Transcatheter aortic valve replacement (TAVR) has been developed as a novel approach for the treatment of high-risk patients with aortic stenosis (AS). Although surgical aortic valve replacement is the standard of care for patients with symptomatic AS, it is associated with poor outcome when applied to patients with extreme operative risk. This subset of patients is usually deferred from surgery and has done poorly with medical therapy alone with or without balloon aortic valvuloplasty (BAV).1–4

The Edwards SAPIEN™ transcatheter heart valve (THV) technology aims to provide treatment for patients with severe, symptomatic AS who are deemed inoperable. On July 20, 2011, the Food and Drug Administration’s (FDA) Circulatory System Devices Panel reviewed the first transcatheter aortic valve system, Edwards SAPIEN™ THV premarket approval application. Meeting materials can be accessed at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm240575.htm.

The premarket approval application was based on data from the pivotal US randomized clinical trial, Placement of Aortic Transcatheter Valves (PARTNER),5,6 which comprised two independent cohorts of patients (high-risk and inoperable patients). For the purpose of the application, only patients in the inoperable cohort (Cohort B) who were randomized to standard therapy versus TAVR were submitted and subsequently presented to the FDA seeking device approval.

Following is a summary of the discussions and recommendations made during the Circulatory System Devices Advisory Panel meeting, along with some important insights regarding the clinical use of the Edwards SAPIEN™ THV in a postapproval era.

Proposed Indication for Use
The proposed indication of use stated, “The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23 mm and 26 mm, and RetroFlex 3 Delivery System are indicated for transfemoral delivery in patients with severe AS who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing comorbidities would not preclude the expected benefit from correction of the AS.”

The Panel members recommended two modifications to the proposed indication for use: add the word “symptomatic” to indicate that these patients are comparable to Cohort B patients of the PARTNER trial, and add the word “native” valve to emphasize that there are not enough data with respect to safety and efficacy for valve-in-valve procedures. An extensive discussion evolved on how to define which patients fit into the spectrum of indication for use and how to conduct postapproval monitoring in order to prevent a drift in indication and labeling. FDA speakers emphasized their perspective about inoperable patients and stated that “inoperable” does not necessarily relate to longevity because an inoperable patient may, for example, in the case of a porcelain aorta, be a fairly young patient. The FDA’s position was that the available data on this device can support approval only for patients like those enrolled in Cohort B of the PARTNER trial. Hence, it is imperative that inclusion/exclusion criteria be followed (Table 1).

Dr Valluvan Jeevanandam, cardiothoracic surgeon and Panel member, requested clarification regarding whether the Sponsor will indicate a specific risk score (Society of Thoracic Surgeons, EuroSCORE, frailty indices) to determine a patient’s inoperability. There was additional concern that the appointment of a single surgeon to serve as the “gate keeper” in deciding if a patient is inoperable might prove to be ineffective in terms of “indication-drift” toward treating less sick patients under the current proposed indication. The majority of the Panel agreed that the agreement of two surgeons is needed when determining a patient’s inoperability, similar to the design in the PARTNER trial. On behalf of the Sponsor, Ms. Jody Akin indicated that because there are no validated tools to determine which patients are inoperable, they would have to rely on multidisciplinary heart teams to make that decision.

Dr David Slotwiner, Panel member, inquired about the measures taken in order to exclude patients deemed to be too...
Table 1. Abbreviated PARTNER Inclusion and Exclusion Criteria

**Inclusion criteria**
1. Senile degenerative aortic valve stenosis.
2. Symptomatic due to aortic valve stenosis as demonstrated by NYHA Functional Class II.
3. The subject or the subject’s legal representative was informed of the nature of the study, agreed to its provisions, and provided written informed consent.
4. The subject, after formal consents by a cardiologist and two cardiovascular surgeons, agreed that medical factors precluding operation, based on a conclusion that the probability of death or serious, irreversible morbidity, exceeded the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity exceeded 50%. The surgeons’ consult notes should specify medical or anatomic factors leading to that conclusion and included should be a printout of the STS score calculation to further identify the risks in these patients.

