Summary of Evidence
Medicare Coverage Advisory Committee
March 12, 2003
Left Ventricular Assist Devices (LVAD) for Destination Therapy

[NOTE: This document reflects the current CMS staff analysis of the evidence related to this coverage decision. It is intended to only to raise issues and promote discussion at the Medicare Coverage Advisory Committee meeting and does not reflect any staff conclusions. Public presenters are encouraged to comment on the material contained in this analysis. The final decision memorandum and National Coverage Determination will reflect the formal policy of CMS and DHHS.]

MCAC Recommendations for Evaluating Effectiveness [TAB 1]

Included for reviewer reference are the Medicare Coverage Advisory Committee (MCAC) Executive Committee "Recommendations for Evaluating Effectiveness."

Background Information Related to LVADs

Heart failure affects an estimated 5 million Americans, resulting in approximately 300,000 deaths annually. Heart failure is primarily a disease of the elderly. Eighty percent of those diagnosed with heart failure are over age 65, and 6-10 percent of the total Medicare population has this disease. Heart failure is the leading cause of hospitalization in the Medicare population, accounting for 5-10 percent of total beneficiary hospitalizations.

Although patients with mild to moderate heart failure have been shown to benefit from drug therapy, the survival and quality of life for those with severe failure remains limited. Cardiac transplantation is the only treatment that provides substantial benefit for end-stage heart failure (ESHF), but the available donor supply limits cardiac transplantation to approximately 3,500 patients worldwide per year. In 2000, there were 2,198 heart transplants performed in the United States. While eligibility criteria differs among transplant centers, most Medicare patients are excluded from receiving a heart transplant because of age, or such comorbid conditions as diabetes, chronic renal failure, or other chronic disease.

Ventricular assist devices are mechanical pumps that take over the function of the damaged heart (the right, left or both ventricles) and restore hemodynamics and end-organ blood flow. Different VAD designs, including electrically or pneumatically powered, implanted or paracorporeal (external), and pulsatile or non-pulsatile (continuous flow) devices currently have Food and Drug Administration (FDA) approval for the indications listed below. Most of these devices assist the left ventricle, and therefore are commonly referred to as left ventricular assist devices (LVAD).

LVADs are currently used in two groups of patients. The first group consists of patients who require ventricular assistance to allow the heart to rest and recover its function (most often patients with cardiogenic shock after open heart surgery). The second group consists of patients who are not expected to recover adequate cardiac function (resulting from myocardial infarction, acute myocarditis, or heart failure) and who require mechanical support to assist heart function until a donor heart becomes available for transplantation. LVADs have been successfully used in this manner as a "bridge to transplant" for several years.

The clinical promise of LVADs and the limitations of existing treatment options for patients in advanced heart failure led researchers to investigate the use of LVADs as an alternative to transplantation ("destination therapy") for those patients who were not candidates for cardiac transplantation. Because the vast majority of these patients are over 65 years of age this potential indication has significant implications for the Medicare program.

Medicare's Current Coverage of LVADs

Currently, Medicare covers the implantation of an LVAD for patients with postcardiotomy complications and as a bridge to transplant in patients who have been approved as heart transplant candidates. (Coverage Issues Manual section 65-15, Artificial Hearts and Related Devices) **[TAB 2]**

Medicare does not presently cover this device as an alternative to medical management in end-stage heart failure (ESHF) patients who are ineligible for a heart transplant. On November 6, 2002, Thoratec, Inc. received FDA approval for an expanded Indication of Use for the Thoratec Heartmate SNAP VE LVAS for these end-stage, non-transplantable patients. The approval states: "This device is now also indicated for use in patients with New York Heart Association Class IV end stage left ventricular failure who have received optimal medical therapy for at least 60 of the last 90 days, and who have a life expectancy of less than two years, and who are not eligible for cardiac transplantation. The device system is approved for use both inside and outside the hospital."

