Transcatheter Aortic Valve Implantation in Lower-Risk Patients With Aortic Stenosis

Is It Justified to Be the Preferred Treatment?

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Abstract—Transcatheter aortic valve implantation underwent progressive improvements until it became the default therapy for inoperable patients, and a recommended therapy in high-risk operable patients with symptomatic severe aortic stenosis. In the lower-risk patient strata, a currently costly therapy that still has important complications with questionable durability is competing with the established effective and still-improving surgical replacement. This report tries to weigh the clinical evidence, the recent technical improvements, the durability, and the cost-effectiveness claims supporting the adoption of transcatheter aortic valve implantation in intermediate-low risk patients. The importance of appropriate patients’ risk stratification and a more comprehensive approach to estimate that risk are also emphasized in the present report.  

Key Words: aortic valve stenosis  ■  heart valve prosthesis implantation  ■  risk assessment  ■  transcatheter aortic valve replacement

Severe aortic stenosis (AS) is a common disease of the elderly. In 2011, 8.5% of the population in Europe was ≥75 years of age, and this number is expected to increase to 10.7% in 2025 and 16.6% in 2050. In North America, similar expansion of the elderly population is expected (2025: 8.3% and 2050: 11.8%). In a large meta-analysis, a random-effects model revealed a 3.4% pooled prevalence of severe AS in the elderly (≥75 years), 76% of whom are symptomatic requiring valve replacement. Although surgical aortic valve replacement (SAVR) is effective, perioperative morbidity and mortality can be significant, particularly in the elderly. Moreover, the population with the highest prevalence of aortic valve disease often finds surgery an undesirable option.  

Transcatheter aortic valve implantation (TAVI) has become the standard of care for high-risk and surgically inoperable patients with symptomatic AS. Recent years have witnessed successive technical improvements to make TAVI safer. Using smaller delivery systems, improving percutaneous access closure techniques, and rendering the valve prosthesis fully retrievable and reusable are examples of those recent advances.  

There has also been an increasing trend toward making the procedure simpler, gradually approaching a simplicity similar to that of typical percutaneous cardiovascular interventions. In the French Aortic National CoreValve and Edwards (FRANCE 2) registry, the parentage of TAVI procedures performed under local anesthesia increased from 14% in January 2010 to 59% in October 2011. Similar trends were reported in single-center experiences. This minimalist approach was shown to be feasible and to be associated with minimal morbidity and mortality and equivalent effectiveness, shorter length of hospitalization, less contrast, and lower resource use when compared with the standard procedure performed under general anesthesia. Early discharge (≤3 days) after transfemoral (TF)-TAVI was also shown to be safe in selected patients. The trend is, obviously, widespread, but harmonization and standardization are still awaited. Identification of the subset of patients that has a higher risk of intra-procedural morbidity requiring surgical intervention seems important to avoid the minimalist approach in such patients. To date, no dependable predictive scheme could be figured out.  

Backed with those improvements, there is a worldwide documented shift in the treatment of AS in the elderly from SAVR to TAVI. Taking Germany—with the highest TAVI penetration rate in Europe—as an example, there has been a 20-fold increase in TAVI performance from 2008 to 2014, and the annual number of TAVI procedures already surpassed that of isolated SAVR since 2013 (Figure 1). Older age was the most frequent reason (70.2%) for the local Heart Team to select TAVI over SAVR followed by a high predicted surgical risk (53.9%). Interestingly, frailty (46.5%) and patients’ wish (27.6%) were 2 important factors...
unchanged for SA VR, but decreased for TA VI over time.12

30-day mortality13 and showed, in many studies, a gradual

Baseline overall risk remains an important predictor of
30-day mortality11 and showed, in many studies, a gradual
reduction in patients considered for TA VI.8,14,15 In some series,
more than one third of patients routinely treated with TA VI had
an intermediate-to-low risk (defined as a Society of Thoracic
Surgeons-predicted risk of operative mortality [STS-PROM] ≤8).14 Notwithstanding, even after adjustment for baseline risk or in healthcare systems where the risk profile of enrolled patients remained high over time, TA VI performance in lower risk patients constitutes a sig-
nificant proportion of the current practice. The aim of this report is to weigh the evidence supporting this increasingly adopted approach.

Contemporary Patients’ Characteristics and Outcomes of the Default Therapy: SAVR

Thourani et al reported the contemporary real-world character-
tistics of patients (n=141 905) undergoing SAVR from 2002 to
2010.17 The majority of patients were considered at low risk (80%), and only 6.2% were stratified as being at high risk with an overall mean and median STS-PROM values of 2.95±3.71 and 1.84.17

When outcomes in the most recent surgical era (from 2007 to 2010) were compared with outcomes from 2002 to 2006, important trends of patients’ risk and outcome became evident.12 There has been a slight increase in the average overall PROM (from 2.8% to 3.1%), whereas the overall operative mortality showed a slight improvement (from 2.7% to 2.5%) between the 2 time periods. The improvement was clearly demonstrated in patients in the intermediate-risk (6.4% versus 5.4%; \( P=0.002 \)) and high-risk (14.4% versus 11.9%; \( P=0.0004 \)) groups, but not in the low-risk group (1.7% versus 1.7%; \( P=0.54 \)).17 Notably, in the latter period, the rate of post-
operative stroke was 1.2%, 2.3%, and 3.5%, and the rate of postoperative stroke or transient ischemic attacks was 2.1%, 4.2%, and 5.4% for those with low, intermediate, and high STS-PROM, respectively (\( P<0.0001 \), for all).

These results are consistent with a previous large-scale study that reported similar decreases in observed/expected mortality ratio from 1.2 in 1997 to 0.8 in 2006.16

In Quebec, Canada, in-hospital mortality of patients undergoing SAVR before (2003 to May 2007; n=529) and after (May 2007–2013; n=1064), the introduction of TA VI showed a significant improvement (3.6% versus 1.8%; \( P=0.03 \)) in spite of greater severity of several markers of risk in the latter period.19

Data from Duke University Medical Center yielded similar impressions.20 Patients treated with SAVR in the TA VI era (2011–2013; n=545) had similar risk (STS-PROM near 3.8%), but tended to have improved 30-day mortality (1.5% versus 2.8%; \( P=0.81 \)) compared with patients treated in the pre-TAVI era (n=505).

