Comments of Edwards Lifesciences LLC
on the Proposed Decision Memo for Transcatheter Aortic Valve Replacement
(CAG-00430R)
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1. Edwards Response to the Centers for Medicare & Medicaid Services' Proposed Coverage Policy

1.1. Edwards Commends the Efforts of CMS to Modernize, Streamline, and Simplify Key Elements of the TAVR NCD

1.1.1. Edwards Agrees With CMS That Access Barriers Remain for Prospective Patients, Resulting in Excess Morbidity and Mortality

Important progress has been made over the past 7 years to enhance the care of Medicare beneficiaries with aortic stenosis (AS). The availability of transcatheter aortic valve replacement (TAVR) – a less-invasive alternative to surgery – resulted in a 20% relative reduction in the rate of untreated AS, and a 17% relative increase in referrals for aortic valve replacement (AVR) evaluation (even in its early introduction).[1] Unfortunately, a significant proportion of severe symptomatic aortic stenosis (SSAS) patients still do not receive AVR.[1] Recent analyses demonstrate that nearly two-thirds of patients in the United States with SSAS remain untreated up to a year after diagnosis.[2] The consequences of this treatment gap are sobering. In the Medicare population, 1-year mortality was 49% among SSAS patients who do not receive AVR, which increased to 88% by 5 years.[3] Survival was even worse among patients at high risk for surgical aortic valve replacement (SAVR), with 1-year mortality of 58% and 5-year mortality of 95%.[3]

Even minor treatment delays are correlated with worse clinical outcomes. In an analysis of patients who initially refused TAVR, the 30-day mortality rate was significantly higher in the refusal group compared with the non-refusal group (7.1% versus 1.3%, p=0.008).[4] In another analysis examining the impact of waiting time for either transcatheter or surgical AVR, mortality while waiting was 3.7% and 11.6% at 30-days and 6 months, respectively.[5] Prolonged waiting time was associated with mortality well in excess of procedural mortality.[5] At 1-year, survival was 25.5% lower (absolute difference) in the no intervention group as compared to those receiving intervention (TAVR or SAVR).[5] These findings highlight the urgent need for timely access to care. It is also noteworthy that the excess morbidity and mortality associated with under treatment likely far exceeds any perceived or real variance in TAVR outcomes between high and low volume centers.

1.2. Edwards Believes That Many of the Proposed Modifications to the Policy Are Appropriate and Timely

1.2.1. Edwards Strongly Supports Increased Flexibility in How Procedure Volume Requirements Are Met to Begin or Maintain a TAVR Program

Since the original NCD was implemented in 2012, in-hospital mortality has declined nationally from 4.7% to 1.5% (2012-2017 Medicare Provider Analysis and Review File) – despite a 4-fold increase in the number of TAVR sites. Now, as a proven, mature, and extensively researched treatment, the time is right to modernize and streamline the coverage policy. These efforts are essential to ensuring Medicare beneficiaries have timely access to all available treatment options for AS.

Flexible minimum volume requirements to begin or maintain TAVR programs are a reasonable interim step (while composite outcome measures are finalized) to ensure TAVR facilities have an active cardiac surgery and interventional cardiology program as well as appropriate infrastructure. Edwards believes the proposed requirements acknowledge the need for experience and expertise while limiting the burden and barriers of unnecessary requirements on hospitals, providers, and patients. As the Centers for Medicare & Medicaid Services (CMS) finalizes its coverage policy for TAVR, Edwards strongly encourages the Agency to adopt the proposed requirements to start and maintain TAVR programs.

1.3. Edwards Recommends That Certain Elements of the Proposed NCD Be Amended

1.3.1. Edwards Strongly Recommends That the Final Coverage Policy Require Either One Cardiac Surgeon OR One Interventional Cardiologist Examine the Patient

When the initial TAVR NCD was implemented, the intent was to mirror as closely as possible the clinical practices in the early trials.[6] In 2007, the PARTNER B Trial was initiated to evaluate patients who were not considered suitable candidates for surgery (i.e., inoperable).[7] The protocol required that at least two surgeons had to agree that the patient was not a suitable candidate for surgery. A similar requirement was adopted in the TAVR NCD.

In subsequent trial experience, the evaluation parameters evolved. For example, in the PARTNER 2 B Trial, these requirements were reduced to at least one surgeon personally examining the patient to make a determination of operability.[8] This approach was also employed in the PARTNER 3 Trial.[9]

Improvements in patient selection, the increasingly well-established role of TAVR, and the recently published data demonstrating superiority for TAVR in low-risk patients obviate the need to limit evaluations to only a single CT surgeon. Instead, a knowledgeable clinician – whether a cardiac surgeon or an interventional cardiologist – is well equipped to evaluate the patients' suitability for all available AS therapies. Limiting the examination to only a cardiac surgeon is unnecessarily restrictive and may inhibit the flexibility of programs to treat patients in a timely manner. As noted previously, even minor delays in treatment are correlated with worse clinical outcomes.[5]

As CMS finalizes its coverage policy for TAVR, we urge CMS to amend the language to allow either one cardiac surgeon or one interventional cardiologist at the TAVR-performing institution to examine the patient, evaluate the patient's suitability for SAVR, TAVR, medical, or palliative therapy, and provide their rationale to the Heart Team.