CMS has received a request to expand Medicare coverage for use of these devices as destination therapy for ESHF patients who are not candidates for heart transplantation. The principal investigator of The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH), Dr. Eric Rose, and three colleagues who were co-investigators in this trial submitted this coverage request. **[TAB 3]**

Evidence for the Use of LVADs as Destination Therapy

This review addresses the evidence related to the use of this device for destination therapy. The Pubmed database was searched in February 2003 for peer-reviewed articles published from 1990 through January 2003. Search terms used included: "heart-assist devices", "left ventricular assist devices", and "left ventricular assist systems" in any field

and in conjunction with the terms "tranplant*" and "heart disease/failure" in the abstract. This search yielded 157 references. Abstracts were reviewed for studies, which specifically evaluated the use of this device in patients with ESHF who were not eligible for transplantation and received an LVAD specifically as destination therapy. Several articles included reports on patients who had received LVADs in anticipation of transplantation and then either recovered cardiac function (obviating the need for a transplant) or who for various other reasons did not receive a new heart. However, the only articles that met our inclusion criteria related to the REMATCH study and specifically dealt with the use of LVADs for destination therapy.

CMS staff also included several articles, which either appear to contain relevant background and/or other pertinent information to this coverage review. In addition, CMS received citations from both the requestors and other interested parties. As a result, we have included several additional articles for review that provide information relevant to this topic. In addition, the ACC/AHA 2001 document "Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult" is also included, as is a Consensus Conference report related to mechanical circulatory support, "Mechanical Cardiac Support 2000: Current Applications and Future Trial Design."

The following section summarizes pertinent articles, guidelines, and the Consensus Conference report relevant to use of LVADs for destination therapy. CMS comments are included.

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) – 2001 [TAB 4]

Design: Randomized clinical trial conducted at 20 experienced cardiac transplantation centers under cooperative agreement between Columbia University, NIH and Thoratec. Patients were randomly assigned (1:1) to either vented electric LVAD or optimal medical therapy. Independent morbidity and mortality committee reviewed causes of death and adverse effects. The trial was designed to enroll 140 patients and to continue until 92 deaths had occurred.

Sample Size: 129 patients enrolled and randomized, LVAD group (68), optimal medical management (61). Trial terminated at the 92nd death.

Primary endpoint: Death from any cause

Secondary endpoints: Incidence of serious adverse events (caused death or permanent disability, were life-threatening, or required or prolonged hospitalization), number of days of hospitalization, quality of life, symptoms of depression, and functional status.

Inclusion Criteria:
<u>Adults with chronic end-stage heart failure and contraindications to transplantation:</u>

- Symptoms of NYHA class IV heart failure for <u>≥</u> 90 days despite ACE inhibitors, diuretics and digoxin;

- LVEF $\leq$ 25%;
- Peak O_2 consumption $\leq$ 12 ml/kg or continued need for IV inotropic therapy for symptomatic hypotension, decreasing renal function or worsening pulmonary congestion;
- Patients could continue to receive beta-blockers if administered $\geq$ 60 of 90 days before randomization.

18 months after the start of the trial, the entry criteria was expanded in order to increase enrollment:

- NYHA class IV heart failure for $\geq$ 60 days;
- Peak O_2 consumption $\leq$ 14 ml/kg;
- Patients in NYHA class III/IV for $\geq$ 28 days, received $\geq$ 14 days support with intra-aortic balloon pump or dependent on IV inotropic agents, with 2 failed weaning attempts.

An additional 3 LVAD patients and 2 medical therapy patients enrolled under the changed criteria.

Transplantation was contraindicated for at least one of the following reason:

- Age > 65 years;
- Insulin-dependent diabetes mellitus with end-organ damage;
- Chronic renal failure (serum creatinine > 2.5.mg/dl for $\geq$ 90 days before randomization);
- Presence of other clinically significant conditions.

Exclusion Criteria

- Cause of heart failure due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis, or active myocarditis;
- Technical obstacles that pose an inordinately high surgical risk in the judgment of the certified surgeon;
- International normalized ratio >1.3 or prothrombin time >15 seconds within 24 hours before randomization;
- Body surface area <1.5 m2;
- Body mass index >40 kg/m2;
- Severe chronic obstructive pulmonary disease as evidenced by forced expiratory volume ≤ 1.5 L/min;
- If premenopausal, positive serum pregnancy test;
- Fixed pulmonary hypertension with pulmonary vascular resistance ≥ 8 Wood units that is unresponsive to pharmacologic intervention, documented within 90 days before randomization;
- Patient under consideration for conventional revascularization procedure, therapeutic valvular repair, left ventricular reduction procedure (i.e., Battista), or cardiomyoplasty;