Even in those with previous surgical valve replacement and degenerated bioprosthesis, redo valve surgery is generally asso-
ciated with a good survival (9.3% at 30-month follow-up).21 Patients with degenerated bioprosthesis at an intermediate sur-
gical risk (The European System for Cardiac Operative Risk Evaluation [EuroSCORE], 14.4±10%) and no active endocarditis or concomitant cardiac procedure have a good outcome when treated with redo SAVR (1-year survival, 96%).22 Young patients (<65 years) have a particularly favorable long-term outcome (78% ± 10-year survival and 97% ± 3% freedom from reoperation).23

Those observations could collectively indicate an even improving outcome of SAVR-treated patients, despite a stable/worsening risk profile. This could reflect a continuous improvement process involving preoperative assessment, intraoperative surgical techniques, and postoperative care.23

How Safe Is TAVI?

Overall, intraprocedural complications during TAVI have declined in countries with a large procedural volume from 9.4% in 2012 to 3.9% in 2014.12 Severe TAVI complications such as annular rupture, aortic dissection, or coronary occlusion now occur in <0.3% of patients, and the rate of conversion to open heart surgery has declined to 0.6% in 2014.12 In the large German experience, vascular complications have declined from 8.5% in 2013 to 6.5% in 2014. In-hospital stroke rate became comparable between TAVI (2014: 1.4%)
and SAVR (2014, isolated SAVR: 1.1%; SAVR+coronary artery bypass grafting: 2.0%), despite differences in baseline characteristics. The need for dialysis after TAVI has decreased considerably from 8.3% in 2008 to 2.6% in 2014, eventually to fall below the rates of dialysis after SAVR (isolated SAVR: 3.6%; SAVR+coronary artery bypass grafting: 5.4%). Overall rates of new pacemaker implantation have remained relatively stable over time (14.9% in 2008 and 12.8% more recently) with important interdevice differences.

However, some important complications of the procedure are still fairly common when compared with SAVR. In a meta-analysis of 39 studies (n=13 130 patients, type of device not specified), TAVI was associated with an increased risk of permanent pacemaker implantation (odds ratio [OR]=3.2), major vascular complications (OR=7.1), and aortic regurgitation (AR; OR=7.4). Compared with SAVR, TAVI was associated with a lower incidence of new-onset atrial fibrillation (AF; OR=0.35), bleeding requiring transfusion (OR=0.39), and acute kidney injury requiring hemodialysis (OR=0.86).24

Cerebral Embolism
Concerns have been raised about an observed higher early risk of neurological events associated with TAVI compared with SAVR.25 High-intensity transient signals have been detected by transcranial Doppler in all patients undergoing TAVI using a balloon or a self-expandable prosthesis through a transfemoral or a transapical approach.26

In the UK TAVI registry, periprocedural stroke was shown as the strongest independent procedural predictor of long-term mortality (hazard ratio, 3.00; P<0.0001).33

In Placement of Aortic Transcatheter Valves (PARTNER) 1 trial,25 periprocedural stroke was associated with a2- to 6-fold increase in hospital mortality, a 3- to 12-fold increase in mortality at 30-day, and a 2- to 16-fold increase in long-term mortality.26 However, although periprocedural stroke or transient ischemic attack was more common after TAVI than after SAVR at 30 days (5.5% versus 2.4%; P=0.04), this difference gradually decreased and by 5 years, the difference had dissipated (TA VI, 14.7% versus SA VR, 15.9%).27 One concern about interpreting PARTNER trial results is that a neurologist was not involved in the neurological assessment of patients, with potential under-reporting of neurological events. However, under-reporting, if ever existed, would occur equally in both treatment groups.

In the more contemporary 2-year results from the CoreValve US pivotal trial (high-risk cohort), the incidence of stroke at 2 years tended to be lower in the TAVI group than in the surgical group (10.9% versus 16.6%; P=0.05). In this study, a specialized neurological surveillance was routinely adopted increasing the credibility of observed results. Although the high stroke rate (16.6%) in surgical patients in this study was not clearly explained, the higher prevalence and new annual incidence of AF in post-SAVR patients may have contributed to this phenomenon.24

Predictors of Neurological Events After TAVI: Relation to Baseline Risk
Risk factors for early post-TAVI neurological events are preexisting/new-onset AF,29,30 smaller aortic valve area index at baseline,25 postimplantation balloon dilation, and valve embolization/dislodgement.30

Risk factors for late neurological events reflect the overall risk of stroke among elderly people undergoing TAVI rather than the procedure-related hazards and include functional impairment (New York Heart Association class), history of stroke within 6 to 12 months before TAVI, chronic AF, cerebrovascular disease,30 and assignment to transapical approach—a marker of the burden of vascular diseases and a predictor of new-onset AF.30,31

Therefore, it is increasingly recognized that neurological complications occur more frequently after TAVI than after SAVR early after the procedure, but thereafter the risk is more determined by the inherent patient’s risk.25

Subclinical Embolization and Silent Brain Infarcts
In the large general population-based Rotterdam Scan Study, the presence of silent brain infarcts more than doubled the risk of dementia and was associated with a steeper decline in global cognitive function.32

Using cerebral diffusion-weighted magnetic resonance imaging, the rate of silent brain infarcts after TAVI ranged from 68% to 91.5%33–37 compared with <50% in SAVR patients.33,38 The clinical correlates of these infarcts are not clearly known. In the short postprocedural period (≤3 months), no direct relation could be demonstrated between those infarcts and cognitive dysfunction36,39 and health-related quality of life.39 In the longer term follow-up (≤2 years), the risk of cognitive dysfunction (which was generally low) was determined by age, but not by the burden of brain infarcts.40

Future Perspective of Brain Protection in TAVI-Treated Patients
Using smaller delivery systems, restricting procedural interventions to the minimal needed, cerebral protection devices, and evidence-based periprocedural antithrombotic therapy (especially for those with preexisting/new onset AF) are countermeasures to reduce the risk of periprocedural stroke.

