\% and 24\% at 30 days and 1 year and rates of any stroke were 3.9\% and 6.7\%, respectively.\textsuperscript{32} These data underline that treatment of inoperable patients with severe aortic stenosis with the self-expanding Medtronic CoreValve prosthesis is also safe and associated with a good short-term outcome. Hence, in inoperable patients with severe aortic stenosis, there is just no alternative to transfemoral TAVR.

Cohort A of the PARTNER study aimed to investigate whether TAVI with either the transfemoral or the transapical approach was noninferior to conventional AVR with regard to the 1-year mortality in operable, high-risk patients.\textsuperscript{29} In cohort A, 699 patients were treated: 492 within the transfemoral arm (244 were randomized to TA VR and 246 had conventional surgery) and 207 within the transapical arm (104
had TAVR with the Edwards SAPIEN valve and 103 had conventional surgery). The mean age was >83 years (83.6±6.8 years for TAVR versus 84.5±6.4 years for AVR); the mean log euroSCORE was 29% (29.3±16.5% versus 29.2±15.6%); and the STS score was 11 (11.8±3.3 versus 11.7±3.5). In the transfemoral cohort, 30-day mortality was 3.3% after TAVR compared with 6.2% after conventional AVR. In addition, there was no difference in the 1-year mortality rates either: 22.2% after transfemoral TAVR versus 26.4% after conventional AVR (P=NS).29

Figure 2. Flow chart summarizing study design of CoreValve US pivotal trials. High-risk patients are randomly assigned to conventional surgery or transcatheter aortic valve replacement using the Medtronic CoreValve System. The primary objective of the trial is to demonstrate that the safety and efficacy of the Medtronic CoreValve System are noninferior to those of surgical aortic valve replacement. Extreme-risk patients with suitable iliofemoral access are treated with the Medtronic CoreValve System; the other patients are treated via noniliofemoral access. The aim of the study is to evaluate the safety and efficacy of the Medtronic CoreValve system for treatment of patients with ≥50% predicted risk of operative mortality or serious, irreversible morbidity at 30 days.

A similar study was conducted to evaluate the impact of Medtronic CoreValve implantation compared with conventional surgery in patients with increased surgical risk (NCT01586910; Figure 2). A total of 795 patients with significant aortic stenosis who were considered at increased risk of surgery were randomized to TAVR (394 patients) with the self-expandable Medtronic CoreValve or to conventional AVR (401 patients). The patients had a mean age of >83 years (83.6±7.1 years for TAVR versus 83.5±6.3 years for AVR); the mean log euroSCORE was 18% (17.6±13.0% versus 18.4±12.8%); and the STS score was 7.4 (7.3±3.0 versus 7.5±3.2). The rate of death resulting from any cause at 1 year was significantly lower in the TAVR group than in the surgical group (14.2% versus 19.1%; P<0.05). In addition, TAVR was noninferior in terms of echocardiographic measure of valve stenosis, functional status, or quality of life.33 Of note, patients in the latter study had much lower risk scores as determined by the STS and log euroSCORE compared with patients in the PARTNER trial. This is indicative of the fact that an assessment of TAVR results in lower-risk patients has already begun in randomized, clinical trials.

Moving Toward Lower-Risk Patients: Circumstantial Evidence From Registries and Meta-Analyses