1.3.2. Edwards Strongly Recommends That Coverage Apply to Aortic Valve Stenosis Rather Than "Symptomatic" Aortic Valve Stenosis

Although TAVR is currently approved for patients with SSAS who are at intermediate or greater surgical risk,[10] recent analyses suggest that early AVR could improve survival in asymptomatic, SSAS patients.[11,12] Several "asymptomatic" patient cohorts may be appropriate for intervention according to the 2017 Appropriate Use Criteria (AUC)[13] jointly developed by the ACC/AATS/AHA/ASE/EACTS/HVS/SCA/SCAI/SCCT/SCMR/STS, including:

- Asymptomatic patients with severe AS and left ventricular ejection fraction (LVEF) <50%
- Asymptomatic patients with very severe AS (defined as V_{max} ≥5 m/sec or mean gradient ≥60 mmHg)
- Asymptomatic patients with paradoxical low-flow, low-gradient severe AS

Reflecting these trends in treatment guidance, the recently published low risk TAVR trials included asymptomatic patients with LVEF <50%[9,14] and other criteria.[14] In addition, several ongoing clinical trials covered under section B of the current TAVR NCD are evaluating the safety and efficacy of TAVR in asymptomatic patients with severe AS (EARLY TAVR) and heart failure patients with moderate AS (TAVR UNLOAD). Moreover, the proposed decision memo covering TAVR for Food and Drug Administration (FDA)-approved indications ensures a rigorous regulatory review prior to Medicare coverage. To preserve flexibility and permit coverage for future potential AS indications, Edwards urges CMS to change the policy language from "symptomatic aortic valve stenosis" to "aortic valve stenosis."

1.3.3. Edwards Supports CMS' Intent to Remove Procedure Volume Requirements in Favor of Validated Outcome Metrics

Volume is an imprecise indicator of quality (see Section 2.2).[15] Recent analyses show that with the latest generation balloon-expandable TAVR, there is no demonstrable learning curve or volume-outcomes relationship.[16] Furthermore, real-world TAVR data show that there are some high-volume programs with unfavorable outcomes and some low-volume programs that achieve excellent outcomes.[17,18] These findings underscore the importance of measuring quality directly, rather than relying on crude surrogates.

The STS/ACC TVT Registry already provides a wide range of resources to enhance quality improvement initiatives, including, but not limited to, quarterly reports containing practice patterns, demographics, and outcomes comparing a facility's performance with that of the national experience. The Registry now contains more than 200,000 TAVR records and a validated TAVR 30-day composite score should be available in the near future, followed by eventual public reporting of outcome measure results. Edwards supports removing volume requirements in favor of validated outcome metrics and seeks additional clarification from CMS on the timing and milestones associated with this transition. We also note that this transition could reasonably coincide with the reopening of the TAVR NCD in the future, as was suggested in the proposed decision memo, and the discontinuation of Coverage with Evidence Development (CED).

As quality assessments have the greatest validity when sufficient case volumes exist,[17] we believe a volume minimum of 20 TAVR cases annually (per the proposed policy), coupled with a 3-year rolling period[19], will allow for appropriate statistical power to measure composite outcomes in a rigorous manner. In fact, this minimum case volume far exceeds the number of cases required in the Society of Thoracic Surgeons (STS) National Adult Cardiac Surgery Database to receive a "star rating" for SAVR programs (10 surgical cases over 3 years).[20]

1.3.4. Edwards Supports Efforts to Render Qualifying National Registries Less Burdensome, More Transparent, and More Useful

Edwards recognizes that the time required for data extraction and registry input places a substantial burden – on average, four hours per patient at the time of implant – on the clinical facility for the TVT Registry.[21] Accordingly, stakeholders should strive to limit the size and scope of registries to minimize the time and cost of data collection while maximizing transparency and availability of data to the public.

We reiterate our recommendation to adopt the following principles to enhance the value and governance of qualifying registries. These are adapted from the recommendations of The Pew Charitable Trusts, the Blue Cross Blue Shield Association, and the Medical Device Epidemiology Network:

- Findings and reports should be publicly released on a regular basis.
- The workings of the system – its governance, operations, and financing – should be made publicly available.
- Registries should provide a clear, reasonable, and responsive process for providing data to outside researchers.
- Registry data should be limited to the data most relevant to the purpose of the registry and should not collect more data than necessary to answer the specific question or questions for which it was established.
- Stakeholder groups should work together to better understand and ultimately reduce unnecessary barriers to registry data collection and use.
- The amount of data collected should balance stakeholder interests with the workload placed on those who collect the data. If possible, stakeholders should work to create registries that can interact with other electronic sources of data.
- To improve public health and patient care, registry findings should be available to stakeholders, assuring that decision-makers—including regulators, clinicians, patients, and payers—have access to key information.
- Given the contribution that patients make in providing their data, an ethical obligation exists to ensure that they have access to registry information. For example, data from registries—written and presented at a lay level—should be available to patients to support informed choices about treatment.