**Exclusion criteria**
1. Evidence of an acute myocardial infarction ≤1 mo before the intended treatment.
2. Aortic valve was a congenital unicuspid or congenital bicuspid valve, or was non-calcified.
4. Any therapeutic invasive cardiac procedure performed within 30 d of the index procedure (or 6 mo if the procedure was a drug-eluting coronary stent implantation).
5. Preexisting prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification, or severe (>3+) mitral regurgitation.
7. Untreated clinically significant coronary artery disease requiring revascularization.
8. Hemodynamic instability requiring inotropic therapy or mechanical hemodynamic support devices.
10. Hypertrophic cardiomyopathy with or without obstruction.
11. Severe ventricular dysfunction with LVEF <20%.
12. Echocardiographic evidence of intracardiac mass, thrombus, or vegetation.
13. Active peptic ulcer or upper gastrointestinal bleeding within the prior 3 mo.
14. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately pre-mediated.
15. Native aortic annulus size <18 mm or >25 mm as measured by echocardiogram.
16. Recent (within 6 mo) cerebrovascular accident or transient ischemic attack.
17. Renal insufficiency (creatinine >3.0 mg/dL) and/or end-stage renal disease requiring chronic dialysis.
18. Life expectancy <12 mo due to noncardiac comorbid conditions.
19. Significant abdominal or thoracic aorta disease, including aneurysm (defined as maximal luminal diameter ≥5 cm), marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [≥5 mm], protruding, or ulcerated), narrowing of the abdominal aorta (especially with calcification and surface irregularities), or severe “unfolding” and tortuosity of the thoracic aorta.
20. Ilio-femoral vessel characteristics that would preclude safe placement of 22-F or 24-F introducer sheath.
21. Currently participating in an investigational drug or another device study.
22. Active bacterial endocarditis or other active infections.
23. Bulky calcified aortic valve leaflets in close proximity to coronary ostia.

PARTNER indicates Placement of Aortic Transcatheter Valves trial; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; LVEF, left ventricular ejection fraction.

**Efficacy Assessment of the Edwards SAPIEN™ Transcatheter Valve**

There was uniform consensus that the primary end point of all-cause mortality risk over the full duration of the study was impressively reduced in patients who received the SAPIEN™ THV (44.1% versus 66.5%; P<0.0001). Dr Julie Swain, the FDA’s clinical reviewer, summarized her clinical presentation by stating that the observed reduction in mortality in this cohort of inoperable patients outweighs the device’s significant safety issues. This statement was also endorsed by Dr Augusto Pichard, who represented the Society for Cardiac Angiography and Interventions and who spoke during the open public hearing.

During the Sponsor Question & Answer session, Dr Richard Lange, Panel member, inquired about additional outcome data for the inoperable, randomized, continued-access patient cohort (n=90). As shown in Figure 1, mortality of SAPIEN™ THV patients was somewhat higher compared with the control group. The Sponsor hypothesized that these high mortality rates may be attributed to the fact that during this continued-access enrollment period, five new centers were initiated, and their learning curves may have had
an effect. This hypothesis emphasizes the need for careful introduction of this technology at new centers. Although Panel members initially showed great concern over these continued access findings, eventually most of the Panel members agreed that this patient cohort was not part of the original PARTNER trial and was not powered to detect differences in mortality.