However, we are still missing data from randomized, controlled trials assessing TAVR in younger, low-risk patients. Hence, data from Edwards transcatheter valve registries,34–38 Medtronic Core valve registries,39–43 and mixed multicenter and national registries44–51 containing a broad range of patients treated transfemorally, transapically, or with a direct aortic, subclavian, and carotid approach are the only resources potentially supporting an expansion of indications. The predominant valves evaluated in these registries were the balloon-expandable Edwards SAPIEN, the Edwards SAPIEN XT, and the self-expandable Medtronic CoreValve prosthesis. This variegated patient population makes it difficult to decide whether TAVI is able to compete with conventional surgery in younger, low-risk patients. In the above-mentioned registries, the logistic euroSCORE as an estimate of operative risk varied between 14.5% and 36%, with mortality rates at 30 days and 1 year reported to be between 0% and 50% and 0% and 37%, respectively (Table). Stroke rates at 30 days varied between 1 and 10%, whereas a new pacemaker was implanted in up to 40% of the patients.34–52 In general, patients treated through the transfemoral approach had fewer comorbidities and hence better short- and long-term survival. Interestingly, 30-day mortality rates after TAVR dropped by >50% from 9.5% in 2009 to 4.2% in 2013, with stroke rates also halved (Table). However, this was at least partially attributed to the decline in the number of patients with multiple comorbidities over time. It suggests that expansion of indications already had occurred, preceding true evidence from randomized, clinical studies.
Preparing for the Head-to-Head Comparison in Younger, Low-Risk Patients: Advantages and Disadvantages of TAVR and Conventional AVR

To estimate the results of a head-to-head comparison between conventional AVR and TAVR in younger, low-risk patients, one has to recall the advantages and disadvantages of both methods (Figure 4). Conventional AVR is an easy operation established for decades that has excellent results with low transvalvular gradients and hardly any aortic regurgitation. On the other hand, it is invasive, requiring full or partial thoracotomy, intubation, and mechanical ventilation, as well as the use of an extracorporeal circulation. In younger, low-risk patients, the thoracotomy and mechanical ventilation probably do not drive mortality, but the extracorporeal circulation might expose the patient to an inflammatory activation, potentially leading to death. In a recent meta-analysis involving data from 700,000 patients, operative and/or 30-day mortality after conventional AVR was found to be 3.8% in patients between 70 and 79 years of age and 6.1% in patients >80 years of age. These data are in favor of the hypothesis that the 30-day mortality after TA VR in younger, lower-risk patients might be at least equal to the risk after conventional AVR. TA VR is clearly less invasive if the procedure is performed with a transfemoral approach, intubation and mechanical ventilation is not required, and the procedure can be performed without extracorporeal circulatory support. However, it is a relatively

Table. Edwards Transcatheter Heart Valve Registries, Medtronic CoreValve Registries, and Mixed Multicenter and National Registries

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DA indicates direct aortic; ES, Edwards Sapien Valve; EuroSCORE, European System of Cardiac Operation Risk Evaluation; MCV, Medtronic CoreValve; PPM, permanent pacemaker; SC, subclavian; STS, Society of Thoracic Surgeons; TA, transapical; TAVI, transcatheter aortic valve implantation; TF, transfemoral; and TV, transvascular. *In hospital.
new method, with interventionalists still being in the learning phase. Therefore, operator failures can easily drive mortality. Moreover, the results of TAVR are suboptimal in patients with severe calcification; there are still too many vascular complications; and the design of the first-generation transcatheter valves evaluated in the above-mentioned studies was not yet optimal (Figure 5). To justify a treatment of younger, low-risk patients, who have an excellent outcome after conventional AVR, the TAVR limitations first have to be addressed. However, the transfemoral TAVR systems are getting smaller, and the development of balloon-expandable, recollapsible sheaths and inline sheath concepts allows transfemoral TAVR even in patients with a vascular access size <6 mm, which further reduces the need for alternative TAVR access, especially with a transapical approach. However, the size of transapical systems also was reduced considerably during the last years, and apical closure systems were developed to reduce access site complications, thereby potentially improving the outcome after transapical TAVR. Currently the percentage of younger, low-risk patients in recent registries is too small to estimate whether transapical TAVR is able to beat conventional surgery in these patients.