1.3.5. Edwards Believes That Shared Decision Making Should Be Applied to All Aortic Valve Disease Patients, Not Just Patients at a TAVR Center

Edwards appreciates CMS' reference to the importance of shared decision-making (SDM) in a variety of clinical scenarios, including AVR. We agree that, in the current environment, there are limited choices for contemporary, evidence-based decision aids or tool for this patient population.

There remains strong evidence to support that SDM increases a patient's knowledge and accuracy of risk perceptions, and that decision making is associated with improved decision quality.[22] As clinical practice has evolved, we gradually see broader application of SDM across various clinical areas. Evidence suggests that SDM may also be associated with improvements in clinical outcomes, especially for individuals with chronic conditions[23]. In the case of patients seeking treatment for aortic valve disease, the choice of SAVR versus TAVR is based on multiple factors, including the surgical risk, patient frailty, comorbid conditions, and patient preferences and values.[10]

Unfortunately, high quality SDM is unlikely at centers that only offer one of the therapies or when there are large disparities in coverage policy. Today, approximately half of centers that offer SAVR also have TAVR available. Without aligned SDM requirements, it is unreasonable to assume that patients will be appropriately informed of all treatment options when they are evaluated at hospitals that do not have a TAVR program.

Specifically, to ensure that SDM is a benefit to patients and the healthcare system, we believe CMS should:

- Only apply a SDM requirement if it applies to all aortic valve disease patients, not just patients at a TAVR center.
- Not reference a specific patient decision aid as demonstrating SDM, but encourage providers to use tools that comply with standards for high quality, in alignment with the National Quality Forum (NQF) performance measure #2962, NQF's National Standards for the Certification of Patient Decision Aids,[24] the National Quality Partners Playbook on Shared Decision-Making,[25] and the Avalere/FasterCures' Patient Perspective Value Framework.[26]

1.3.6. Edwards Believes the Policy Should Address All AVR Therapies (Both TAVR and SAVR)

There are two definitive treatments available for AS – TAVR and SAVR. A TAVR-specific coverage policy only provides half the solution. We believe that equitable policy and quality standards are necessary for all Medicare beneficiaries with AS, regardless of treatment. At present, no similar volume, infrastructure, Heart Team or registry reporting requirements are imposed by CMS for SAVR centers. Analyzing the 2017 Medicare SAF, 1,071 hospitals currently perform SAVR for Medicare beneficiaries and only just over half of those (551) also offer TAVR. Using the same data sources, SAVR in-hospital mortality (unadjusted) was lower at comprehensive programs (offering TAVR and SAVR) as compared with SAVR only facilities (4.1% vs. 5.3%, $p<0.001$). These data support the need for a broader focus on quality and access (beyond just TAVR). We continue to encourage CMS to consider a uniform policy across the continuum of care to ensure high quality treatment for all patients with AS.

1.4. Edwards Recommends That Certain Elements of the Current NCD Should Be Preserved

1.4.1. Edwards Recommends That CMS Maintain Coverage to Label When Other Conditions Are Met

TAVR technologies continue to be researched and evaluated in a variety of new patient populations and will likely result in the FDA assessing new indications in the coming years. Edwards believes that maintaining TAVR coverage for FDA-approved indications ensures Medicare beneficiaries have timely and efficient access to appropriate care without having to reopen the policy for each newly approved indication. As CMS finalizes its coverage policy for TAVR, we urge CMS to maintain coverage for FDA approved indications.

1.4.2. Edwards Recommends That CMS Maintain Requirements for the Heart Team, Appropriate Hospital Infrastructure, and Participation in a Prospective, National, Audited Registry

Edwards recognizes the importance of Heart Teams, appropriate hospital infrastructure, and participation in a prospective, national, audited registry. The multi-disciplinary Heart Team is essential to ensuring the success of TAVR programs and the delivery of optimal outcomes with the best possible patient-centered care. In addition, the proposed hospital infrastructure requirements acknowledge the resources and

training required to ensure high quality care without being overly prescriptive or restrictive. Finally, registries can advance clinical knowledge and can be used as a platform for developing and monitoring quality metrics. As CMS finalizes the TAVR coverage policy, we urge CMS to maintain these important elements.

1.4.3. Edwards Recommends That CMS Maintain Coverage For Uses That Are Not Expressly Listed As an FDA-approved Indication When Performed Within a Clinical Study

Edwards remains firmly committed to rigorous evidence generation on TAVR. Coverage of TAVR in clinical trials ensures that additional Medicare patients can benefit in the near-term from improvements in this less invasive approach. Clinical trials assist in growing the evidence base for the use of TAVR and other technologies in the treatment of aortic valve disease, while also informing improvements in clinical practice and helping Medicare beneficiaries and providers make the most appropriate therapeutic decisions. As CMS finalizes its coverage policy for TAVR, we urge the Agency to retain coverage for uses that are not expressly listed as an FDA-approved indication when performed within a clinical study that fulfills CMS' requirements.

2. Key Evidence Considerations

In the proposed decision memo, CMS referenced several potential evidence gaps related to TAVR outcomes. In view of that, in the following sections, we review the PARTNER 3 Trial in low risk AS patients, examine key literature evaluating the relationship between procedure volumes and TAVR outcomes, and address other remaining perceived evidence gaps (e.g., durability and long-term survival). While there is a large body of evidence supporting multiple THV therapies, we focus on reviewing evidence specific to the Edwards SAPIEN THV platform.