Relatively small exploratory studies showed the feasibility and safety of using cerebral protection devices during TAVI with a complete cerebral vessel coverage in the majority of patients. This was associated with a reduction in brain ischemic lesion volume, but efficacy in preventing cerebral microembolism and new transient ischemic lesions is still contentious.41,42 Concerns have been raised about lengthening the procedure and more instrumentation, further increasing the risk of thrombogenicity.43 Some authors43 proposed that this might have contributed to the unexpectedly high thrombotic burden (in 52% of patients) revealed by histopathologic examination of embolic debris captured in the device filter.44

The justification of the currently recommended dual-antiplatelet therapy after TAVI has recently been questioned, whereas arguments supporting a potential benefit of oral anticoagulation have emerged.45,46 A large proportion of strokes occur during the recommended period of dual-antiplatelet therapy42 and the majority of reported cases of TAVI thrombosis took place after completing, or despite on-going, dual-antiplatelet therapy.46 Warfarin anticoagulation has been recently shown to be associated with a lower risk of TAVI leaflet thickening and immobility (surrogates of subclinical thrombosis).
The latter occurred in 10% to 40% of screened patients (treated by different TAVs) and was associated with increased risk of stroke or transient ischemic attack. This observation is expected to further provoke a serious search for an evidence-based antithrombotic regimen. Table I (Data Supplement) summarizes some upcoming trials exploring the optimal peri-TAVI antithrombotic therapy.

Conduction Defects and PACING

Data on pacing-induced cardiopathy are conflicting. Life expectancy among permanent pacemaker recipients, including surgical patients, without significant comorbidity was reported to be comparable with that of the general population. In other studies, however, cardiac pacing was shown to induce electric and mechanical ventricular dyssynchrony, abnormalities in myocardial perfusion and chronic adverse left ventricular remodeling and lead to adverse cardiovascular outcomes. Ventricular desynchronization induced by ventricular pacing was also shown to increase the risk of heart failure hospitalization and AF, with the risk of heart failure being higher in those with preimplantation older age, AF, myocardial infarction, or lower ejection fraction and in those with a long (>3 years) pacing and a high percentage of cumulative pacing.

Therefore, pacing-induced cardiac dysfunction seems to reflect the interaction between the negative electromechanical sequelae of ventricular pacing and the preexisting cardiac morbidity and to be related to the duration of pacing.

Many studies failed to demonstrate a negative effect of permanent pacing on clinical outcomes in TAVI patients. Short follow-up time and low percentage of cumulative pacing (because of the fact that >50% of patients requiring permanent pacemaker after TAVI are not pacing dependent) might account for these findings.

Data from PARTNER 1 trial contrast with those earlier reports exonerating permanent pacemaker from association with worse outcome after TAVI. TAVI patients with a new or previous permanent pacemaker were shown to have significantly longer hospitalization, higher mortality and rehospitalization, and lower ejection fraction at 1 year. Although this study included a large number of patients and event adjudication committee ensured data quality, the results were not adjusted for the occurrence of renal failure requiring dialysis and the need for hemodynamic support during the procedure, both of which were more frequent in patients who required a permanent pacemaker.

Notably, important interdevice differences in the rates of permanent pacing exist. In healthcare systems mainly utilizing a balloon-expandable device, lower rates of permanent pacemaker implantation are reported (6.6% in the STS/ACC TVT registry). In PARTNER 1 trial, TAVI was not associated with an increased risk of permanent pacing compared with SAVR (6.4% versus 5.3% at 1 year and 9.7% versus 9.1% at 5 years). A significantly higher incidence of permanent pacemaker was observed in the more recent nonrandomized continuous access cohort (9.6%) than in the earlier randomized cohort (5.6%). This finding, which is to date poorly understood, indicates that this complication of TAVI is not expected to vanish only by increasing the centers’ operators’ experience. Moreover, newer balloon- and self-expandable TAVI devices are provided with improved paravalvular sealing mechanisms, but no specific features seem to have been implemented to reduce the incidence of conduction defects. Compared with the second-generation device, the third-generation balloon-expandable prosthesis demonstrated a significantly improved paravalvular sealing, whereas the need for permanent pacemaker did not improve, with a trend toward a higher rate of new-onset conduction abnormalities.

Some procedural precautions might reduce the risk of postimplantation conduction abnormalities. Although deep implantation has long been considered the main correctable cause of new-onset conduction defects after TAVI, results of the CoreValve Advance-II Study: Prospective International Post-Market Study (ADVANCE II) trial did not promote confidence in this concept. An optimal implantation depth could be achieved in only 43% of patients and led to a nonsignificantly lower need for permanent pacemaker implantation compared with deep implants.

Another potentially correctable cause of new-onset conduction defects is a higher prosthesis diameter/left ventricular outflow tract diameter ratio—a relation that needs yet to be further confirmed. Modest balloon predilation in patients implanted with a self-expanding prosthesis has also been reported to reduce the permanent pacemaker implantation rate without affecting procedural success.

Finally, adherence to guidelines of indications for pacing and adjusting the criteria for and timing of pacemaker implantation after TAVI are thought to reduce the rate of pacemaker implantation given the high rate of spontaneous resolution and the low rate of pacemaker dependence in TAVI patients with new-onset conduction defects.

To explore the possibility of expanding TAVI toward lower-risk and younger patients, technological and procedural improvements to reduce the need for permanent pacemaker implantation or more solid evidence of a safe long-term outcome of permanent pacemaker is needed.

Vascular Complications

Vascular complications were frequent (major: 15.3% and minor: 11.9%) after TF-TAVI in the PARTNER 1 trial (using a first-generation device through a 22F or 24F sheath). Major vascular complications were associated with significantly higher 30-day rates of major bleeding, transfusions, and renal failure requiring dialysis, and with a significantly higher rate of 30-day and 1-year mortality. The only identifiable independent predictor of major vascular complications in PARTNER 1 trial was female sex (hazard ratio, 2.31).

