December 11, 2012

Marilyn Tavenner
Acting Administrator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Room 445-G, Hubert H. Humphrey Building
200 Independence Avenue SW
Washington, DC 20201

Re: Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) meeting pertaining to Management of Heart Failure with the Use of Ventricular Assist Devices

Dear Ms. Tavenner:

On behalf of The Society of Thoracic Surgeons (STS), the largest organization representing cardiothoracic surgeons in the United States and internationally, I write to provide comments representing The Society’s responses to the questions presented to the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) at the November 14th meeting pertaining to Management of Heart Failure with the Use of Ventricular Assist Devices (VADs). The STS appreciates the opportunity and privilege to provide perspective to this important therapy for our patients with advanced heart failure.

About STS

Founded in 1964, The STS is an international not-for-profit organization representing more than 6,600 cardiothoracic surgeons, researchers, and other health care professionals who are part of the cardiothoracic surgery team providing surgical therapies for the heart, lung, esophagus and chest. The Society’s mission is to enhance the ability of cardiothoracic surgeons to provide the highest quality patient care through education, research, and advocacy.

The STS has been a strong advocate of a number of important patient quality and safety outcomes improvement initiatives. The STS National Database was established in 1989 as an initiative for quality improvement and patient safety among cardiothoracic surgeons. The STS National Database has four components—Adult Cardiac, General Thoracic, Congenital Heart Surgery, and the STS/ACC TVT Registry, with the availability of anesthesiology participation within the Congenital Heart Surgery Database. The STS Adult Cardiac Surgery Database is the world’s premier clinical registry for cardiac surgery. The Database houses more than 4.7 million surgical records and gathers information from more than 95% of the ~1,100 groups that perform cardiac surgery in the United States. In 2012, the Database expanded to include its first two international participants: Brazil and Israel.
The STS National Database provides:

- A standardized format for examining the care of patients undergoing cardiothoracic operations;
- A tool that can be used to target specific areas for clinical practice improvement;
- The ability to obtain an accurate reflection of practice patterns;
- The ability to research the national aggregate data set; and
- The opportunity to participate in a national quality improvement effort for cardiothoracic surgery that has an impact at the local, regional, and national levels.

Launched in 2011, the STS Research Center is a nationally recognized leader in outcomes research. The Center seeks to capitalize on the value of the STS National Database and other resources to provide scientific evidence and support cutting-edge research that ultimately helps cardiothoracic surgeons, government, industry, and other interested parties improve surgical outcomes and the quality of patient care.

The Database continues to expand with new initiatives. Launched in January 2011, STS Public Reporting Online enables Adult Cardiac Surgery Database participants to voluntarily report to the public their heart bypass surgery performance. Overall composite star ratings as well as their component ratings are listed on www.sts.org for more than 250 Database participants. With the success of participation nationally, STS launched in 2011 an initiative to accommodate Database participation worldwide by including international participants in the Adult Cardiac Surgery Database.

**MEDCAC Questions**

1. **How confident are you that there is adequate evidence that specific patient criteria can be used to prospectively identify clinically meaningful changes in the health outcomes listed above (improved, equivalent or worsened) that are likely to be experienced by patients who receive a VAD in addition to optimal medical therapy compared with optimal medical therapy alone?**

Alternative Therapies for Patients with Advanced Heart Failure

In the past decade, biventricular pacing has been proven beneficial for earlier stages of heart failure mainly for improvement of symptoms and improvement of functional class. These findings have led to marked increases in utilization of these devices to improve heart failure symptoms. Use of biventricular pacing for certain subsets of patients with NYHA class IV functional status has been shown to improve symptoms, but definitive overall survival benefits have been difficult to demonstrate. For example, the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) trial, randomized patients to three groups, showed survival benefits only for the CRT-D group, with this survival benefit being attributed to the defibrillator therapy. For the three referenced studies that describe the outcomes for OMM, the majority of these patients had internal defibrillators. Therefore, one could argue that the OMM or non-LVAD Stage D patient population has not experienced significant changes in survival within the last decade; survival remains dismal with up to 80% mortality at the one-year interval. While biventricular pacing is a treatment that may afford functional benefits for certain groups of NYHA functional class IV heart failure patients, it is unlikely that the OMM survival would be significantly altered had all patients in these groups received biventricular pacing devices.
Patient Characteristics from Clinical Trials of Destination VAD Therapy