Several Panel members made the point that despite the dramatic superiority in terms of mortality reduction, the survival of the patients assigned to the valve was not prolonged by a significant time and at 2 years, nearly half of these patients were deceased. Therefore, Drs. Jeffery Borer and David Good commented that the QOL data may be more important than mortality data in this population, which has poor long-term outcome irrespective of treatment. They also inquired about the rationale for selection of the Kansas City Cardiomyopathy Questionnaire (KCCQ) score, which is not validated for patients with valve disease. Dr Matthew Reynolds responded on behalf of the Sponsor that there is no validated QOL tool for AS patients, and the investigators believed that this score performed as well as, if not better than, other available scores (Minnesota Living with Heart Failure Questionnaire). The Sponsor also presented data on QOL based on the Short-Form-12 Mental and Physical scores and on EuroQol-5D score (Table 2). The extensive discussion on this topic seems to reflect a growing interest in evaluating and justifying new therapies that will not only prolong survival but also improve patients’ QOL.

**Heterogeneity of the Control Group**

The control group in the PARTNER trial, which was described as the “standard therapy” group, was not a homogeneous group of patients; (Table 3) furthermore, the majority of this group (92.1%) ended up receiving some kind of intervention, primarily balloon aortic valvuloplasty, during the study period (Table 3). Patient heterogeneity in the control group was raised as a limitation of the study design, but all agreed that with no “standard of care” for these inoperable patients with AS, this control group is the best available control. Of note, in agreement with historic experience of BAV, control patients in the PARTNER trial who underwent the BAV procedure had reduction in early mortality, which disappeared rapidly thereafter.7 However, the study was not designed or powered to investigate differences in outcome between BAV and medical therapy.

**Neurological Adverse Events**

Extensive discussion on the analysis and implications of neurological outcomes was undertaken. The Panel acknowledged that neurological adverse events emerged as a major safety concern in the PARTNER trial. Drilling into the true meaning of neurological outcomes was challenging because of several confounding factors.

First, all parties agreed that direct comparison between the SAPIEN™ patients and control patients is impossible because of high mortality in the control group and inaccuracy of the data on “time to stroke” in the control group, which was calculated from randomization without any adjustment to interventional procedures the patients might have had later in the course of the trial.

Second, the Panel strongly believed that there is an unmet need for using QOL measures to quantify the severity of neurological events, and the used tools did not assess this outcome adequately. The Sponsor presented QOL assessment (KCCQ) for the subset of patients with stroke. Several Panel members found it comforting that, according to this analysis, the majority of patients who had stroke and survived experienced improvement in KCCQ score despite the neurological

---

**Table 2. Comparison of Mean Scores of Quality of Life Over Time**

<table>
<thead>
<tr>
<th></th>
<th>SAPIEN™</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-12 Physical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>34.3</td>
<td>29.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>6 mo</td>
<td>35.6</td>
<td>31.0</td>
<td>0.0013</td>
</tr>
<tr>
<td>1 y</td>
<td>34.8</td>
<td>30.1</td>
<td>0.0055</td>
</tr>
<tr>
<td>SF-12 Mental</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>48.0</td>
<td>48.3</td>
<td>0.8</td>
</tr>
<tr>
<td>6 mo</td>
<td>51.7</td>
<td>47.4</td>
<td>0.005</td>
</tr>
<tr>
<td>1 y</td>
<td>52.8</td>
<td>46.9</td>
<td>0.0006</td>
</tr>
<tr>
<td>EQ-5D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mo</td>
<td>0.71</td>
<td>0.63</td>
<td>0.005</td>
</tr>
<tr>
<td>6 mo</td>
<td>0.71</td>
<td>0.67</td>
<td>0.025</td>
</tr>
<tr>
<td>1 y</td>
<td>0.73</td>
<td>0.63</td>
<td>0.0035</td>
</tr>
</tbody>
</table>

SF indicates Short-Form; EQ, EuroQol.