2.1. Edwards SAPIEN 3 Valve Superior to Surgery in Low Risk Patients

The proposed decision memo states that: "Two studies on TAVR in symptomatic low surgical risk patients were published on March 16, 2019 (Mack et al., 2019; Popma et al., 2019). We are actively reviewing these studies along with other related studies (Witberg et al., 2018). Given the timeframe we have not been able to fully evaluate these studies for the analysis in this proposed decision" (p. 81). Below is a brief summary of the findings from the PARTNER 3 Trial of SAPIEN 3 in low risk AS patients.

In the PARTNER 3 Trial, 1,000 low-risk patients were randomized 1:1 at 71 clinical sites to either transfemoral TAVR with the SAPIEN 3 valve or surgical AVR with a commercially available bioprosthetic valve. SAPIEN 3 was superior to SAVR for the primary endpoint of death, stroke, or rehospitalization at 1 year.[9]

Efficacy

Composite Death, Stroke, or Rehospitalization: Based on the PARTNER 3 Trial, composite death, stroke, or rehospitalization was lower in patients who received the SAPIEN 3 valve than in those who received SAVR at 30 days (4.2% vs. 9.3%, respectively; $p<0.05$) and at 1 year (8.5% vs. 15.1%, $p<0.05$) (Table 2.1). The PARTNER 3 Trial results demonstrated that TAVR was superior to surgery in low risk patients, with a 46% reduction in the composite primary endpoint at 1 year.

Table 2.1: Composite Death, Stroke, or Rehospitalization in Low Risk Patients with Severe Symptomatic AS Treated with TAVR or SAVR

	All-cause Death, All Stroke, and Rehospitalization	
	30 days	**1 year**
PARTNER 3 Trial[9]		
SAPIEN 3 valve (TF-TAVR)	4.2%	8.5%
SAVR	9.3%	15.1%
Treatment effect [95% CI]	0.45 [0.27, 0.76]	0.54 [0.37, 0.79]
Key: TF = transfemoral, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.		

Mortality: Through one year of follow-up in the PARTNER 3 Trial, mortality was numerically lower in patients who received the SAPIEN 3 valve compared with patients who underwent SAVR at 30 days (0.4% vs. 1.1%, respectively; p=0.21) and at 1 year (1.0% vs. 2.5%; p=0.09) (Table 2.2).[9]

Table 2.2: Mortality in Low Risk Patients with Severe Symptomatic AS Treated with TAVR or SAVR

	Mortality Rates	
	30 days	**1 year**
PARTNER 3 Trial[9]		
SAPIEN 3 valve (TF-TAVR)	0.4%	1.0%
SAVR	1.1%	2.5%
Treatment effect [95% CI]	0.37 [0.07, 1.88]	0.41 [0.14, 1.17]
Key: TF = transfemoral, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.		

Safety

Major Stroke: At 30 days in the PARTNER 3 Trial, there were no major/disabling strokes among patients treated with the SAPIEN 3 valve (0.0% with SAPIEN 3 vs. 0.4% with SAVR) (Table 2.3). Rates of disabling stroke remained low through 1 year. The rate of any stroke with the SAPIEN 3 valve was significantly lower than with SAVR at 30 days (0.6% vs. 2.4%, respectively; p<0.05) and 1 year (1.2% vs. 3.1%; p<0.05).[9]

Table 2.3: Rates of disabling stroke in studies of Low Risk Patients with Severe Symptomatic AS Treated with TAVR or SAVR

	Disabling Stroke Rates	
	30 days	**1 year**
PARTNER 3 Trial[9]		
SAPIEN 3 valve (TF-TAVR)	0.0%	0.2%
SAVR	0.4%	0.9%
Treatment effect [95% CI]	0.00 [NA]	0.22 [0.03, 2.00]
Key: TF = transfemoral, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.		

New-onset Atrial Fibrillation: In the PARTNER 3 Trial, the risk of new-onset atrial fibrillation (AF) was significantly lower with the SAPIEN 3 valve than with SAVR at 30 days (5.0% vs. 39.5%, respectively; p<0.001) and 1 year (7.0% vs. 40.9%, p<0.001) (Table 2.4).[9]

Table 2.4: Rates of new-onset AF in studies of Low Risk Patients with Severe Symptomatic AS Treated with TAVR or SAVR

	New Onset Atrial Fibrillation Rates	
	30 days	**1 year**
PARTNER 3 Trial[9]		
SAPIEN 3 valve (TF-TAVR)	5.0%	7.0%
SAVR	39.5%	40.9%
Treatment effect [95% CI]	0.10 [0.06, 0.16]	0.13 [0.09, 0.20]
Key: TF = transfemoral, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.		

Major Vascular Complications: Through 1 year of follow-up in the PARTNER 3 Trial, rates of major vascular complications were low and not significantly different with the SAPIEN 3 valve compared with SAVR (Table 2.5).[9]

Table 2.5: Rates of major vascular complication in studies of Low Risk Patients with Severe Symptomatic AS Treated with TAVR or SAVR

	Rate of Major Vascular Complications	
	30 days	**1 year**
PARTNER 3 Trial[9]		
SAPIEN 3 valve (TF-TAVR)	2.2%	2.8%
SAVR	1.5%	1.5%
Treatment effect [95% CI]	1.44 [0.56, 3.73]	1.83 [0.74, 4.55]
Key: TF = transfemoral, SAVR = surgical aortic valve replacement, TAVR = transcatheter aortic valve replacement.		

