



The Society for Cardiovascular Angiography and Interventions

2400 N Street NW, Suite 604, Washington, DC 20037-1153

Main: 202.741.9854 ♦ Toll Free: 800.992.7224 ♦ Fax: 202.689.7224 ♦ E-mail: info@scai.org

Statement of the
Society for Cardiovascular Angiography & Interventions

Presented by

Augusto D. Pichard, MD, FSCAI

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Review of premarket approval application for the Edwards
SAPIEN Transcatheter Heart Valve

Contact: Wayne Powell
Sr. Director, Advocacy and Guidelines, SCAI
Email: wpowell@scai.org

Good afternoon members of the Advisory Panel, FDA staff, and guests:

My name is Dr. Augusto Pichard. I am the Director of the Catheterization Laboratory at the Washington Hospital Center. I am a practicing interventional cardiologist with over 30 years of experience. I am also a Professor of Medicine (Cardiology) at Georgetown University. My conflicts of interest include that I am both the Principal Investigator for the PARTNER Trial at the Washington Hospital Center, and a Proctor for the Percutaneous Valve for Edwards Lifesciences.

Today, I am speaking on behalf of the Society for Cardiovascular Angiography and Interventions (SCAI or The Society).

SCAI is the leader in science, education, and advocacy for interventional Cardiologists and their patients. The Society promotes excellence in cardiac catheterization, angiography, and interventional cardiology through physician education and representation, and through quality initiatives to enhance patient care. The Society represents over 4,000 invasive and interventional cardiologists. The Society is committed to providing the best care possible for patients with severe aortic stenosis.

The Society believes the recent advent of transcatheter treatment of aortic stenosis (TAVR) is a viable alternative to standard open valve replacement in select patient populations at specialized heart centers with expert physicians and a multidisciplinary heart team approach. Patients with severe aortic disease are currently treated with medication only if they are too sick or too old to undergo surgery, despite the extensive historical information that medical therapy alone has no effect on the natural history of the disease. The Edwards SAPIEN device clinical trial demonstrated that TAVR is a superior alternative to medical management in many select inoperable patients with or without aortic valvuloplasty and is “non-inferior” in patients at high risk for open heart surgery. Many patients, who did not qualify for this particular clinical trial, ultimately do not undergo surgery and might benefit from this therapy.

Compared to surgery patients, those undergoing TAVR procedures experience less pain and much quicker recoveries. We also note the lower stroke rate in the continued access Registry and in the prospective, monitored European SOURCE registries as an indication that future studies will find increasingly favorable results.

The Society believes the PARTNER clinical trial provides a foundation for the essential requirements of a percutaneous valve program; and, if this medical device is deemed to be reasonably safe and effective by the Agency, these requirements must be implemented in the real world environment to help assure a successful patient outcome. The clinical trial provides evidence that the most successful patient outcomes occur under the following circumstances: (1) performance in a specialized heart center with sufficient patient volume, (2) management using a multidisciplinary team in which each member has appropriate expertise, (3) access to a modified conventional cardiac laboratory or hybrid operating room that contains the specialized equipment necessary for the procedure, and (4) a planned approach to co-management decision making as well as proficient technical insertion of the medical device.

The Society, in partnership with other medical societies, is committed to ensuring that these essential requirements of a percutaneous valve program continue in the real world so that this technology continues to benefit the sickest patients. SCAI and other medical societies are committed to the

development of expert consensus statements, guidelines, appropriate use criteria, credentialing criteria, and training paradigms, thereby supporting responsible diffusion of this technology. Specialized heart centers could be accredited through Accreditation for Cardiovascular Excellence (ACE), an organization currently accrediting facilities for other invasive and interventional cardiovascular procedures. The Society agrees that the sponsor's proposed comprehensive training program for new practitioners is essential to evaluate operator experience level and management of vascular complications. The Society recommends that all TAVR Patients be entered into the nationwide TAVR registry to track long-term follow-up in the real world and provide data to answer critical research questions not addressed by the clinical trials. The Society led the development of a SCAI/AATS/ACC/STS multi-societal competency statement on institutional and operator requirements to define the essential criteria for optimal patient outcomes and that document is available on our [website](#). We agree that defining these characteristics is challenging and that many factors need to be taken under consideration rather than a single rigid set of criteria.

The Society provides the following responses to key questions for the Circulatory System Device Advisory Panel.

Q1. Please provide input regarding refinements that may be warranted for the indication statement if the device is approved

The PARTNER requirement for 2 surgical opinions in the current language may be adequate for determination of surgical risk in these patients. We suggest that the 2 surgeon review remain the cornerstone of the selection process.

Q2. Please comment on these findings and discuss your opinion as to whether this device can be considered clinically equivalent to AVR in patients who cannot have transfemoral implantation

While the randomized TA arm showed concerning differences especially considering the differences in stroke, the patients were also noted to have a higher atherosclerotic burden and are not likely similar to the control arm. The larger continued access group showed a remarkable reduction in stroke. This is likely due to a steep learning curve and a better understanding of patient selection for the TA approach. Considering all the available data the TA approach appears equivalent to AVR.

Q3a. Please discuss these findings and whether a claim can be made for improved survival in the SAPIEN arm.

Like many randomized trials unanticipated variations in patient treatment and time to treatment can occur. Based on the large body of Sapien data outside the PARTNER trial with results consistent with non inferiority to AVR it is not highly likely that the trial was biased to a lower risk TAVR group by these clinical variations.

Q3b. Please discuss how we may better address this in future studies of similar devices to avoid these trial conduct issues.

We encourage the panel to carefully consider whether crossovers should be allowed in future studies.

Q4d. Please comment on whether the post-implant aortic insufficiency in the SAPIEN group affects your decision as to whether the SAPIEN device is clinically equivalent to AVR.