- History of cardiac transplantation, left ventricular reduction procedure, or cardiomyoplasty;
- Presence of implanted mechanical aortic valve that will not be converted to bioprosthesis at time of LVAD implantation;
- Evidence of intrinsic hepatic disease defined as liver enzyme values (aspartate aminotransferase, alanine aminotransferase, or total bilirubin) > five times the upper limit of normal within 4 days before randomization, or biopsy-proved liver cirrhosis;
- Occurrence of stroke within 90 days before randomization or history of cerebrovascular disease with major (>80%) extracranial or carotid stenosis documented by Doppler study;
- Confirmation by neurologist of impairment of cognitive function, presence of Alzheimer's disease or any other form of irreversible dementia, or both;
- Evidence of untreated abdominal aortic aneurysm ≥ 5 cm as measured by abdominal ultrasound within 30 days before randomization;
- Suspected or active systemic infection 48 hours before randomization;
- Platelet count 50 X 10/mm3 within 24 hours before randomization;
- Serum creatinine ≥ 3.5 mg/dL or regimen of long-term dialysis;
- Major peripheral vascular disease accompanied by pain on rest or leg ulceration;
- Receiving calcium-channel blocker (except amlodipine besylate) or type I (e.g., quinidine, procainamide hydrochloride, disopyramide phosphate) or type III antiarrhythmic agent (e.g., encainide hydrochloride, flecainide acetate, propafenone hydrochloride, moricizine hydrochloride) within 28 days before randomization;
- Abdominal operation planned;
- Recent history of psychiatric disease (including drug or alcohol abuse) that is likely to impair compliance with study protocol;
- Receiving therapy with investigational intervention or participating in another clinical study;
- Presence of condition other than heart failure that would limit survival to less than 3 years;

Enrollment: Block randomization was used to ensure equivalence of group size and was stratified according to center. The eligibility of patients was determined by investigators at each site and confirmed by a gatekeeper at the coordinating center. Optimal medical management patients (OMM) followed guidelines developed by the medical committee, with the goals of optimizing organ perfusion and minimizing symptoms of CHF. Their medications included: digoxin, diuretics, angiotensin-converting enzyme inhibitors and beta-blockers as directed by heart failure specialists.

Results: Kaplan-Meier survival analysis showed a reduction of 48 percent in the risk of death from any cause in the group that received left ventricular assist devices as compared with the medical-therapy group (relative risk, 0.52; 95 percent confidence interval, 0.34 to 0.78; P=0.001). The rates of survival at one year were 52 percent in the device group and 25 percent in the medical-therapy group (P=0.002), and the rates at two years were 23 percent and 8 percent (P=0.09), respectively. The frequency of serious adverse events in the device group was 2.35 (95 percent confidence interval, 1.86 to 2.95) times that in the medical-therapy group, with a predominance of infection, bleeding, and

malfunction of the device. The quality of life was significantly improved at one year in the device group.

Authors' Conclusions: "The use of a left ventricular assist device in patients with advanced heart failure resulted in a clinically meaningful survival benefit and an improved quality of life. A left ventricular assist device is an acceptable alternative therapy in selected patients who are not candidates for cardiac transplantation."

CMS Comments: The majority of patients in this study were in the Medicare population age range. Female patients were proportionally under-represented. The study was powered for its primary endpoint- all cause mortality- but not for performance of subanalyses other than age. Among secondary endpoints reported in the study, there was a significant difference in the incidence of serious adverse events for device recipients of 6.45/patient/year compared to 2.75/patient/year in the medical management group. The cause of death for nearly all medical management patients reported (51 of 54) was left ventricular dysfunction. The main causes of death for device patients (41 patients reported) were sepsis (n=17) and failure of LVAD (n=7). The median number of days of hospitalization was 88 for the device group compared to 24 for OMM patients. Of the median number of days of life for LVAD patients (408), 340 days were spent out of the hospital, while of the median days of life of OMM patients (150), 106 days were spent out of the hospital. Quality of life and functional status at one year showed advantage for the LVAD group by several measures, but response rates were low overall with data for only 23 of 24 LVAD patients and 6 of 11 OMM patients presented. Functional status was reported as responses to a questionnaire rather than by more objective measures such as 6-minute hall walk or peak oxygen consumption.