---

**Table 3. Invasive Procedure Rates in PARTNER Control Group**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Standard therapy n=179 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>14 (7.9)</td>
</tr>
<tr>
<td>Balloon aortic valvuloplasty</td>
<td>140 (78.2)</td>
</tr>
<tr>
<td>Surgical aortic valve replacement*</td>
<td>11 (6.1)</td>
</tr>
<tr>
<td>Apical aortic conduit</td>
<td>6 (3.4)</td>
</tr>
<tr>
<td>Transcatheter valve replacement</td>
<td>4 (2.2)</td>
</tr>
<tr>
<td>Unknown data</td>
<td>4 (2.2)</td>
</tr>
</tbody>
</table>

*Either aortic valve replacement only (27%) or combined with mitral or tricuspid valve replacement, coronary artery bypass, or intracardiac defibrillator implantation (73%).
event as compared to baseline, probably because their valve was fixed so the overall QOL is generally better. The Panel recommended that a great deal of resources in future studies and postmarket studies be devoted to better understanding of the causality of the stroke and its impact in this patient population.

A third confounder was a post hoc readjudication of stroke severity according to modified Rankin score that was performed by the Sponsor. The FDA argued that (1) this readjudication process was a deviation from the prespecified end point definition that may affect stroke rates and major adverse cardiac and cerebrovascular event rates; and (2) the modified Rankin score used by the Sponsor was not a validated tool for post hoc analysis of stroke severity. The Panel found it worrisome that the Sponsor performed a post hoc analysis, which was different from the prespecified criteria. Both the FDA and the Sponsor agreed that this readjudication process would be adjunctive to the premarket approval evaluation process and that, for the sake of discussion, the original prespecified definition would be used.

With respect to the actual available data, neurological adverse event rates were higher for SAPIEN™ THV patients compared with control patients at all time points tested (Figure 2). Dr Swain argued that the actual stroke rates might have been even higher than the reported rates considering the fact the no brain imaging was performed in most patients and, if done, typically it was computed tomography and not magnetic resonance imaging. The FDA indicated that it will require protocolized neurological assessment of at least 50% of the patients to be performed by a neurologist in future Investigational Device Exemption studies of THV or equivalent devices.

Unfortunately, the PARTNER trial did not provide any additional information on the possible mechanisms of stroke in SAPIEN™ THV patients. Attempting to identify the best timing for intervention to prevent adverse neurological events, Dr Martin Leon described on behalf of the Sponsor, that a significant amount of the adverse neurological events were identified early (<5 days) after the TAVR procedure (Figure 3); however, neurological events continued to occur throughout the study period. He also indicated that the recommended antiplatelet regimen in the PARTNER trial was 6 months’ dual antiplatelet therapy; however, the majority of the patients did not continue dual antiplatelet therapy for the entirety of this period. Also, among patients with atrial fibrillation, only about half of the patients received long-term anticoagulant treatment.

The Panel members stressed the critical need for a protocolized antiplatelet or anticoagulation approach in order to determine a better pharmacological strategy to decrease neurological event rates; this was amended as part of a postapproval study. The Panel also stressed that given the late neurological events in PARTNER, there might be a benefit for long-term antiplatelet or anticoagulation treatment following TAVR.

Vascular Complications

Delivery sheath sizes for the SAPIEN™ THV were 22–24 F (for 23- or 26-mm valves, respectively). The PARTNER trial did not require a protocolized access or vascular closure procedure.

Vascular complication rates reported in Cohort B of the PARTNER trial were 32.4% in the SAPIEN™ THV group compared with 7.3% in the control group. The FDA requested additional analysis that incorporated any blood transfusion (unless blood was given for another, clearly documented, indication) with all vascular complications to define “hemorrhagic vascular complication.” According to this definition, hemorrhagic vascular complications occurred in more than half of the SAPIEN™ THV patients (55.9%) and in 14% of the control group.

Panel members experienced difficulty in judging the clinical significance of these complications because of the lack of data on how they were managed and their long-term effects. However, as some Panel members expressed, because the patient population under discussion is a very sick population with a limited life span, the Panel did not view vascular complications as “show stoppers.” There was consensus that the learning curve of sites and operators had a significant effect on the rates of vascular complications and that appropriate training may at least partially mitigate this complication.
Hemodynamic Performance of the SAPIEN™ THV

Valve performance meters were reported both in the PARTNER trial and per the FDA’s request. Average aortic valve area in SAPIEN™ THV patients improved from 0.6±0.2 cm² at baseline to 1.5±0.4 cm² at 30 days and remained similar up to 1-year follow up (1.6±0.5 cm²). The Panel was satisfied with the presented, relatively short-term data on valve performance by means of maintaining effective orifice area; however, they recommend collecting long-term data.