PARTNER I met the predetermined non-inferior band and therefore should be considered clinically equivalent to AVR. The issue of valve regurgitation has surfaced with longer follow-up and the signal is at present confusing. Additional analysis will occur in PARTNER II and a better understanding of appropriate valve sizing is occurring using 3D techniques such as CT and 3D echo to assess perimeter area. At this time it is unclear whether aortic insufficiency impacts outcome or whether it is a confounder among many other reasons for increased mortality in these patients. It is important to recognize that the primary endpoint of total mortality was equivalent for both TAVR and surgical groups at one and also at 2 years.

Q4. Please comment on whether this device can be considered clinically equivalent to AVR in the male population.

The overall trial showed equivalency to AVR and while the results in males may be a signal the trial was not powered to make that distinction.

Q4d. Please comment on whether the post-implant aortic insufficiency in the SAPIEN group affects your decision as to whether the SAPIEN device is clinically equivalent to AVR. Please comment on whether there is any reason to believe that this rate will decrease with the device that was used in this trial.

TAVR met the pre-determined non-inferiority endpoint and should be considered equivalent to AVR. The aortic regurgitation signal did not appear until 2-year follow-up. At this point the relationship to outcome is not well understood, especially the impact of relatively clinically insignificant regurgitation. This relationship should be closely examined in the mandated registry and PARTNER II. The use of 3D imaging, such as CT to more adequately assess Sapien valve implant size, is being strongly encouraged. Available data suggest that this has an important impact on the degree of regurgitation.

Q5a. Please comment on whether this affects your decision as to whether the SAPIEN device is clinically equivalent to AVR.

It is clinically equivalent to AVR because it met its pre-determined end points.

Q5b. Please comment on whether you think that the anticoagulation/antiplatelet regimen for this device is sufficiently understood.

It is not well understood and additional data would be helpful. Dual antiplatelet therapy and anticoagulation in general in these typically elderly patients will be associated with a tendency for increased bleeding. We expect that the TAVR registry will help clinicians identify the best antithrombotic platelet strategies.

Q5c. Please provide any other thoughts you have regarding additional recommendations for mitigating stroke.

Meticulous attention to detail and patient selection are important. CT and other imaging techniques can be used in those at high risk for CVA event. The use of cerebral protection devices may be of help but that data is not yet available.

Q5d. Please comment on the CAP results, particularly as they apply to the TA patients.

The TA CAP results are very encouraging and suggest with proper patient selection and appropriate training that the higher incidence of stroke seen in the TA arm can be significantly mitigated with site experience and better patient selection.

Q6a. Please comment on the evidence of long-term durability of the SAPIEN Heart Valve System and whether this affects your decision as to clinical comparability with the known durability of heart valves used for open AVR.

Based on bench testing and the age of the patients who are likely to receive the valve its durability seems adequate. There are limited longer-term data outside the PARTNER I trial that have shown continued good function of the valve. The TVT registry's infrastructure for PAS studies on TAVR durability will be helpful.

Q6b. Please comment on possible risk mitigation measures that should be taken to address the safety and effectiveness of using the Valve-In-Valve technique.

This is an emerging area of use and there are limited data regarding outcome. The nested registry in PARTNER II should add to the body of literature regarding safety and effectiveness of valve in valve. Approval for use in the inoperable patient, as assessed by 2 surgeons, should allow this potentially life-saving technology to be applied to this group and mitigate risk.

Q6c. Please provide comment on whether you think the use of Valve-In-Valve technique can be addressed in the labeling

Labeling could state that outcomes of valve in valve are inadequate to assess its use at the present time but that in certain very high-risk patients (heart team assessment of mortality and morbidity $\geq 50\%$) may be warranted vs. medical therapy. The valve in valve therapy is by definition for people with prior operation. Many of these patients are judged to be inoperable for repeat surgery. While registries for this approach are ongoing, valve and valve should be available for patients with no other option.

Q7a. Please comment on the need for a more detailed informed consent in general.

We do not believe that the agency should mandate the information contained in informed consents. Informed consent is a process. The implementation of a multidisciplinary heart team has brought a greater level of informed consent for patient's and family's for this therapy both in the PARTNER trial and in our early experience with commercial use than we have seen for any cardiovascular therapy in the past. The heart team approach should meet the requirement to inform the patient of their

Q7b. Please comment on the appropriateness of requiring such a form as given in the example above for the SAPIEN transcatheter valve patients.

This seems redundant considering the requirement of a heart team assessment for TAVR patients.

Q8a. Should the relationship between mortality and aortic regurgitation severity (no/trace vs. mild/moderate/severe) within TAVR patients be monitored in the PAS?

We support that requirement.

Q8b. Should the PAS be used to monitor short-term and long-term effects of safety and effectiveness of valve-in-valve implantation?

We support that requirement.

Q8c. The VARC definition of composite safety includes “disabling stroke”, which is traditionally assessed through the Modified Rankin Scale. This scale is included in the PAS Protocol, but not included in the TVT registry. Therefore, please discuss if the composite primary endpoint should include all strokes, rather than only disabling strokes.

We believe it should include only disabling stroke. Including all strokes increases the likelihood that less clear neurologic events will be included which makes the outcome less clinically meaningful.

Q8d. Please comment on any additional endpoints that should be followed in the PAS

We do not have any additional recommendations at this time.

Conclusion

Thank you for accepting our testimony today, and for considering our comments. The Society is fully committed to providing the best patient care possible and welcomes all opportunities to provide recommendations to the FDA Circulatory System Panel and the Agency. The Society is encouraged by the information provided to date and looks forward to the Advisory Panel’s recommendations and FDA’s final regulatory decision.