The Randomized Evaluation of Mechanical Assistance for Treatment of Congestive Heart Failure (REMATCH) provided the first evidence to demonstrate the superiority of left ventricular assist device (LVAD) therapy over optimal medical management (OMM) for patients with advanced heart failure who are not eligible for heart transplantation. This prospective, randomized, multicenter trial enrolled patients; 1) ineligible for heart transplantation; 2) had a left ventricular ejection less than or equal to 25%; 3) had symptoms of heart failure on optimal medical management that were consistent with NYHA class IV limitations for 60 of 90 days unless dependent on intravenous inotropes for 14 days or intra-aortic balloon pump for 7 days; and 4) a peak exercise oxygen consumption less than or equal to 12 ml/Kg/min (later modified to less than or equal to 14 ml/Kg/min to increase trial enrollment). Approximately 71% of patients enrolled in REMATCH were dependent on intravenous inotropes at the time of randomization. In REMATCH survival at 1 year (52% vs. 25%; \( P = .002 \)) and 2 years (23% vs. 8%; \( P = .09 \)) was superior (significantly) in the VAD patients compared with the patients randomly assigned to optimal medical management. The relative risk reduction for mortality was 0.52 (range 0.34 to 0.78; \( P = .001 \)) at 12 months. The trial was analyzed by intent-to-treat analysis despite an open access to crossover from the medical arm to receive a device at 1 year, which occurred in eight patients. Patients receiving device therapy also experienced superior quality of life and functional status compared to patients randomized to optimal medical management. The specific inclusion criteria for REMATCH listed above have identified a group of patients with advanced heart failure at high risk of death who benefit from mechanical assistance. The mode of death in nearly all of the patients in the medical therapy arm was heart failure, whereas patients who received a pulsatile flow VAD (HeartMate VE, Thoratec, Inc., Pleasanton, CA) were more likely to die from infectious complications or device failure. The overall adverse event rate was higher in patients in the VAD cohort (risk ratio 2.35; 95% CI 1.86 to 2.95), with higher rates of bleeding, neurologic dysfunction, infections, thromboembolic complications, and renal failure.

Over the past decade there has been important advances in implantable, durable LVAD technology with the development of continuous flow devices. These devices offer a much smaller size (and therefore a less invasive implant procedure), fewer moving parts, and improved durability. In a prospective, randomized, multicenter pivotal evaluation (HeartMate II Pivotal DT Trial) of pulsatile flow technology used in the REMATCH trial to newer continuous flow technology (HeartMate II; Thoratec, Inc., Pleasanton, CA) for patients not eligible for heart transplantation, the newer continuous flow technology demonstrated superior survival at 2 years compared to the older pulsatile flow technology (actuarial survival rates at two years were 58% and 24% for the continuous flow and pulsatile flow devices, respectively (p=0.008). Of the 134 patients randomized to a continuous flow device, 62 survived at least two years without suffering a stroke or requiring their device to be repaired or replaced. Only seven of the 66 patients randomized to the older pulsatile flow technology survived two years without a reintervention or stroke (hazard ratio 0.38, p<0.001). The difference in stroke- or surgery-free survival, the primary end point of the study, was driven primarily by a difference in the need to reoperate to repair or replace the older pulsatile flow device. Furthermore, these patients receiving the continuous flow technology experienced impressive functional improvement.

Inclusion criteria for the HeartMate II Pivotal DT trial were similar to REMATCH except that patient enrollment was less restrictive and included patients with symptoms of advanced heart failure consistent
with NYHA functional class IIIB or IV for 45 of 60 days prior to randomization. Despite this reduced duration of heart failure symptoms required, nearly 80% of patients were on intravenous inotrope therapy at the time of randomization. When comparing outcomes for patients receiving the continuous flow device in the HeartMate II Pivotal DT trial to the patients in the OMM arm of the REMATCH trial, who had similar characteristics, the absolute survival benefit at one year is approximately 45%. This absolute survival benefit for continuous flow LVAD support for destination therapy exceeds the survival benefit seen with beta-blockers or ACE inhibitors or ICDs (for earlier class HF). Furthermore, other than heart transplantation, no other heart failure therapy affords as significant a functional improvement.