Other studies demonstrated an important role of the delivery system caliber and the sheath/femoral artery diameter ratio, moderate or severe calcification, and peripheral vascular disease in increasing the risk of vascular complications. Accumulating experience, smaller sheaths, rigorous angiographic and multislice computed tomographic screening, and improved vascular closure techniques were increasingly used and resulted in a markedly lowered rate of vascular complications. The use of newer vascular closure devices is associated with lower rates of major vascular complications.
The reported rates of late SVD requiring reoperation vary widely, from 6% to 47% by 12 to 20 years, after surgery but are generally lower (15%–19% at 15 years) in patients treated with the second-generation Hancock (Medtronic, Minneapolis, MN) and Carpentier-Edwards (Edwards Lifesciences LLC, Irvine, CA) valves that have many improvements including treatment with anticalcification agents. After introduction of the third-generation bioprosthesis, an even lower rate of SVD (<8% at 12 years) has been reported, interestingly, with no difference between the younger (≤50 years) and older age groups. In the Valve-in-Valve International Data (VIVID) Registry, median time from SAVR to reintervention for SVD was 9 (interquartile range, 6–12) years.

TAVI Durability

Concerns were raised about the possibility of early structural deterioration of TAVs as a result of possible leaflet damage during the crimping process and the asymmetrical/incomplete expansion with secondary suboptimal leaflet coaptation. This concern would be even more relevant when TAV bioprosthesis is implanted in younger, lower-risk patients with expected longer survival.

Durability of the clinical benefits and the valve integrity after TAVI has been shown in the 5-year data from the PARTNER 1A trial. Valve hemodynamics (valve area, 1.6 versus 1.5 cm²; P=0.29 and mean pressure gradient, 10.7 versus 10.6 mm Hg; P=0.92) were much the same in TAVI and SAVR groups. Moderate-to-severe paravalvular regurgitation was, however, more common in TAVI than in SAVR group and was associated with higher mortality. Notwithstanding, <60 patients in the TAVI arm were alive and had echocardiographic data available at 5 years, and 5 years is a too short time to expect differences in durability between transcatheter and surgical prostheses.

In a series of 122 patients (treated with balloon-expandable or self-expanding TAVs, with a median follow-up of 3.6 years), 5 patients had prosthetic dysfunction (3 patients had mild-to-moderate stenosis developing at 1.3–5 years and 2 had transvalvular moderate-to-severe AR developing at 2 and 4.8 years).

Five-year follow-up data are also available from 353 patients treated with the self-expanding CoreValve. On echocardiography, mean pressure gradient slightly increased at 5 years (from 10.3±6.5 post implantation to 12.8±10.9 mm Hg). Late significant prosthesis failure occurred in 5 cases (1.4%; 2 patients with symptomatic prosthesis stenosis at days 1693 and 1465, 1 case of endocarditis with severe AR at day 1681, 1 case of asymptomatic valve degeneration with severe AR at day 1674, and 1 case of worsening from moderate-to-severe paravalvular AR at day 355). Ten other patients (2.8%) showed late moderate stenosis (mean pressure gradient, 20–40 mm Hg).

In a recent systematic review of reported cases of TAV failure by Mylotte et al., SVD was reported in 13 individual cases (9 SAPIEN and 4 CoreValve) including moderate prosthesis stenosis or regurgitation in 5 cases, severe stenosis in 5, and severe regurgitation in 3 cases. Structural valve failure was attributed to severe leaflet calcification (n=3), cusp rupture (n=1), TAV underexpansion (n=2), and tissue ingrowth (n=2) causing restrictive leaflet function.
Although to date infrequent or under-reported, it is increasingly recognized that TAVs are susceptible to several failure modes, some are similar to those of surgical bioprosthetic valves and others are unique to TAVs.\textsuperscript{48} Although the data of the first 5-year follow-up studies are encouraging, the existing studies were too small and the follow-up period was too short to address valve failure as a safety end point.

**TAVI in Lower-Risk Patients: What the Evidence Shows**

**The Nordic Aortic Valve Intervention Trial**

Nordic Aortic Valve Intervention (NOTION) trial\textsuperscript{114} was a randomized trial comparing TAVI (with a CoreValve, via a transfemoral \textendash\textsuperscript{[96.5\%]} or subclavian approach) and SAVR in all comers >70 years old with AS enrolled between December 2009 and April 2013. The study retained 95\% of patients at 2-year follow-up and used VARC-2 definitions for end points. The composite rate of all-cause mortality, stroke, and myocardial infarction at 1 year was the primary end-point.

In the intention-to-treat analysis, the rate of primary outcome at 1 year was 13.1\% versus 16.3\% for TAVI and SAVR, respectively (\(P=0.43\) for superiority). By 2 years, those numbers were 15.8\% and 18.8\% (\(P=0.43\)).\textsuperscript{115} Mortality (all-cause and cardiac) remained similar between surgically and transcatheter-treated patients at 2 years.

TAVI patients had more conduction defects requiring a permanent pacemaker, moderate-to-severe AR, and minor vascular complications, whereas SAVR patients had more bleeding complications, cardiogenic shock, acute kidney injury, new-onset or worsening AF, and a longer hospital stay.

**Interpretation of the Results of NOTION Trial**

1. During a period of \(3.5\) years, 1576 patients in 3 hospitals were evaluated by heart teams, but only 280 patients were included in the study. It is difficult to describe a study that enrolled <20\% of screened patients as an all-comers trial.\textsuperscript{116}

2. The NOTION trial was designed to test TAVI’s superiority with the sample size calculated on the assumption that primary outcome would occur 3 times more frequently in the SAVR group (15\% versus 5\%).\textsuperscript{114} Given the much less observed outcome difference (16.3\% versus 13.1\%) than expected, it turns out that NOTION is an under-powered study that provides valuable but not definitive data.\textsuperscript{116} To have a positive superiority study in low-risk patients (in whom SAVR is an effective therapy), it must be adequately powered.