The REMATCH Trial: Rationale, Design, and End Points. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure – 1999 [TAB 5]

The rationale for conducting REMATCH, obstacles to designing randomized surgical trials, lessons learned in conducting the multicenter pilot study, and features of the REMATCH study design (objectives, target population, treatments, end points, analysis, and trial organization) are presented.

Discussion: The authors describe the unique challenges to conducting randomized surgical clinical trials, including the skill of the surgeon and support available at a particular site; that there may be a refinement of the procedure during the trial; that there are ethical issues related to random assignment; and the impossibility of blinding of the treating surgeon.

REMATCH trial phases and objectives

- *Pilot study*. The pilot study was done for planning purposes, to familiarize the surgeons with device modifications, and to meet an FDA mandate to determine whether randomization was feasible in a surgical trial for a life-threatening condition.

- *Purpose.* The randomized controlled study's primary purpose was to determine the effect of the LVAD on mortality from all causes.
- *Design and end point analysis.* The trial was a parallel group study with random assignment of eligible patients to implantation of an LVAD or optimal medical management in a 1:1 ratio. The hypothesis was that the LVAD would reduce by a third the 2-year mortality in ESHF patients from 75% to 50% or more. To detect a difference of this magnitude with 80% power it was determined that 92 deaths would need to occur.
- *Organization and conduct of trial.* Both public and private support was obtained for this multisite study, which began enrolling patients in May 1998.

The investigators hoped to gain information about the long-term effect of LVADs on survival, quality of life, and costs. These factors were considered critical in determining the role of this treatment option in end-stage heart failure.

Destination Mechanical Circulatory Support – Proposal for Clinical Standards (Peer reviewed and accepted for publication in the April 2003 Journal of Heart and Lung Transplantation). [TAB 6]

A discussion of the issues to be considered when determining where LVAD implantation as destination therapy should be performed. Offers a number of options with a specific recommendation from the Board of Directors of the International Society for Heart and Lung Transplantation for consideration.

Advanced Mechanical Circulatory Support with the HeartMate Left Ventricular Assist Device in the Year 2000. [TAB 7]

This paper describes the HeartMate left ventricular assist device technology, used in more than 2,400 implants as of the year 2000. The review summarizes the clinical experience, and identifies the benefits and limitations of the current state-of-the-art technology of the leading implantable circulatory support system.

Overview:

- The HeartMate LVAD is described as "a pulsatile, implantable blood pump made of titanium with a polyurethane diaphragm backed by a pusher plate activated by either an external pneumatic driver (the IP, Implantable Pneumatic version) or by an internal electric motor (the VE, Vented Electric version)."
- *Blood path*. The "pump is interposed between the left ventricular apex and the ascending aorta."
- Textured blood contacting surfaces are "unique textured …promotes a thin, adherent coagulum that organizes into a biological matrix…The combination of this bioengineered, hybrid surface, the use of tissue valves, and well-engineered blood flow pathways produces a biocompatible interface for blood."
- *Operation*. The control system can operate in the fixed-rate mode or an autoregulating mode. In the auto mode, stroke volume is maintained at an effective 78 cc while rate is varied in response to preload. The VE can pump

between 50 and 120 bpm, varying pump flow output from 4 to 10 L/min. In the fixed rate mode…stroke volume depends on filling."

- *Availability and regulatory status*. Both versions of the pump have been approved by the FDA and are available internationally.
- *Clinical implementation*. The device "is designed to provide mechanical circulatory support for patients with compromising hemodynamic deterioration…Patients of small size are excluded…Contraindications other than size are relative…Major risk factors include hepatic, renal, or pulmonary failure, active infection or susceptibility, and technical challenges such as right heart dysfunction and redo operations."
- *Implantation and management*. Includes a description of the surgical procedure. "Infection precautions perioperatively are continued with wide-spectrum antimicrobial use for 48 hours…Anticoagulation requirements are generally limited to aspirin with or without Persantine. Coumadin is recommended only for non-LVAD indications."

Results:

- *Clinical experience*: "In 1999, 440 HeartMate LVADs were implanted…"
- *Clinical outcomes*:
    - Clinical trials. Clinical trials of both the pneumatic IP model and the electric VE model established their utility as a bridge to transplant.
    - TCI Registry data. This company registry contained data on 2365 patients who had received device implants as of the publication of this article with 65% characterized as successful outcomes. Experience with mortality, complications and device failure is discussed.