Despite the knowledge obtained from clinical trials that we have identified a large group of patients with specific characteristics who benefit from VAD therapy for destination indication, there is still incomplete knowledge regarding specific characteristics of subsets of higher or lower risk patients that may derive less or more benefit. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) has provided critical information with respect to outcomes and patient characteristics.\(^3\) INTERMACS Patient Profiles are a subjective scale that assesses the severity of illness of patients undergoing VAD implant. The profiles incorporate a subjective assessment of the acuity of illness incorporating hemodynamic stability and findings, end-organ function, and interventions necessary to stabilize the patient, including hospitalizations. Although the INTERMACS profiles have been important to assessment of patient risk, and have changed referral practices of physicians to earlier VAD implant, these profiles are subjective in nature and not, by themselves, adequate for determining appropriateness of VAD therapy for specific patient characteristics.

One important aspect of the current guidelines that CMS should consider is the criteria requiring “transplant ineligibility” for destination therapy. Destination therapy currently implies permanent device therapy, but a broader interpretation could include patients with anticipated long-term durations of support. Many patients currently undergoing VAD implant have relative contraindications that are resolvable only with the use of VAD therapy. Evaluation for heart transplantation is a dynamic process and contraindications present at the time of VAD implant may resolve with time. Conversely, patients listed for heart transplantation and receiving VAD implant are not necessarily guaranteed transplantation in the event that a significant complication occurs that poses a significant or absolute contraindication to transplant. Thus, neither bridge to transplant or destination therapy labels identify the ultimate path in all cases of VAD implant. Currently, approximately one-third of all patients who receive a VAD fall into the category of “bridge-to-decision,\(^3\)” where the providers are not certain if the patient will eventually be a transplant candidate or not; however the patient’s worsening condition does not provide an opportunity to wait without the placement of a VAD without risking imminent death.

2. **How confident are you that there is adequate evidence that one or more facility and/or operator characteristics predict clinically meaningful improvements in the health outcomes listed above for patients who receive a VAD in addition to optimal medical therapy compared with optimal medical therapy alone?**

The Relationship of Volume and Outcome for VAD Therapy

Recently, Park et. al.\(^4\) reported on a study comparing outcomes from the HeartMate II Pivotal DT trial, segregating patients into an early versus late enrollment cohort. There was significant reduction in several key adverse events for the more recent cohort, most important of which was the incidence of
hemorrhagic stroke, which was the leading cause for mortality. Greater experience with the device appeared to lead to alterations in anticoagulation management and improved outcomes. This is an interesting observation as centers in this trial were relatively experienced in VAD implant procedures. These finding suggests that optimal management of patients with VAD therapy continues to evolve during these trials. This study also suggests and supports the notion that a learning curve exists with introduction of any new technology.

More recently, Hernandez et. al. reported a study on the outcomes of patients receiving LVAD therapy from the CMS database. Given that this study analyzed Medicare beneficiaries, it was logical to assume a significant proportion of these patients received device therapy for destination indication. This study demonstrated an important relationship between center experience and short-term survival, with an almost a direct relationship observed at volumes less than 20 cases per previous year. These examples demonstrate that the experience of the operator and facility impact patient outcomes. However, the reduction in survival benefit associated with inexperience is relative small compared to the overall absolute survival benefit for the therapy.

Available Databases to Analyze the Relationship between Center or Surgeon Volume and Outcome

INTERMACS has extensive data available for analysis of the impact of center volume and outcome. However, patients enrolled in INTERMACS receive therapy with a commercially available, FDA-approved durable device. Many centers participating in INTERMACS implant significant numbers of investigational devices as part of FDA clinical trials and this activity is not reflected in INTERMACS. Further, INTERMACS has no information on surgeon-specific data. The STS database does include data on surgeon-specific volumes and includes data on both FDA-approved commercially-available devices and investigational devices. However, STS does not have long-term outcome data on patient outcomes.

Current Centers for Medicare and Medicaid Services (CMS) Volume Requirements

CMS has set broad requirements for “surgeon” qualifications for VAD implant procedures stating that, “Implantation of durable long-term ventricular assist devices for destination therapy requires placement of 10 ventricular assist devices in the last 36 months with current activity in the last 12 months and with volume requirement met by including artificial heart placements for no more than 50% of the total volume.”