3. Patients were excluded if they had another severe heart valve disease or coronary artery disease requiring intervention, previous cardiac surgery, severe renal failure requiring dialysis, or pulmonary failure, and outcomes for this large patient population cannot necessarily be inferred from this trial. In fact, some important fairly common comorbidities in typical patients undergoing isolated SAVR\textsuperscript{17} were considered as exclusion criteria in the NOTION trial. Table 1 compares the baseline characteristics and the 30-day outcomes of patients treated with isolated SAVR in the NOTION trial and in the STS national database.\textsuperscript{15} Despite close average STS-PROM (3.1\% versus 2.95\%), important differences in patients’ risk existed (Table 1).

4. After considering the important dissimilarities in baseline (Table 2) and procedural characteristics between patients in the NOTION trial and in the CoreValve US pivotal trial (both utilized similar TAVI technologies), some important differences in outcomes are noteworthy. In the CoreValve pivotal trial (high-risk cohort),\textsuperscript{119} TAVI patients had a significantly lower mortality with no significant difference in functional status than SAVR patients at 1 year. In NOTION, the lower rate of mortality in TAVI patients did not reach statistical significance and patients were more likely to have residual symptoms (New York Heart}

<p>| Table 1. Comparison of the Baseline Characteristics and 30-Day Outcomes of Patients Treated With Isolated Surgical Aortic Valve Replacement in the NOTION Trial\textsuperscript{117} and in the STS Database\textsuperscript{88} |
|-------------------------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th><strong>Baseline risk factors</strong></th>
<th>STS National Database (n=141,905)</th>
<th>The NOTION Trial (n=135)</th>
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<tr>
<td>STS-PROM, %</td>
<td>2.95±3.7</td>
<td>3.1±1.7</td>
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<tr>
<td>Previous CABG, %</td>
<td>9.8</td>
<td>Excluded</td>
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<tr>
<td>Prior cerebrovascular accident, %</td>
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<td>PVD, %</td>
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<td>COPD, %</td>
<td>22</td>
<td>11.9</td>
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<td>Renal impairment (creatinine &gt;2 mg %)</td>
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<tr>
<td>Renal failure on hemodialysis</td>
<td>2.3%</td>
<td>Excluded</td>
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<tr>
<td><strong>30-d outcomes</strong></td>
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<tr>
<td>All-cause mortality, %</td>
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<tr>
<td>Stroke, %</td>
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<tr>
<td>Length of hospital stay (d)</td>
<td>7.9±7.2</td>
<td>13±12</td>
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AKI indicates acute kidney injury; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; NOTION, Nordic Aortic Valve Intervention; PROM, predicted risk of operative mortality; PVD, peripheral vascular disease; STS, The Society of Thoracic Surgeons; and TIA, transient ischemic attack.

*a. In the STS registry, operative mortality was defined as death during the same hospitalization as surgical aortic valve replacement or after discharge but within 30 days of surgical aortic valve replacement.*
Association ≥2 at 1 year if treated with TAVI versus SAVR. The rates of moderate-to-severe AR (15.7%) and permanent pacemaker implantation (34.1%) after TAVI were higher than seen in the CoreValve pivotal trial (6.1% and 19.8%, respectively), and this might have contributed to eroding the mortality and symptomatic benefit of TAVI in the NOTION trial. On the contrary, there was a markedly lower rate of neurological events in this trial than in the CoreValve pivotal trial that was evident in both arms (TAVI and SAVR). Formal neurological assessments were done to all patients in the CoreValve pivotal trial but not in the NOTION trial, and more subtle neurological events might have been overlooked in the latter.

**Other Observational Data**

Tamburino et al. found that the outcome of patients, principally treated with a CoreValve, who were at lower risk (logistic EuroSCORE [LES] <20%), is better than those at higher risk (30-day and 1-year mortality rate, 2.4% and 6.8% versus 15.6% and 25.7%). The rate of major adverse cardiovascular events was also lower at 30 days (6% versus 20.8%) and at 1 year (11.4% versus 27.1%).

Lange et al. subcategorized TAVI patients into quartiles defined by enrollment date. A lower estimated risk was demonstrated in the later quartile (STS-PROM, 4.8±2.6%) than in the earlier quartile (STS-PROM, 7.1±5.5%). The earlier quartile with a higher risk had numerically higher rates of 30-day mortality (11.4% versus 3.8%), stroke/transient ischemic attack (6.7% versus 1%), vascular complications (28.6% versus 14.7%), and permanent pacemaker implantation (24.8% versus 18.6%) and 6-month mortality (23.5% versus 12.4%), with the difference being statistically significant for vascular complications (28.6% versus 14.7%; P=0.01). Caution should be exercised as we look at these results that reflect the combined effect of lowered patients’ risk and the improving technology and expertise in the later quartile of patients. After adjustment for baseline characteristics, there was no significant difference between the 2 quartiles in 30-day and 6-month mortality rate, denoting that the major part of the mortality benefit was derived from the improved baseline risk.

Similar results were also reported in a study by Wenaweser et al., where patients were divided according to their baseline predicted risk into low-risk (STS-PTOM <3; n=41), intermediate-risk (STS-PTOM 3–8; n=254), and high-risk (STS-PTOM >8; n=94) groups. Thirty-day (2.4% versus 3.9% versus 14.9%) and 1-year (10.1% versus 16.1% versus 34.5%) all-cause mortality increased with increasing predicted risk. No differences were observed, however, with regards to neurological events and myocardial infarction during a 1-year follow-up.

Similar results were demonstrated in the ADVANCE study (n=1015 patients), where the 1-year rates of all-cause mortality were 23.6%, 16.5%, and 11.1% in patients with an LES of >20%, 10% to 20%, and ≤10% (P<0.05).

More recently, data from the PARTNER Sapien 3 registry provided a large-scale assessment of intermediate-risk patient...
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outcomes. At the 2015 American College of Cardiology Scientific Sessions, 30-day outcomes of 1076 intermediate-risk (STS-PROM, 4–8%; average 5.3%) patients treated with the Sapien 3 valve (Edwards Lifesciences, Irvine, CA) were presented. Thirty-day rates of all-cause death and disabling stroke were 1.1% and 1.0%, respectively.116

Although these results from observational comparisons of TAVI outcomes in different patients’ risk strata imply that a significantly better clinical outcome is expected in lower than in higher risk patients, they do not answer the more important question: Are those patients better treated with TAVI or with the default therapy-SA VR?