Meta-analyses of TAVR vs SAVR in low risk patients

Many of the meta-analyses of studies on low risk patients that currently exist, including the Witberg et al. publication referenced in the CMS proposal on page 81, include poorly-controlled observational studies. Many of these purport to include low risk patients, despite the fact that this indication has not been approved in any country.[27] It is important to critically weigh the quality of previously published observational studies and meta-analyses in light of the newly published, high-quality randomized controlled trial (RCT) data for low risk patients.

Summary of SAPIEN valve RCTs

The efficacy and safety of the SAPIEN THV platform have been studied in a comprehensive clinical program including RCTs and non-randomized studies.[7,28-33]. The PARTNER randomized trials over the past 12 years, including the recent PARTNER 3 Trial in low risk patients, clearly demonstrate the value of TAVR compared with surgery across all surgical risk profiles.

> *"When you put it all together, at least up until 1 year this is a very exciting therapy, and it should probably allow you to have a much different discussion with patients…Patients and referring doctors should feel empowered that—rather than relying on surgical risk stratification—good sense, understanding the anatomy, and the clinical circumstance will allow us to develop a shared decision-making process where patients have a choice between TAVR and surgery irrespective of risk profile."*
>
> *-Martin Leon, MD, a PARTNER 3 Trial lead investigator, speaking to TCTMD in March 2019*

2.2. Edwards Agrees With CMS That Available Evidence Does Not Definitively Identify Procedural Volume Requirements for Hospitals or Operators to Begin or Maintain TAVR Programs

As stated on page 82 of the proposed decision memo, the available evidence does not definitively identify appropriate procedural volume thresholds for hospitals and operators to begin or maintain programs. We agree with CMS' characterization and note the following details regarding recently published evidence.

Literature Review on Volume and Outcomes Relationship

There is limited relevant evidence on the relationship between TAVR outcomes and both non-TAVR or TAVR volumes (Appendix: Literature Review). In a review of 3,976 articles:

- No studies were identified that directly assess the impact of SAVR and/or percutaneous coronary intervention (PCI) volumes on the set-up of new TAVR programs. Thus, there is no published evidence that a certain threshold of SAVR and/or PCI procedural volumes would predict quality or outcomes for TAVR procedures performed in new TAVR programs without prior TAVR experience.
- Only three studies assessed the relationship between annual SAVR procedural volumes and outcomes (mortality) in patients undergoing TAVR in hospitals with TAVR programs; all three studies reported that there was no statistically significant association between annual SAVR procedural volume and TAVR mortality.[34-36]
- There is only one study that specifically examined PCI volume and TAVR outcomes using the Nationwide Inpatient Sample (NIS) database.[37] No association was found regarding outcomes of in-hospital mortality, vascular complications, bleeding complications, or neurological complications.

Furthermore, there is also limited support of the relationship between TAVR volumes and outcomes. In a recent review of the available literature, 35 studies commented on TAVR volumes (in terms of average case volume and cumulative case experience) and their relationship to outcomes,[16,18,34,36,38-68] with 15

papers showing an impact on inpatient or 30-day mortality following appropriate risk adjustment for patient factors.

Overall, these studies had significant limitations, including small sample size and/or single institution setting, conducted outside of the U.S., and/or an early time bias given that these studies primarily focused on volume-outcomes data up to 2015, prior to the introduction of current generation, widely-used devices. Thus, these data represent historical TAVR practice and technology, and are not relevant to contemporary practice (Appendix: Literature Review).

Recent Key Studies Examining Volume and Outcomes Relationship

Two recently published studies examine the volume-outcomes relationship using TVT Registry data. Notably, Russo et al. (2019) reported that, after controlling for an initial learning curve effect, a volume-outcomes relationship is no longer evident for balloon-expandable TAVR valves. When analyses were limited to the latest generation SAPIEN 3 valve, there was no detectable learning curve or volume-outcomes relationship.[16] In a separate analysis of the TVT Registry, Vemulapalli (2019) and colleagues analyzed the difference in outcomes between the highest quartile TAVR volume hospitals and the lowest quartile, and estimated a 0.49% mortality difference between the highest and lowest volume quartiles.[18] Interestingly, lower volume centers were more likely to be located in rural areas and treat a greater proportion of racial and ethnic minorities.[18] Additionally, no optimal volume threshold could be determined from the Vemulapalli et al. analysis.[18]

2.3. Overview of Key Studies Addressing Stated Evidence Gaps

The proposed coverage decision states that: “Despite great progress, important gaps remain in the evidence base” (p. 91). While we support and are committed to continued data collection for this therapy, we believe key studies currently exist to address some of these questions pertaining to TAVR, reviewed below, with a focus on the Edwards SAPIEN THV platform:

“… What are the long term (5-year) survival and device durability outcomes for each surgical risk group? Are the outcomes of TVT Registry patients similar to those observed in pivotal studies?” (p. 91)

Long term survival

In the PARTNER B RCT, the SAPIEN valve was associated with significantly lower all-cause mortality compared with medical management throughout 5 years of follow-up.[7,69,70] Importantly, among inoperable patients, cardiovascular mortality was also significantly reduced with TAVR compared with medical management through 5 years (57.5% vs. 85.9%; p<0.0001).[69,70] In the PARTNER A landmark RCT (in high risk patients), survival rates were comparable for patients randomized to the SAPIEN valve or SAVR through 5 years of follow-up (32.2% vs. 37.6%, respectively).[28,31,71]

Edwards is committed to collecting follow-up through 10 years for intermediate and low-risk patients through the PARTNER 2 and PARTNER 3 Trials.