Another area of disagreement between the Sponsor and FDA was related to the significant adverse event definition of aortic regurgitation (AR). According to Dr Julie Swain of the FDA, the Sponsor defined AR significant adverse event as AR >2+, whereas the FDA views AR ≥2+ as a significant adverse event (Figure 4). However, according to all analyses, only a small minority of patients developed severe AR. Although the outcome and consequences of severe AR are known, few data are available on the long-term effect of mild to moderate AR in patients with aortic valve disease. Thus, the Panel generally agreed that the fact that the population under consideration is very sick mitigates the worries with regard to the long-term effects of AR. The Panel emphasized the importance of collecting long-term data on valve performance.

Valve-in-Valve Experience

Despite the fact that valve-in-valve procedures were rarely done in Cohort B of the PARTNER trial (n=4), the FDA was concerned that such a procedure might be performed more frequently once the device is approved. This concern was based on the fact that no bench-side or preclinical studies were performed to test this application and that neither the functionality nor the durability of the device in this situation is known.

The Panel’s view was that a specific bench testing should be undertaken but did not define the particular details. Dr Ralph Brindis, Panel member, stated that currently no data are collected on devices used for “off-label” indication. He urged all parties to change the paradigm of how patients are followed and to start collecting such data in order to understand where these off-label indications are appropriate.

With regard to prescription issues, the Panel’s view was that the FDA should not explicitly proscribe the use of the Edwards SAPIEN™ THV in another valve for the sake of situations in which there are no other options.

Post-Approval Study

Two post-approval studies (PAS) were requested by the FDA, which the Sponsor agreed to perform pending device approval with the aim to assess long-term safety and effectiveness, as well as adherence to indication of the SAPIEN™ THV utilization.

As presented by the Sponsor, PAS-1 will continue clinical and echocardiographic follow-up on an annual basis and will monitor the incidence of clinical events for all previously enrolled patients in Cohort B of the PARTNER trial, as well as the continuous-access patients (n=425). The FDA requested additional 4- and 5-year QOL assessments to PAS-1. Because of the disagreement between the FDA and the Sponsor with respect to these long-term end points, the Panel was asked to comment specifically on these issues. Given the high complication rates observed in Cohort B with the use of this new technology, the Panel stressed the need for PAS to assess adverse events, learning curve, valve durability, and off-label use. The Panel also endorsed the FDA’s request to add QOL assessment to the long-term (4- and 5-year) follow-up of these patients.

The Sponsor described their proposal for PAS-2. The study will be an observational, controlled prospective trial with a noninferiority design of consecutive patient enrollment (n=750) from a random sample (n=75) of new sites previously selected by the Sponsor (n=200). The proposed end points of this noninferiority study will capture all neurological events, major vascular events, major bleeding, learning curve assessment, valve durability to 5 years, and QOL measures to 5 years. To be eligible, potential sites will include a multidisciplinary heart valve approach, including heart teams (cardiac surgeon, cardiologist, echocardiographer, and anesthesiologist), infrastructure for imaging, sterile environment (ie, hybrid cath labs), and the ability to track and report clinical outcomes.

The Sponsor declared that it would eventually like to transition this study into a national, longitudinal AS outcome registry ultimately conducted by the national, professional societies. Representatives from the American College of Cardiology (Dr David Holmes) and the Society of Thoracic Surgery (Dr Michael Mack) described their societies’ intentions to join forces and create an aortic valve registry in collaboration with the Sponsor and the FDA. The professional societies’ representatives believe the registry will provide data on aortic valve technologies and their outcomes in the post-approval period.