Table 3 summarizes the results of 3 studies where intermediate- to low-risk patients treated with TAVI were propensity-score matched with SA VR-treated counterparts.14,123,124 Mortality, stroke, and myocardial infarction at 30-day and mortality at 1 year were comparable after both treatment strategies. However, important differences exist in other outcome measures. Major bleeding123,124 (1.5-fold) and acute kidney injury124 (1.8-fold) were more common after SA VR while major vascular injury123,124 (5- to 14-fold), permanent pacemaker implantation123,124 (4- to 15-fold) and AR123,124 (mild: ≤21-fold, moderate to severe: 2- to 3-fold) were more common after TAVI.

Two randomized trials, designed to investigate the safety and efficacy of TAVI in intermediate-risk patients, began enrollment a few years ago. PARTNER 2A trial (NCT01314313), in which patients are randomized to TAVI using a balloon-expandable valve or SA VR, completed enrollment in 2014 with the results expected in 2016. The Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTA VI; NCT01586910) trial, which has a similar design using a self-expanding valve, is continuing enrollment.116

### Table 3. Comparison of TAVI and SA VR in Propensity-Score–Matched Cohorts

<table>
<thead>
<tr>
<th></th>
<th>No. of Matched Pairs</th>
<th>Risk Score</th>
<th>Baseline Predicted Risk</th>
<th>30-d Mortality</th>
<th>30-d Stroke</th>
<th>1-y Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TAVI</td>
<td>SAVR</td>
<td>TAVI</td>
<td>SAVR</td>
<td>P Value</td>
</tr>
<tr>
<td>D’Errigo et al123</td>
<td>133</td>
<td>LES</td>
<td>8.9±9.5%</td>
<td>9.4±10.4%</td>
<td>3.80%</td>
<td>3.80%</td>
</tr>
<tr>
<td>Latib et al124</td>
<td>111</td>
<td>STS</td>
<td>4.6±2.3</td>
<td>4.6±2.6</td>
<td>1.80%</td>
<td>1.80%</td>
</tr>
<tr>
<td>Piazza et al14</td>
<td>255</td>
<td>LES</td>
<td>17.30%</td>
<td>17.60%</td>
<td>7.8%</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

LES indicates logistic EuroSCORE; NA, not applicable; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; and TAVI, transcatheter aortic valve implantation.

Figure 2. Utility vs futility of transcatheter aortic valve implantation (TAVI) at different levels of patients’ risk. As any other treatment, TAVI can be utile or futile depending on the balance of the benefit gained, the treatment-related risks and the costs imposed on the community. In the pathophysiologic development of symptomatic severe aortic stenosis, ultrastructural changes are followed by phenotypic valve changes eventually leading to a disturbed physiology. After a long preclinical period, once symptoms develop the need for intervention becomes unavoidable but the risk of intervention could be low, high, or unacceptable basically determined by age and comorbidities. BAV indicates bicuspid aortic valve; QALY, quality-adjusted life years; and SVD, structural valve deterioration.
Table 4. Pros and Cons of Transcatheter Aortic Valve Implantation (Compared With Surgical Aortic Valve Replacement) as a Default Therapy of Lower Risk, Younger Patients With Aortic Stenosis

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient convenience and acceptance</td>
<td></td>
</tr>
<tr>
<td>Less invasive (intubation needed in progressively less percentage of procedures, no extracorporeal circulation...)</td>
<td></td>
</tr>
<tr>
<td>Less pain (no thoracotomy in the majority of cases)</td>
<td></td>
</tr>
<tr>
<td>Faster recovery</td>
<td></td>
</tr>
<tr>
<td>Faster improvement of functional status and QOL</td>
<td></td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>Favorable outcomes in female patients</td>
<td></td>
</tr>
<tr>
<td>Valve hemodynamics: larger EOAi and less prosthesis–patient mismatch*</td>
<td></td>
</tr>
<tr>
<td>Less detrimental effect on RV function</td>
<td></td>
</tr>
<tr>
<td>More total and paravalvar AR†</td>
<td></td>
</tr>
<tr>
<td>Less effective in BAV and significant AR at baseline (both are more likely encountered in younger patients)*</td>
<td></td>
</tr>
<tr>
<td>Reverse LV remodeling incomplete*</td>
<td></td>
</tr>
<tr>
<td>Proper device positioning and sizing are significantly influenced by patients’ anatomy‡</td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td></td>
</tr>
<tr>
<td>Less atrial fibrillation and less late stroke</td>
<td></td>
</tr>
<tr>
<td>Less bleeding requiring transfusion</td>
<td></td>
</tr>
<tr>
<td>Less kidney injury</td>
<td></td>
</tr>
<tr>
<td>Less cardiogenic shock</td>
<td></td>
</tr>
<tr>
<td>More conduction defects requiring permanent pacing*</td>
<td></td>
</tr>
<tr>
<td>More vascular complications†</td>
<td></td>
</tr>
<tr>
<td>More periprocedural cerebral embolism and silent brain infarcts*</td>
<td></td>
</tr>
<tr>
<td>Durability</td>
<td></td>
</tr>
<tr>
<td>Durability beyond 5 y unknown</td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td></td>
</tr>
<tr>
<td>The majority of procedures can be performed under local anesthesia</td>
<td></td>
</tr>
<tr>
<td>Less utilization of ICU and blood products</td>
<td></td>
</tr>
<tr>
<td>Shorter hospital stay</td>
<td></td>
</tr>
<tr>
<td>Costly device†</td>
<td></td>
</tr>
<tr>
<td>Periprocedural complications are common and derive extra costs†</td>
<td></td>
</tr>
</tbody>
</table>

AR indicates aortic regurgitation; BAV, bicuspid aortic valve; EOAi, indexed effective orifice area; ICU, intensive care unit; LV, left ventricle; QOL, quality of life; and RV, right ventricle.