Durability

TAVR has demonstrated excellent mid-term durability compared with surgical valves out to 5 years in the largest echo-based study of transcatheter heart valves performed to date. In this study, conducted in 2,482 patients from the PARTNER Trial, Douglas, et al. showed that the SAPIEN valve demonstrated a stable reduction of mean gradients and increase in effective orifice area (EOA) out to 5 years. The rate of re-intervention due to structural valve deterioration (SVD) was a low 0.2%. The conclusion revealed the excellent longitudinal durability of the SAPIEN valve using both population hemodynamic trends as well as case reviews of re-intervention and of patients with large adverse changes between echoes.[72]

Additionally, a recent study from Blackman, et al. sought to evaluate the incidence of hemodynamic structural valve deterioration up to 10 years following TAVR from The United Kingdom Transcatheter Aortic Valve Implantation Registry. The study found excellent overall long-term durability with TAVR valves. Peak gradient was lower at follow-up compared with baseline in the overall cohort (17.1 vs. 19.1

mm Hg; p = 0.002). Only one case of severe SVD (self-expandable valve) was found, and no patient underwent re-intervention for SVD. There were 21 cases (8.7%) of moderate SVD. Twelve of these were due to new moderate aortic regurgitation, and 9 were due to an increased transvalvular gradient.[73]

A recent multicenter study from France also confirmed promising long-term durability of TAVR valves. The study reported the 7-year cumulative incidence of bioprosthetic valve failure (BVF) was 1.9%, and moderate and severe SVD was 7.0% and 4.2%, respectively. These outcomes were based on the newly published European criteria for BVF and SVD.[74]

A seven year follow-up based on a Swiss registry found very low rates of valve re-intervention in both the SAVR and TAVR groups (0.9% vs. 0.4%, respectively). After 5 years, there was no difference in mean gradient (12.7 vs. 10.0 for SAVR and TAVR, respectively) or aortic valve area (1.5 vs. 1.7).[75]

Registry vs. clinical data

A propensity-matched analysis comparing real-world data collected from the TVT Registry with outcomes of patients enrolled in the PARTNER II studies of the SAPIEN 3 valve was presented at EuroPCR 2018. The 30-day data demonstrated that treatment with the Edwards SAPIEN 3 valve in more than 450 commercial centers around the U.S. showed consistently positive patient outcomes. The data, involving almost 2,000 SSAS patients at intermediate-risk, demonstrated consistency with those results achieved in earlier controlled clinical trials in a limited number of hospitals. This study confirms that real-world outcomes are consistent with clinical trials for patients treated with the SAPIEN 3 valve.[76]

"What is the echocardiographic, CT and/or MR assessment of transcatheter aortic valvular performance, deterioration and durability as compared to surgical AVR?" (p. 91)

Clinical and echocardiographic findings

In inoperable patients from the PARTNER B Trial, valve performance improved significantly after treatment with the SAPIEN valve: mean aortic valve area increased from 0.6±0.2 cm^2 at baseline to 1.5±0.5 cm^2 (p<0.001) at 30 days and mean valve gradient decreased significantly from 44.5±15.7 mm Hg at baseline to 11.1±6.9 mm Hg at 30 days (p<0.001).[69] Valve function was maintained for up to 5 years after valve implantation.[70,77] Similarly, a prospective, non-randomized, single-center study showed that mean valve gradient was also significantly lower at 1 year in patients who underwent TAVR (8 mm Hg) than in those who received medical management (46.2 mm Hg) or with balloon aortic valvuloplasty (37.2 mm Hg; p<0.001 for both comparisons).[78]

At 30 days and through 5 years of follow-up in the PARTNER A Trial, high risk patients with AS treated with the SAPIEN valve or SAVR experienced significant improvements from baseline in aortic valve area and aortic pressure gradient; these improvements were similar between treatment groups.[28,31,71] There was no evidence of SVD in either group at 5 years.[71]

At all evaluated time points in the PARTNER 2A Trial (intermediate risk patients), a significantly greater improvement in mean aortic valve area was achieved in the overall SAPIEN XT group than in the overall SAVR group at 30 days (1.7 vs. 1.5 cm^2, respectively; p<0.001), 1 year (1.6 vs. 1.4 cm^2, p<0.001), and 2 years (1.5 vs. 1.4 cm^2, p<0.001).[33] Moreover, the overall SAPIEN XT group also achieved a lower postoperative mean valve pressure gradient than the overall SAVR group at all time points (30 days: 9.7 vs. 10.9 mm Hg; 1 year: 10.7 vs. 11.5 mm Hg; 2 years: 10.8 vs. 11.7 mm Hg; p<0.001 for all comparisons). Similar results were shown for the SAPIEN 3 valve in the PARTNER 2 propensity score analysis: after TAVR, the improvements in mean aortic valve areas and gradients observed at 30 days were maintained at 1 year (1 year: valve area, 1.7 cm^2, and gradient 11.4 mm Hg).[29]