**TAVR in Younger, Lower-Risk Patients: Are the Requirements Met?**

Despite the fact that residual aortic regurgitation was more frequent after TAVR and elucidated a predictor of mortality, mortality rates were not higher after TAVR over the long term compared with conventional surgery in high-risk operable patients. If the degree of paravalvular AR could be reduced by transcatheter heart valve refinements, would this translate into a better long-term survival after TAVR? This question remains unanswered at the moment, but studies evaluating the next-generation devices, which are able to seal paravalvular leaks much better, are on the way. The majority of the patients after TAVR and conventional AVR are dying as a result of their comorbidities and procedural complications. Because of the improved knowledge of patient screening, assessment of the access vessels and annulus, prosthesis selection, procedural planning, and safety networks (e.g., crossover wires) to avoid the deleterious outcome after vascular insults, complications are prevented or treated at an early stage of occurrence, which has made TAVR much safer in 2014 compared with 2006. This is underlined by the fact that vascular and bleeding complications lost their deleterious effects on outcome in recent studies. Recently, Wenaweser and coworkers assessed clinical outcomes among patients with estimated low (STS score <3%) or intermediate (STS score, 3%–8%) surgical risk undergoing transfemoral TAVR. Patients with a low risk (STS score, 2.3±0.4; log euroSCORE, 13.1±6.4) were younger (79.5±4.3 versus 83.5±4.7 years) and less often had prevalent chronic renal failure (39% versus 67%) compared with the intermediate-risk patients (STS score, 5.2±1.4; log euroSCORE, 21.4±12.0). At 30 days,
all-cause mortality was 0% and 3.5%, the rate of cerebrovascular events was 0% versus 4.5%, and the rate of major strokes was 0% versus 3.5% in the low- and intermediate-risk group, respectively. There were no differences between the 2 groups with regard to major or life-threatening bleeding, the occurrence of acute renal failure, and major or minor access site complications. At 1 year, all-cause mortality was 9.3% versus 14.8%, cardiovascular mortality was 6.3% versus 9.3%, the cerebrovascular event rate was 7.7% versus 4.5%, and the combined end point of all-cause death, or stroke occurred in 16.3% versus 16.7% in the low- and intermediate-risk groups. These data clearly underline that the outcome in low- and intermediate-risk patients after TAVR with the transfemoral approach is equivalent to the results achieved in a similar cohort with conventional aortic valve surgery. This is further confirmed by data from the CoreValve CE study, which assessed the outcome of TA VR compared with conventional AVR.65 The need of a rigorous assessment of neurological function not only after TAVR but also after conventional surgery.65

From the data of the studies mentioned above, there is no reason to believe that TAVR in younger, lower-risk patients with significant aortic stenosis would be associated with a higher short-term mortality or more complications compared with conventional AVR.

The Future: Better Results With Next-Generation TAVI Devices?