*Relevance to patients’ outcomes uncertain or inadequate comparative data.
†A moving target; rapidly evolving improvements.
‡Landing zone calcification, aortic root dilation, and aortic annular size (patients with large annuli are more prone to paravalvar AR and those with smaller annuli are more prone to prosthesis–patient mismatch).
TA VI in only a minority (10%) of patients considered for treatment—those who are considered inoperable because of technical reasons such as previous operations or irradiation of the chest wall.

The second precaution is avoiding intercountry generalization of results especially those driven from hospitalization/follow-up costs that considerably vary across different countries.

Utility/Futility Perspective

Cost-effectiveness is to date a weakness point of TAVI adoption in lower risk patients. However, and as this is mainly due to the lack of large randomized trials, a customized index needs to be prospectively tested, ideally in a randomized setting. Such new integrative index needs to be prospectively tested, ideally in a randomized setting. AF indicates atrial fibrillation; AV, aortic valve; BMI, body mass index; BNP, brain natriuretic peptide; CA, cancer antigen; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; FRANCE 2, French Aortic National CoreValve and Edwards; GDF, growth differentiation factor; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; LV, left ventricle; NYHA, New York Heart association; PARTNER, Placement of Aortic Transcatheter Valves; sST, soluble ST2; TA, transapical; and TF, transfemoral.

References: PARTNER 1A154,155; PARTNER 1B156; FRANCE 2 Registry157; UK Registry158; SOURCe (TF) Registry159; SOURCe (TA) Registry159; Rodès-Cabau et al160; Himbert et al161; Stähli et al162; Koskinas et al, 2015163; O’Sullivan et al164; Baldenhofer et al165; Green et al166; Stortecky et al167; Husser et al168; Lindman et al169; Sinning et al169.

Figure 3. Baseline predictors of mortality after transcatheter aortic valve implantation (TAVI). A list of baseline predictors of all-cause mortality after TAVI, many are biomarkers, with their respective hazard ratios. All factors are the result of multivariate analysis of data derived from randomized trials and large registries. The list is not exhaustive, eg, age and sex are not included, and the definition of each comorbidity and the confounders accounted for vary across different studies. An exhaustive model that integrates and differentially weighs those factors can provide a customized individual prediction of risk. Such new integrative index needs to be prospectively tested, ideally in a randomized setting. AF indicates atrial fibrillation; AV, aortic valve; BMI, body mass index; BNP, brain natriuretic peptide; CA, cancer antigen; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; FRANCE 2, French Aortic National CoreValve and Edwards; GDF, growth differentiation factor; hsCRP, high-sensitivity C-reactive protein; IL, interleukin, LV, left ventricle; NYHA, New York Heart association; PARTNER, Placement of Aortic Transcatheter Valves; sST, soluble ST2; TA, transapical; and TF, transfemoral. References: PARTNER 1A154,155; PARTNER 1B156; FRANCE 2 Registry157; UK Registry158; SOURCe (TF) Registry159; SOURCe (TA) Registry159; Rodès-Cabau et al160; Himbert et al161; Stähli et al162; Koskinas et al, 2015163; O’Sullivan et al164; Baldenhofer et al165; Green et al166; Stortecky et al167; Husser et al168; Lindman et al169; Sinning et al169.

TA VI in only a minority (10%) of patients considered for treatment—those who are considered inoperable because of technical reasons such as previous operations or irradiation of the chest wall.144

The second precaution is avoiding intercountry generalization of results especially those driven from hospitalization/follow-up costs that considerably vary across different countries.
derived from the device price, the cost difference is largely artificial. It has been only few months since the introduction of a lump-sum of competing devices into the market. The result would be a rapid reduction of device price. It is, therefore, just a matter of time until the cost-effectiveness gap erodes.

The question of utility/futility is, in fact, more important and difficult to answer. This concept is wider and more complex than the simple efficacy, safety, and cost-effectiveness concepts (Figure 2). To achieve the best utility and the least futility (to the patient and the community), patient's morbidity profile and the burden it imposes to the healthcare system, procedural costs, risks and expected benefit (in terms of quality-adjusted life years [QALYs]), as well as durability of the prosthesis should all be taken into account. Table 4 summarizes the advantages and disadvantages of TAVI compared with SAVR.

**A Word of Caution: How Accurate Can We Predict the Risk?**

The dilemma of extending TAVI indications and directing its penetration is based on patients’ risk stratification. The 2 risk models most commonly used for risk stratification of patients planned for TAVI are the LES and the STS-PROM systems.

The LES (predominantly derived from data of 14,799 patients undergoing coronary artery bypass grafting) has been clearly demonstrated to overestimate (by 3- to 7-fold) the expected mortality in high-risk patients undergoing SAVR. The STS-PROM risk model was derived from data of 67,292 patients undergoing isolated SAVR. The highest-risk patients, observed mortality was shown to be much closer to the STS-PROM (with an underestimation by a factor of 0.8) than to the LES (with a 3-fold overprediction). Although the STS score outperformed LES, EuroSCORE II, and age-creatinine-ejection fraction scores in multiple studies, it can only provide moderate discriminatory power for predicting mortality after TAVI.

New versions of both the LES (EuroSCORE II) and the STS score (STS 2.73) have been developed, but data are still insufficient to judge their accuracy. Some studies reported a better, yet still suboptimal, performance of EuroSCORE II especially in TF-TAVI.

Many factors that affect mortality after TAVI (including liver disease, frailty, dementia, porcelain aorta, severe pulmonary hypertension, and previous chest irradiation) are not included in surgical risk estimation models. In a metanalysis of PARTNER data (n=2137 patients), a multivariable model was generated to identify the risk of death or impaired quality of life at 1 year. The model conferred only moderate discriminatory power (C-statistic=0.66).

The TAVI risk score included besides sex and age; body mass index, glomerular filtration rate, hemoglobin, pulmonary hypertension, mean aortic pressure gradient, and left ventricular ejection fraction at baseline. Compared with other available risk evaluation schemes, the TAVI risk score algorithm showed a modestly higher C-statistic for predicting 1-year
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mortality (0.66 versus 0.57–0.62 for the German Aortic Valve Registry [GARY] score, EuroSCORE II, LES, and STS score) with a further slight improvement of the C-statistic when frailty was added to the model.