In the recent PARTNER 3 Trial in low risk patients, the mean aortic valve gradients for TAVR and SAVR were 12.8 mm Hg and 11.2 mm Hg, respectively, at 30 days (p<0.05); the mean aortic valve area was 1.7 cm^2 and 1.8 cm^2, respectively (NS). The percentage of patients with moderate or severe paravalvular regurgitation was not significantly different.[9]

"How can complications associated with various TAVR devices and delivery systems, such as paravalvular regurgitation, need for permanent pacemaker implantation, and vascular events, be further reduced in severity and frequency?" (p. 91)

Paravalvular regurgitation

After TAVR, aortic regurgitation (AR) may occur because of imperfect valve sizing, positioning, or deployment and is mainly paravalvular in nature.[79] In the PARTNER B Trial of inoperable patients with AS, the rate of moderate-to-severe AR was 11.8% at 30 days after implantation of SAPIEN and generally decreased over time.[69,77] The incidence of transvalvular AR, an adverse event typically experienced by patients who are medically managed, was lower in SAPIEN patients than in medically managed patients at 30 days (1.3% vs. 16.9%, respectively) and 1 year (4.2% vs. 15.2%).[69] Comparison of the pooled PARTNER A and B RCT cohort with the Non-Randomized Continued Access (NRCA) cohort showed similar rates of moderate-to-severe AR at 30-day follow-up.[80] Further, in the PARTNER 2B Trial, similar rates of moderate-to-severe AR were reported for patients randomized to SAPIEN or SAPIEN XT at 30 days and 1 year.[32] This outcome was not reported in the PARTNER 2 S3HR study.

Rates of moderate-to-severe AR in high risk patients with AS have also improved with the introduction of next-generation TAVR devices. In the PARTNER A Trial, the risk of this adverse event was significantly higher in the SAPIEN group than in the SAVR group between 30 days and 2 years.[28,31,71] These elevated rates were attributed, in part, to the design of this first-generation device, as well as imaging practices and limitations in valve sizes.[28,31,71,81] Introduction of the SAPIEN 3 valve has resulted in lower rates of moderate-to-severe AR. In the PARTNER 2 S3HR Trial, the rate of this adverse event was 1.2% at 1 year after implantation of SAPIEN 3.[82] Similarly, in the SAPIEN 3 CE Mark Trial, a low rate of moderate AR was observed at both 30 days and 1 year; no patient developed severe AR at either time point.[83] This improvement in AR rates compared with the previous-generation SAPIEN device may be partially attributed to SAPIEN 3's new design, which includes an expandable outer skirt, as well as the optimization of imaging techniques for valve sizing and positioning.[84,85]

In the PARTNER 2A Trial and the PARTNER 2 S3i propensity score analysis (intermediate risk patients), comparison of the SAPIEN XT and SAPIEN 3 valves with SAVR suggested that rates of moderate-to-severe AR are similar between treatment groups and SAPIEN valve types across all follow-up periods.[29,33]

In the most recent PARTNER 3 Trial of low risk patients, there was no difference in moderate or severe paravalvular regurgitation between TAVR and SAVR patients (0.8%vs. 0.0% at 30 days and 0.6% vs. 0.5% at 1 year, respectively; NS).[9]

Pacemaker

Balloon-expandable valves have achieved consistently low pacemaker rates across clinical trials. In the PARTNER B study of inoperable patients, rates of new permanent pacemaker implantation (PPI) were comparable in the SAPIEN and medical management groups at 30 days, 1 year, 2 years, and 3 years.[7,69,86] . In the PARTNER 2B Trial (inoperable patients), patients who received SAPIEN XT showed low rates of new PPI at 30 days and 1 year; these rates were similar to those in patients who received the SAPIEN valve.[30,41]

In the PARTNER A Trial, rates of new PPI in high risk patients were similar in the SAPIEN and SAVR groups at 30 days and through 5 years of follow-up.[28,31,71] In the PARTNER 2 S3HR study, rates of new PPI with SAPIEN 3 were higher than those observed with earlier devices.[19,20] This finding may relate the differences in valve size and positioning.

In the PARTNER 2A Trial and the PARTNER II S3i propensity score analysis, rates of new PPI were comparable between both SAPIEN XT and SAVR and SAPIEN 3 and SAVR across all follow-up periods.[29,33]

In the most recent PARTNER 3 Trial of low risk patients, new pacemaker rates were not different between SAPIEN 3 and SAVR (6.5% vs. 4.0% at 30 days and 7.3% vs. 5.4% at 1 year, respectively; NS).[9] Taken together, these results suggest that rates of new pacemaker in contemporary practice with SAPIEN 3 are low and comparable with surgery.