To really compete with surgery in younger, low-risk patients, outcomes have to be as good as those after conventional surgery. However, one has to keep in mind that not all low-risk patients are good TAVR candidates. Currently, depending on the TAVR device used, deployment and accurate positioning are still difficult in patients with horizontal aorta. The experience in patients with bicuspid valves, which are more frequent in younger patients, is limited largely to case reports, and there are still cases in which the annulus is too big or too small to accommodate the current transcatheter heart valves. Heavily calcified valves still represent a challenge in transcatheter valve implantation because they are often associated with significant residual postprocedural paravalvular leak with residual aortic regurgitation affecting survival or an annular tear if the sizing was too aggressive. Although in patients with relevant coronary artery disease a combination of TAVR and percutaneous coronary intervention is possible, the impact on long-term prognosis compared with coronary artery bypass graft surgery and conventional AVR still needs to be determined in randomized, controlled trials. In some studies, there appears to be a higher risk of stroke and transient ischemic attack, which is not restricted to the perioperative period after TAVR; there are still vascular and bleeding complications potentially affecting mortality, a higher rate of permanent pacemaker implantations, and uncertainties about valve durability. These limitations have been at least partially addressed by the engineers, providing us with improved second-generation TAVR devices (Figure 6). Patients treated with the transapical version of the JenaValve,66 which consists of a porcine pericardial tissue valve sutured into a nitinol stent,
had mild or absence of perivalvular leak in 97.6% after the procedure, and the rate of permanent pacemaker implantation was 12.5%. The initial results of the transfemoral version of the Portico valve (St. Jude Medical, St. Paul, MN), which is partially recapturable, repositionable, and retrievable, are also encouraging. This valve consists of a bovine pericardial tissue valve sutured into a self-expanding nitinol frame. At 30 days, 95% of the patients had either no or only mild aortic regurgitation, which does not affect long-term survival, and the rate of neurological complications and permanent pacemaker dependency was also low. Implantation of the SAPIEN 3 (Edwards Life Sciences, Irvine, CA), consisting of a bovine pericardial tissue valve in a balloon-expandable cobalt chromium stent, which is delivered through a 14F sheath with dynamic expansion mechanism, had a procedural success rate of 100% in the first-in-humans series. There were no death, no stroke, and no patients with aortic regurgitation more than mild, and only 6.7% of patients required a permanent pacemaker implantation. The data from Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System: Evaluation of Safety and Performance (REPRISE II) evaluating the Lotus valve (Boston Scientific, Natick, MA) confirm the ease of use of the second-generation transcatheter valves. Lotus consists of a bovine pericardial tissue valve sutured into a self-expanding braided nitinol frame, which is 1 of the 2 transcatheter valves that are fully repositionable, recapturable, and retrievable. The procedural success in REPRISE II was 100%, with no patient with more than mild aortic regurgitation, but 8.7% had an ischemic stroke and >25% required a permanent pacemaker. The Direct Flow Medical valve (Direct Flow Medical, Santa Rosa, CA) is the second valve to be fully repositionable, recapturable, and retrievable. It consists of a bovine pericardial tissue valve between 2 polymer rings filled with polymer solution. Data from the multicenter prospective trial of the direct flow medical transcatheter aortic valve (DISCOVER CE) trial evaluating this valve reported 2.7% with major strokes, 16% with permanent pacemaker implantation, with 99% with absent...
or only mild aortic regurgitation. These data are in line with the recent experience from the ACURATE TF study, investigating the performance of the Symetis ACURATE valve (Symetis, Ecublens, Switzerland). The procedural success was high; 13% required a permanent pacemaker; and 95% had mild or absent perivalvular leak at 30 days after implantation. Although these are only small trials with a limited number of patients, they all speak a similar language: TAVR, especially through a transfemoral access, has become safer for the patient. The success rate (according to VARC2) increased to almost 100%; the vascular and bleeding complications dropped secondary to better patient screening and the smaller profiles of the valve; the level of perivalvular regurgitation was almost negligible, most likely not affecting long-term survival in a negative way; and the rate of permanent pacemaker implantation came down to values around 10%. However, larger randomized, multicenter studies are necessary to confirm that these second-generation devices represent a major breakthrough in the treatment of a broad range of patients with severe aortic stenosis. The Safety and Efficacy Study of the Medtronic CoreValve® System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement (SURTAVI; NCT01586910) and PARTNER 2 trial (NCT01314313) will provide the scientific answer. The SURTAVI trial (Figure 3) is comparing the performance of Medtronic CoreValve implantation with conventional surgery in younger, lower-risk patients, and the PARTNER 2 trial (cohort A) is studying performance in intermediate-risk patients. It is tempting to speculate that US Food and Drug Administration approval for TAVI in lower-risk patients in the United States will likely be dependent on demonstration of noninferiority of TAVR compared with conventional surgery in these studies.

Beside investigation of TAVR in lower-risk patients, future studies should focus on comparison of one TAVR device with another and on strategies to minimize the degree of aortic regurgitation and paravalvular leakage because even the presence of mild aortic regurgitation impairs outcome. To date, to the best of our knowledge, the A Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis (CHOICE) trial is the first study to compare a balloon-expandable system with a self-expandable system. The REPRISE III trial will compare the performance and outcome of the Boston Lotus valve system with the Medtronic CoreValve in patients at increased risk for conventional surgery. This study will shed more light into the head-to-head comparison of different transcatheter heart valves and help the treating physician to select the right transcatheter heart valve for the right patient.