Other issues under discussion were the selection of hypothesis-driven end points and the determination of an appropriate noninferiority margin for PAS-2. The FDA requested to select both mortality and neurological events as hypothesis-driven end points and to have a tight noninferiority margin (20%). The Panel was asked to specifically...
address these issues and subsequently generally endorsed the FDA view.

The Panel expressed concern about the number of new sites to be included in PAS-2, specifically with respect to the fact that it would be hard to evaluate learning curves if each site enrolls 10 to 20 patients. However, as concluded by the Panel Chair, Dr Richard Page, having 75 sites is a reasonable compromise between the goals of assessing learning curve and evaluating the various end points in a real-world setting, which require a larger number of sites. The Panel recommended that the rate of site enrollment be tightly monitored. The Panel also stressed that this PAS should be monitored carefully with respect to inclusion criteria of enrolled patients as it is very important that the criteria are similar to Cohort B of the PARTNER trial patients.

The Panel’s industry representative, Mr. Burke Barrett, inquired why the FDA would mandate a post-approval nonrandomized study, which would be larger than the recently completed randomized controlled trials. Dr Bram Zuckerman, Division of Cardiovascular Devices, commented that the FDA is a public health agency as well as device approval agency and, as such, the scope of its regulatory mission is not only to approve devices but also to monitor and regulate devices utilization post approval. When a “transformational” technology such as the THV enters the market, it is important to monitor and learn about the device performance in the real world. Although several thousand patients in Europe have been implanted with this device, there are multiple problems with these data that limit interpretability. The FDA is intent on following device performance throughout the total product life cycle of the device in the United States.

**Panel Recommendations**

The Panel was asked to vote on three questions with respect to the approvability of the Edwards SAPIEN™ THV. The Panel voted 7 to 3 that there is reasonable assurance that the Edwards SAPIEN™ THV is safe for use in patients with severe symptomatic AS who meet the criteria specified in the proposed indication. Three Panel members thought that although the device usage is superior to standard therapy, they cannot consider it safe because of the high neurological event rates.

The Panel voted 9 to 1 that the Edwards SAPIEN™ THV is effective for use in patients with severe symptomatic AS who meet the criteria specified in the proposed indication. The Panel voted 9 to 0 (with 1 abstention) that the benefits do outweigh the risks of the Edwards SAPIEN™ THV for use in the indicated patient population. The abstaining member commented that the new data on the continued access patients’ outcome offset his vote.

**Summary and Conclusions**

The Panel commended the Sponsor for conducting a well-designed study to evaluate the Edwards SAPIEN™ THV. The majority of Panel members agreed that that the discussed device and procedure is effective in lowering mortality in the specific population studied. The Panel recommended tight monitoring of this technology in a post-approval period.

Stroke emerged as a major issue even though the reduction in mortality outweighed it. Hence, it is critical that elderly patients be made aware of the tradeoff. Some patients may decide that living with a stroke and its sequelae is worse than a shortened lifespan.

The available QOL data were insufficient for shedding light on what metrics are important for elderly patients. It is essential to conduct vigorous research to assess QOL in unblinded percutaneous heart valve trials.

Statements made by the professional societies in support of the device, and adherence to indications, were very important. It seems critical that physicians respect this technology so that once approved there is not another “DES stent thrombosis scare” with limited data to figure out what has happened.

Based on the Panel recommendation, it is anticipated that the device will be approved by the FDA.

**Disclosures**

None.

**References**


**Key Words:** transcatheter heart valve, aortic stenosis, Food and Drug Administration
Overview of the 2011 Food and Drug Administration Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting on the Edwards SAPIEN Transcatheter Heart Valve
Israel M. Barbash and Ron Waksman

Circulation. 2012;125:550-555
doi: 10.1161/CIRCULATIONAHA.111.059873

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/125/3/550

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/