Vascular Events

Vascular complications have generally decreased over time with valve technology evolution. In high-risk patients, vascular complications were higher in the original PARTNER A Trial (11% vs. 3.2% for SAPIEN vs. SAVR, respectively; $p<0.001$). However, the single-arm PARTNER 2 S3HR Trial showed rates of

vascular events with SAPIEN 3 as low as 5.1% at 30 days.[87] These results are echoed with the SAPIEN 3 CE Mark Trial (high risk), with 5.3% vascular complications overall, and 4.2% in the TF cohort.[8]

Throughout 2 years of follow-up in the PARTNER 2A Trial (intermediate risk), rates of major vascular complications were higher with SAPIEN XT than with SAVR in both the overall and TF cohorts (8.6% vs. 5.5%, respectively, at 2 years; p<0.001).[33] In the PARTNER 2 S3i propensity score analysis, the 30-day rate of this outcome was only slightly higher with SAPIEN 3 than with SAVR (6.1% vs. 5.4%, respectively), but was lower than that observed at 30 days in the PARTNER 2A Trial, indicating a meaningful reduction in vascular complications with the current generation SAPIEN 3 valve.[29]

In the most recent PARTNER 3 Trial of low risk patients, major vascular complications were no different between SAPIEN 3 and SAVR (2.2% vs. 1.5% at 30 days and 2.8% vs. 1.5% at 1 year, respectively; NS).[9] This indicates a meaningful reduction in vascular complications as the SAPIEN valve technology has evolved.

3. Conclusion

The benefits of TAVR for the Medicare population have been nothing short of remarkable. Initially, the treatment approach was to consider whether a patient was inappropriate for SAVR and then consider TAVR. With rapid technology refinement and continued improvement in clinical outcomes, the question is shifting to who is inappropriate for TAVR, with surgery reserved for cases where the less invasive therapy is not optimal.[88] This evolution was punctuated by the recent PARTNER 3 Trial results demonstrating that TAVR was superior to SAVR in low risk patients receiving the SAPIEN 3 transcatheter heart valve.[9] These results were described by leading experts as “practice-changing,” a “paradigm shift,” and an “incredible advance in the care of patients with aortic stenosis.”[89,90] In the near future, this could pave the way for TAVR to serve as the initial treatment of choice, regardless of estimated risk scores.[91]

While we continue to believe that establishing a uniform policy across the continuum of aortic valve replacement (whether surgical or transcatheter) is in the best interest of all patients with AS, we commend CMS for proposing many elements that move toward broadening access to TAVR by modernizing and streamlining coverage provisions. Edwards believes the proposed policy, with important refinements recommended in this comment letter, will ensure a more streamlined care process under the direction of Heart Teams with appropriate expertise and infrastructure, while providing increased flexibility for programs to meet and maintain requirements. This is essential in an evolving AS treatment landscape. Additional protections will remain in place to ensure continued quality monitoring and that the remaining evidence gaps for this therapy are addressed.

In our view, the persistent and unacceptably high burdens of under diagnosis and under treatment are the most important clinical issues AS patients face today. To this end, our shared goals should be to ensure that there is expanded and equitable access to high-quality care so that all people with heart valve disease have the ability to consider all safe and effective treatment options with their clinicians at the appropriate time. Edwards thanks CMS for its consideration of our recommendations for the NCD. We look forward to working closely with CMS throughout the NCA process and to providing any additional information that CMS may require.

4. Appendix: Literature Review

A focused assessment of published literature was performed to evaluate the strength of evidence for the relationship between procedural volumes and patient outcomes of TAVR, SAVR, and PCI. This review encompassed all THV platforms. The initial PubMed database was searched using the search filters of, “Year 2012 to present (June 5, 2018)” AND “Abstract Available” AND “Search terms present in Title/Abstract.” The search was subsequently updated by conducting the same literature review following the initial review, filtering articles for the dates “June 5 2018 to present (April 11, 2019)” The following search terms were used:

- The primary terms were as follows:
    - *Percutaneous Coronary Intervention"[Mesh] OR "Balloon Angioplasty,*

    - *"SAVR" OR "SAVI" OR "Surgical Aortic Valve Implant" OR "Surgical Aortic Valve Replacement,*
    - *“TAVR" OR "TAVR" OR "transcatheter aortic valve replacement" OR "transcatheter aortic valve implant”*
- The secondary terms were as follows:
    - *"TAVR" OR "TAVR" OR "transcatheter aortic valve replacement" OR "transcatheter aortic valve implant"*
    - *"TAVR" OR "TAVR" OR "transcatheter aortic valve replacement" OR "transcatheter aortic valve implant”*
- The tertiary terms were as follows:
    - *"Volume" OR "Outcome*" OR "Volume-Outcome*" OR "Experience*" OR "Professional Competence" OR "Caseload" OR "Case-load" OR "Case load" OR "Learning curve" OR "Learning-curve" Or "Threshold"*

These search terms were used to find articles in PubMed (n=3,976) then results were filtered based on article titles and abstracts (n=77 remaining, n=3,899 eliminated).

Articles were filtered by English language and full-text provided. Of the 43 remaining articles, 35 studies were found to assess the relationship between institutional TAVR volumes and outcomes in patients undergoing TAVR (n=35 remaining, n=12 eliminated).

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