Although data generally supports a link between outcome and volume for many cardiac procedures including heart transplantation, there is presently insufficient data to support specific volume criteria for VAD therapy. There is currently no data available to validate this volume criteria, either with respects to it being too low or high.

Impact of Current Interpretation of Centers for Medicare and Medicaid Services on Surgeon Certification

Although not specifically excluded by CMS criteria, surgeon experience obtained from an ABTS-approved Cardiothoracic Residency or through an advanced cardiothoracic fellowship for advanced heart failure therapies is currently not recognized by the Joint Commission. However, these types of
experiences are accepted pathways for surgeon certification for heart transplantation, a procedure of similar complexity to VAD therapy. The United Network for Organ Sharing has established specific guidelines for these types of experiences. In addition to the lack of recognition of residency or fellowship experiences, there is no accepted criteria for assessing and accounting for surgeon experience obtained from international or foreign training experiences.

Another important aspect of surgeon training is the recognition of preceptor or teaching role. Currently, there is a very narrow interpretation of what constitutes the “primary surgeon” of record. The Joint Commission currently interprets CMS requirements to include only the billing surgeon as the surgeon of record. This narrow interpretation of the requirement is significantly limiting training and educational opportunities for other surgeons who are performing key aspects of the pre- and postoperative care and key technical aspects of the VAD implant under the supervision of a qualified surgeon with expertise in VAD therapy.

To that end, STS recommends further clarification of the CMS requirements to include:
- Documentation of other aspects of training and experience that are essential to the overall qualifications of a VAD surgeon.
- Recognition of residency and fellowship experiences.
- Expansion of the definition of “Primary Surgeon” to follow guidelines outlined by the American Board of Thoracic Surgeons in teaching or “preceptor” settings.
- Recognition of international training experiences.
- Establish a pathway for certification and criteria for established, board-certified cardiothoracic surgeons without prior VAD experience

Further, STS recommends a collaborative process for revision of VAD surgeon certification requirements to include representation from CMS, the Joint Commission or other agency that would assume oversight responsibility, the American Board of Thoracic Surgery (ABTS), and The Society of Thoracic Surgeons. VAD surgeon certification should recognize that the skill set of VAD caregivers differs from that of others in cardiology, and while similar to that of heart failure and transplant, it has the additional dimension of mechanical support issues. It is reasonable to continue the certification process for DT VAD therapy, given the many unique features of the specialty. Further, given the multidisciplinary nature and the unique features of the VAD specialty, the Heart Team concept should improve patient outcomes. The recent American Board of Internal Medicine certification for Advanced Heart Failure and Transplant, and CMS certification for DT therapy, support the concept that an experienced and skilled infrastructure should result in improved outcomes.

### 3. **How confident are you that these conclusions are generalizable to the Medicare beneficiary population?**

Several concerns can be raised regarding whether trial outcomes regarding DT LVAD therapy can be generalized to the majority of Medicare beneficiaries. First, centers participating in these trials typically have high levels of experience. As this therapy is dispersed to less experienced centers, some initial decrement in outcomes may be anticipated which could impact overall survival benefit and QOL benefit. Second current CMS guidelines focus on defining a patient population with very advanced heart failure and do not follow inclusion criteria of recent clinical trials. Thus, results in clinical trials may reflect better outcomes of patients with less severe forms of heart failure. Additionally, CMS guidelines
do not include the substantial number of exclusion criteria present in recent trials of DT LVAD therapy and do not seek to define which patients may be too sick or too advanced to derive benefits. Notably, the Heartmate II Pivotal DT trial and the Heartware Pivotal DT trial (ENDURANCE) had important exclusion criteria which are absent from CMS criteria. These exclusion criteria sought to prevent enrollment of patients who were at highest risk for procedural morbidity and mortality. There were about 20 exclusion criteria for each of these two trials. Examples from these trials include:

- Exclusion criteria #16: serum creatinine > 3.0 mg/dl within 72 hours of randomization or requiring dialysis.
- Exclusion criteria #17 Heartware DT trial: all three liver enzymes greater than three times upper limit of normal or bilirubin > 3 mg/dl within 72 hrs of randomization or biopsy proven cirrhosis.