Furthermore, few data are available for patients with bicuspid valves because they are excluded in major trials. Some case reports suggest that TAVR is feasible and safe in these patients, but randomized, controlled trials are lacking.

Besides long-term valve durability, the only issue remaining is that of procedural neurological complications, which are in the lower 1-digit range and therefore not higher compared with conventional surgery (Table). However, they are always deleterious for the patient. Devices have been developed to prevent the occurrence of procedural, neurological complications (eg, Montage Dual Filter System, ClarJet Medical, Santa Rosa, CA; Embrella Embolic Deflector System, Edwards Life Sciences; TriGuard Cerebral Protection Device, Keystone Heart Ltd, Caesarea Business Park, Keisarya, Israel). These devices are currently under investigation (NCT01833052 and NCT02070731), some in randomized, controlled trials, with the first results expected by the end of the year. It will be exciting to see if they are able to make TAVR even safer.

Conclusions

TAVR is the treatment of choice—significantly improving prognosis—in inoperable patients with aortic stenosis. In addition, TAVR is a potentially superior alternative to conventional AVR in operable, high-risk patients. However, the major shortcomings of the first-generation devices were success rates <90%, perivalvular leaks, bleeding and vascular complications, strokes and transient ischemic attacks, and a high rate of pacemaker implantations. These limitations have been addressed by engineers, providing us with improved second-generation TAVR devices. Given the 30-day mortality rates of <1% in experienced centers, the excellent TAVR results in recently published randomized, controlled trials, and the improved performance of the second-generation transcatheter heart valve systems, there is good reason to believe that TAVR will also prevail in a younger, lower-risk cohort, given appropriate patient selection. However, despite the fact that circumstantial evidence is compelling, one has to wait for the results of trials in intermediate- and lower-risk patients like PARTNER 2 and SURTAVI before further expansion of indications is scientifically justified.

Disclosures

Dr Linke is a consultant to Medtronic and St. Jude Medical. He received speaker honoraria from Edwards, Medtronic, Boston Scientific, and St. Jude Medical and is a proctor for Medtronic, Edwards, and St. Jude Medical. Dr. Haussig reports no conflicts.

References


Haussig and Linke  TAVR in Lower-Risk and Younger Patients  2331

Response to Haussig and Linke

Volkmar Falk, MD

Drs Linke and Haussig provide a thorough update of the current outcomes and results of transcatheter aortic valve replacement (TAVR) and try to make an argument for its use in low-risk patients. To support their argument, they refer to recent articles on postmarket registries and CE trials of second-generation devices, some of which show improved outcomes for TAVR. When interpreting these data, one has to consider that most of these trials were very selective in patient inclusion and that follow-up is in general limited to 1 year. Patients with peripheral artery disease, renal failure, bicuspid valves, severe annular calcification, and other known risk factors for TAVR were often excluded, especially in CE trials. This renders a comparison with surgical aortic valve replacement all-comer data impossible. The authors discuss at length the work of Wenaweser, who treated a number of low- and intermediate-risk patients with TAVR. Unfortunately, the original article is largely misquoted. The 30-day mortality in low- and intermediate-risk patients was not 0% as referred to by the authors but 2.4% and 3.9%, respectively. Likewise, the major stroke rate was not 0% but 2.4% in the low-risk and 3.2% in the intermediate-risk group. Although it is true that the rate life-threatening bleeding was the same for low- (14.6%), intermediate- (14.2%), and high- (23.5%) risk patients, the rates exceed 14%, which for low-risk patients seems unacceptable. So far, neither this article nor any other article quoted by the authors provides proof that TAVR provides better major adverse cardiac event outcomes in low- or intermediate-risk groups of patients than surgical aortic valve replacement. What these studies show is that the excess need for pacemakers, the problem of paravalvular aortic leakage, and vascular complications after TAVR remain an issue. In addition, its long-term durability is still unknown. Before the indication can be expanded to low-risk groups, randomized, controlled trials with appropriate follow-up have to be completed.
Transcatheter Aortic Valve Replacement Indications Should be Expanded to Lower-Risk and Younger Patients
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