Authors' Conclusions: A generally positive assessment in which the authors conclude that survival in bridging to transplant is improved and "(b)eneficial outcomes with "permanent" use and bridging to recovery appear possible." Complication rates are "reasonable"; "strokes and thromboembolic events occur with remarkable infrequency"; and quality of life is "improved substantially". On the other hand, "(d)evice reliability will limit the use of this technology to 2- to 3-year durations, after which end-of-life replacements will be expected…Infections…remain a significant challenge."

Mechanical Circulatory Support for Advanced Heart Failure: Effect of Patient Selection on Outcome – 2001 [TAB 8]

Methods: Data were obtained from the Novacor European Registry. Between 1993 and 1999, 464 patients were implanted with the Novacor LVAS in 22 European centers, of which 11 centers have performed >10 implants each. Multivariate regression analysis was conducted to identify factors for survival after LVAS implantation.

Because this model (N100 PC) was released in Europe as a commercial product, clinicians in participating centers were not bound by the constraints of an investigational protocol and predefined implantation criteria. This resulted in patient selection practices that varied greatly between centers. In addition, a large percentage of patients were

moribund at the time of implantation. Examination of the consequences of this less rigorous patient selection is one of the major purposes of the study. The Novacor Registry was instituted in 1997 at the instigation of a number of clinicians (European Advisory Board) who were active in the use of MCS in an endeavor to promote an evidence-based perspective in mechanically supported advanced heart failure patients. The format for data collection and definitions of complications were a result of an expert consensus process, and the system was refined over the subsequent years.

Results: The majority of patients had idiopathic (60%) or ischemic (27%) cardiomyopathy. The median age at implant was 49 years (16 to 75). The median support time was 100 days (4.1 years maximum). Forty-nine percent of the recipients were discharged from the hospital on LVAS. These patients spent 75% of their time out of the hospital. For a subset of 366 recipients for whom a complete set of data was available, multivariate analysis revealed that the following preimplant conditions were independent risk factors for survival after LVAS implantation: respiratory failure associated with septicemia (odds ratio 11.2), right heart failure (odds ratio 3.2), age >65 years (odds ratio 3.01), acute postcardiotomy (odds ratio 1.8), and acute infarction (odds ratio 1.7). For patients without any of these factors, the 1-year survival after LVAS implantation including the posttransplantation period was 60%; for the combined group with at least 1 risk factor, it was 24%.

At the time of implantation, median age was 49 (16 to 75) years, with 5% of recipients aged >65 years. The majority of recipients were male (89%); body surface area was 1.92 (1.39 to 2.68) m^2. Diagnoses were dilated cardiomyopathy in 221 (60%) patients, ischemic heart disease in 100 (27%), acute myocardial infarction in 24 (7%), acute myocarditis in 19 (5%), and other causes in 2 (1%). Sixty-four (18%) patients had undergone prior thoracic surgical procedures. Preimplant hemodynamic, renal, and hepatic data showed a pattern of cardiac decompensation despite maximal medical therapy: pulmonary capillary wedge pressure was 25 (2 to 45) mm Hg, and the cardiac index was 1.9 (0.6 to 3.7) $L \cdot min^{-1} \cdot m^{-2}$. Serum creatinine levels were 1.3 (0.6 to 10.3) mg/dL, serum sodium was 135 (109 to 165) mmol/L, and total bilirubin was 1.7 (0.3 to 6.7) mg/dL. The intention to treat was as follows: bridge to transplant in the majority (321 recipients, 88%), followed by bridge to recovery (33 of 366 recipients, 9%), and definitive therapy (contraindication to transplant, 12 of 366 recipients, 3%).

Authors' Conclusions: Careful selection, specifically, implantation while patients can still derive benefit, and improvement in management may result in improved outcomes of LVAS treatment for advanced heart failure.

CMS Comments: This paper demonstrates the value of registry data in providing ongoing information about LVAD recipients. Of note was the finding that age >65 years was an independent risk factor for survival in the 5% of patients in that age group, who got devices. The authors also note that the absence of the constraints of a clinical study "allowed unrestrained use with regard to application and patient selection" and that "a large percentage of patients were moribund at the time of implantation…management varied widely between centers. The preponderance of early complications, such as right

heart failure, renal failure, stroke and respiratory infections suggests the strong influence of patient selection and reflects preimplant morbidity. Extended utilization of intensive care is, besides its impact on resources, associated with an increased incidence of infection, with more problematic organisms and a spiral of negative sequelae."