Outside of the trial, these exclusions do not formally exist and the judgment of the clinician or heart failure team is relied upon to decide whether to extend the therapy to individual patients. Some potential Medicare beneficiaries being evaluated for LVAD therapy have these high-risk features and may not experience the benefits of the therapy relative to the more censored trial population. Conversely, these high-risk patients may experience the same benefits or even greater relative benefit as their outcome with OMM may be even worse than expected from prior datasets.

Therefore, one area that warrants greater investigation relates to the exclusion of high risk patients. Specific questions include:

- Which high risk patients do not benefit from the therapy?
- When do patients have profound end organ dysfunction which is not recoverable?
- Under what clinical circumstances are implants futile?

Despite these concerns regarding the ability to generalize results from clinical trials to Medicare beneficiaries, there is data to support that results are applicable to Medicare beneficiaries. The median age in the HeartMate II Pivotal Trail for DT indication was 62 years and thus included a significant proportion of patients greater than 65 years of age. Additionally, approximately 25% of patients in INTERMACS are 65 years of age or older. As more, longer-term data become available, we will better predict what risk factors, such as advanced age, may have a negative effect on outcomes.

Another area where evidence and knowledge is lacking relates to the frailty of elderly patients. Some patients who meet CMS criteria for DT LVAD may display frailty that can preclude successful recovery from the surgical procedure. Stated differently these patients display functional limitations independent from hemodynamics and may not recover after LVAD support which mainly restores normal hemodynamics. Measuring or gauging this frailty is complex and has not been vetted in the LVAD population.

Yet another area in which additional clinical evidence is required relates to overlap between biventricular pacing therapy and DT LVAD. The Companion trial and the CARE-HF trial both demonstrated clinical benefits for patients with NYHA functional class IV limitations with biventricular pacing. Therefore, an advanced heart failure patient may qualify for both therapies. Guidelines for utilization of one therapy versus the other are not based on strong clinical evidence. At times it seems as if the therapy that is administered relates to which type of specialist is seeing the patient. Utilization of
both therapies on all such patients seems very inefficient, particularly since the treatments are probably not synergistic.

4. **How confident are you that clinically significant evidentiary gaps remain regarding the use of VADs?**

Clinically significant evidentiary gaps remain regarding the use of VADs for DT. There are substantial data supporting the use of VAD therapy for DT in patients having characteristics similar to those subjects enrolled in the REMATCH trial; e.g., NYHA Class IV functional limitations. In REMATCH, approximately 71% of patients were dependent on inotrope therapy at the time of LVAD implant. Whether VAD therapy is beneficial in patients with less advanced forms of heart failure; e.g., NYHA Class III or IIIB functional class, who are not inotrope dependent is not known at this time. Prospective, randomized clinical trials to investigate the use of VAD therapy in patients with less advanced forms of heart failure who are not inotrope dependent are necessary to address this question. The Randomized Evaluation of VAD Intervention Before Inotrope Therapy (REVIVE-IT) is a NHLBI-sponsored initiative to assess the benefit of VAD therapy in patients with less advanced stages of heart failure. This prospective, randomized, multicenter trial will investigate the use of VAD therapy compared to optimal medical management in ambulatory, non-inotrope dependent patients with NYHA Class III limitations who have an expected 1 year mortality of 20-25%.

Additionally, there is insufficient data to risk stratify subsets of patients who may have high VAD mortality. Although, preliminary attempts have been made to develop risk stratification scores for patients receiving VAD therapy, these risk models all suffer from significant limitations including either; 1) single center populations; 2) lack of validation; 3) small number of patients; or 4) derived from clinical trial data that may not be generalizable to commercial use. INTERMACS is a significant resource where risk stratification models can be developed and validated and that are derived from large populations of patients receiving VAD therapy outside of clinical trials. However, it has only been in the past two years since the introduction of continuous flow rotary pumps that reasonable numbers of patients have received VAD therapy for DT indication. Further time will be needed for larger numbers of patients to be accrued before reliable prognostic models can be developed.

The Society of Thoracic Surgeons looks forward to collaborating with the Centers for Medicare and Medicaid Services to improve outcomes of VAD therapy for patients with advanced heart failure.

Sincerely,

[Signature]

Jeffrey B. Rich, MD
President
References