The SURTAVI model is another example, among few other examples, of a TAVI-oriented risk stratification system. The model included risk factors, ignored by classic surgical risk scores, that are relatively prevalent, easy to capture, and with a reasonable impact on operative mortality. In addition to age, significant coronary artery disease, frailty, LV dysfunction, neurological, pulmonary, peripheral vascular and renal diseases, redo cardiac surgery, pulmonary hypertension and diabetes mellitus were included in the risk model. Data supporting the inclusion of risk parameters and the relative weight of each were, however, mainly derived from surgical series and an experimental retrospective application of the model finally involved a predominantly surgical cohort. Another attempt to test the model in a small TAVI cohort showed no advantage over other established risk models. Further prospective large-scale validation did not take place.

The concept was, however, increasingly applied in the SURTAVI trial, and the incremental risk markers (of the SURTAVI risk model) are used complementarily by the heart team to risk-stratify patients before enrollment. In the last phase of enrollment (version 8), patients with an STS score of <4% were possibly enrolled if considered at ≥3% risk of 30-day mortality based on the incremental risk model analogous to the SURTAVI model. Interestingly, when risk estimation relied on this model (instead of the STS score), the risk profile of patients showed a significant shift (Figure 4). Prospective large-scale validation of SURTAVI model remains, however, the only way to prove its discriminatory power.

**Novel Risk Markers**

Some novel markers of risk are proposed to be complementary to the current heart-team and risk-scores strategies (Figure 3). Examples of investigated biomarkers include growth differentiation factor 15, soluble ST2, and N-terminal pro-B-type natriuretic peptide. Complementing the STS score with growth differentiation factor 15, soluble ST2, and N-terminal pro-B-type natriuretic peptide improved its 1-year survival C-statistic from 0.667 to 0.702. Similarly, supplementing the EuroSCORE II with growth differentiation factor 15 improved its 1-year survival C-statistic from 0.711 to 0.743.

**Future Perspective: Power Calculation and End Point Definition for Upcoming Trials**

As shown in Figure 5, mortality trends after TAVI versus SAVR diverge in favor of TAVI at higher STS-PROM but start to overlap when PROM drops <10%. As initial comparisons between both treatment strategies were performed in the highest patients’ risk stratum, it was easy to demonstrate noninferiority and even reflex superiority, of TAVI. If we consider this linear relationship, only strict noninferiority is the reasonable end point when lower risk patients are
studied. Besides the hard clinical end points of mortality and stroke that will require a large sample size to prove non-inferiority, the overall clinical risk/benefit ratio (which weighs early and late symptomatic and quality of life benefits versus mortality) might be an alternative end point. From a societal point of view, cost-effectiveness can also be a future target but only after the device price becomes more affordable and not inflated by the consideration of return on investment.

Disclosures
Dr. Serruys is the chairman of the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial.

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Transcatheter Aortic Valve Implantation in Lower-Risk Patients With Aortic Stenosis: Is It Justified to Be the Preferred Treatment?
Mohammad Abdelghani and Patrick W. Serruys

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**Supplemental Material**

**Supplemental Table.** Upcoming clinical trials of antithrombotic treatment periprocedural and after TAVI.

<table>
<thead>
<tr>
<th>Trial name and acronym</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of Bivalirudin on Aortic Valve Intervention Outcomes <em>(BRACO 2/3)</em> trial (NCT01651780)</td>
<td>A multicentre open-label pilot study, randomizing 870 patients to bivalirudin or unfractionated heparin for procedural anticoagulation.</td>
</tr>
<tr>
<td>The Aspirin Versus Aspirin+Clopidogrel Following Transcatheter Aortic Valve Implantation <em>(ARTE)</em> trial (NCT01559298)</td>
<td>Compares the use of aspirin alone (80 mg/day for at least 6 months) versus aspirin (80 mg/day for at least 6 months) + clopidogrel (75 mg/day for 3 months) regarding the rates of death, myocardial infarction, ischaemic stroke/transient ischaemic attack or life-threatening/major bleeding at one year in 200 patients with no indication for oral anticoagulation (OAC).</td>
</tr>
<tr>
<td>The Dual Antiplatelet Therapy Versus Oral Anticoagulation for a Short Time to Prevent Cerebral Embolism After TAVI <em>(AUREA)</em> trial (NCT01642134)</td>
<td>Assesses the efficacy of DuoPlavin (aspirin 80 mg/day + clopidogrel 75 mg/day, for three months) compared with acenocumarol in preventing cerebral thromboembolism identified using magnetic resonance at 3 months in 124 patients with no indication for OAC.</td>
</tr>
<tr>
<td>The Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation <em>(POPular-TAVI)</em> trial (NCT02247128)</td>
<td>A multicentre open-label randomised all-comers trial comparing safety, net clinical benefit and efficacy of aspirin alone compared to aspirin (100 mg/day for at least one year)+clopidogrel (75 mg/day for three months) or OAC+clopidogrel in 1,000 patients over 1-year follow-up.</td>
</tr>
<tr>
<td>A Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivAraxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement to Optimize clinical outcomes <em>(GALILEO)</em> (NCT02556203)</td>
<td>Planned to compare rivaroxaban-based (rivaroxaban 10 mg/day long-term with aspirin 75-100 mg/day for three months) and antiplatelet-based strategies (aspirin 75-100 mg/day long-term + clopidogrel 75 mg/day for three months) after TAVI in patients without indication for OAC.</td>
</tr>
<tr>
<td>Anti-Thrombotic strategy to Lower All cardiovascular and Neurologic ischemic and</td>
<td>A randomized trial planned to compare apixaban (5 mg bd or 2.5 mg bd in specific settings) with the standard of care,</td>
</tr>
</tbody>
</table>


| Hemorrhagic events after Trans-aortic valve Implantation for aortic Stenosis (*ATLANTIS*) trial | Irrespective of need for OAC in 1,509 patients. |