Consensus Conference Report: Mechanical Cardiac Support 2000: Current Applications and Future Trial Design: June 15–16, 2000 Bethesda, Maryland – 2001 [TAB 9]

Impact statement: Heart failure presents an increasing public health burden of morbidity and mortality even as the mortality from coronary artery disease and hypertension is decreasing. While effective pharmacologic therapies have improved outcomes for mild-moderate heart failure, the impact of newer therapies and mechanical circulatory support for advanced heart failure has not yet been realized. Implantable devices have been shown to be safe and effective as bridges to cardiac transplantation, but further work is needed to establish the role of mechanical support for myocardial recovery and for long-term support. This conference was held to assess current mechanical support applications and future trial designs for investigation affecting this public health issue.

The participants concluded that important differences between devices and drugs might warrant novel study designs characterized by innovation and flexibility. While the randomized clinical trial remains the most powerful tool for unambiguous comparison of interventions, variations may include timed graduation from control to investigational therapies, assignment influenced by patient risk or patient preferences, and criteria for an optional crossover to compassionate device use. A major impact would result from a national outcomes database for advanced heart failure that identifies high-risk populations with the greatest potential for benefit from newer therapies and thus facilitates the design of devices and device trials. A separate registry with industry of outcomes after device placement would help to identify "breakthrough" device therapies and facilitate the refinement and acceptance of this new technology. As represented in this conference, progress in mechanical circulatory support will be accelerated by the continued coordination of scientists, engineers, industry, clinical investigators and regulatory and payment agencies in prospective partnership.

Current status of mechanical cardiac support. The authors discuss uses and limitations of cardiac support devices available at the time of writing. They point out that "(o)f the more than 3,000 patients who have been implanted with circulatory support devices as a bridge to transplantation, approximately 60% to 70% actually received a transplant. Of those that received a transplant, 85% to 90% survived to be discharged from the hospital. Among those implanted as a bridge to transplantation, approximately 5% recovered ventricular function and survived without transplantation…During the past year, at least 50% of patients receiving wearable LVADs have been able to be discharged from the hospital, and patients have been supported from periods of a few weeks to >4 years." Upon completion of successful studies proving the utility of LVADs for "destination therapy", those devices could be considered as an alternative to transplantation for "the

50,000 to 100,000 patients in the U.S., who have been estimated to potentially benefit from this technology."

Evolution of therapies for heart failure. Both medical and surgical therapies are discussed, although for non-surgical therapies "randomized placebo-controlled trials have, in general, not included patients desperate for relief from severe heart failure symptoms or hoping to be rescued from imminent death." The obstacles encountered in randomized surgical trials are discussed and it is noted that the then "ongoing REMATCH trial faces the double challenge posed by both a surgical trial and study of a more compromised heart failure population than was ever enrolled in a controlled trial…concern was raised that this trial was unethical because it denied patients a life-saving therapy." The authors also discuss the concept of downshifting of risk as new surgical therapies become available after first being proven in more seriously ill patients. This lowering of risk in potential recipients also lowers potential benefit and "it remains crucial to monitor the target populations and ensure that the benefits expected from earlier experience are being derived."

Target populations and end points for mechanical circulatory support. The original candidates for REMATCH were expected to have a two-year survival of 25%. This section deals with indications for cardiac support for patients with heart failure such that 50% mortality is expected over various time periods. There is also discussion of criteria that could be used to exclude patients from device use such as renal or respiratory failure. A section on device selection includes a chart showing the importance of LVAD characteristics by potential patient populations. Finally there is a section on endpoints appropriate to LVAD trials.

Establishing efficacy for devices: ethical and practical challenges. A thoughtful presentation of issues unique to the efforts to prove the worth of support devices and to define the appropriate patient population to receive them.

Future devices entering clinical development. Discussion of how devices get to the trial stage and what particular devices are on the horizon.

Authors' Conclusions: Results and lessons learned from trials such as the REMATCH trial will inevitably influence future trial design in the field of mechanical circulatory support. As the field moves ahead, it has become clear that no one trial design will be ideal or appropriate for all devices, populations and stages of development. A variety of research designs will be necessary. Creation of a national outcomes database for advanced HF will facilitate effective trial design and identify populations that may potentially benefit.

Responsible progress in this field requires the establishment and maintenance of a mandatory registry that includes all implantable devices, both before and after approval. The combined effort of the various stakeholders is required to address issues of funding, data format and management, compliance and access, while balancing proprietary concerns. A major achievement of this conference is the recognition that the field will

advance further and more rapidly if the various groups involved in developing and testing new devices can collaborate effectively in the future.

Medical Management of Advanced Heart Failure – 2002 [TAB 10]

Objective: To review current medical therapy for advanced heart failure.

Data Sources: Searched MEDLINE for all articles containing the term *advanced heart failure* that were published between 1980 and 2001; EMBASE was searched from 1987-1999, Best Evidence from 1991-1998, and Evidence-Based Medicine from 1995-1999. The Cochrane Library also was searched for critical reviews and meta-analyses of congestive heart failure.

Study Selection: Randomized controlled trials of therapy for 150 patients or more were included if advanced heart failure was represented. Other common clinical situations were addressed from smaller trials as available, trials of milder heart failure, consensus guidelines, and both published and personal clinical experience.

Results: A primary focus for care of advanced heart failure is ongoing identification and treatment of the elevated filling pressures that cause disabling symptoms. While angiotensin-converting enzyme inhibitors and [beta]-adrenergic agents can slow disease progression and prolong survival, titration and tolerability often present challenges. Most patients are not eligible for surgical intervention but do benefit from a medical regimen tailored to individual clinical and hemodynamic profiles and from heart failure management programs that reduce rehospitalization. Survival ranges from 80% at 2 years for patients rendered free of congestion to less than 50% at 6 months for patients with refractory symptoms, in whom end-of-life options may include hospice care and inactivation of implantable defibrillators.

Conclusions: Current management of advanced heart failure is based more on consensus than on randomized trials. Systematic investigation should address not only new therapies but also strategies for selecting and optimizing therapies already available.

CMS Comments: Sections on prognosis for advanced heart failure, quality of life and end stage disease are particularly useful in consideration of LVAD utility.

Multicenter Clinical Evaluation of the HeartMate Vented Electric Left Ventricular Assist System in Patients Awaiting Heart Transplantation – 2001 [TAB 11]

Background: Despite advances in heart transplantation and mechanical circulatory support, mortality among transplant candidates remains high. Better ways are needed to ensure the survival of transplant candidates both inside and outside the hospital.

Methods: Prospective, (non-randomized) multicenter clinical trial conducted at 24 centers in the United States. Study population included 280 transplant candidates

(232 men, 48 women; median age, 55 years; range, 11-72 years) unresponsive to inotropic drugs, intra-aortic balloon counterpulsation, or both, were treated with the HeartMate Vented Electric Left Ventricular Assist System (VE LVAS). A cohort of 48 patients (40 men, 8 women; median age, 50 years; range, 21-67 years) not supported with an LVAS served as a historical control group. Outcomes were measured in terms of laboratory data (hemodynamic, hematologic, and biochemical), adverse events, New York Heart Association functional class, and survival.

Results: The VE LVAS-treated and non-VE LVAS-treated (control) groups were similar in terms of age, sex, and distribution of patients by diagnosis (ischemic cardiomyopathy, idiopathic cardiomyopathy, and subacute myocardial infarction). VE LVAS support lasted an average of 112 days (range, < 1-691 days), with 54 patients supported for > 180 days. Mean VE LVAS flow (expressed as pump index) throughout support was 2.8 L x min (-1) x m(-2). Median total bilirubin values decreased from 1.2 mg/dL at baseline to 0.7 mg/dL (P =.0001); median creatinine values decreased from 1.5 mg/dL at baseline to 1.1 mg/dL (P =.0001). VE LVAS-related adverse events included bleeding in 31 patients (11%), infection in 113 (40%), neurologic dysfunction in 14 (5%), and thromboembolic events in 17 (6%). A total of 160 (58%) patients were enrolled in a hospital release program. Twenty-nine percent of the VE LVAS-treated patients (82/280) died before receiving a transplant, compared with 67% of controls (32/48) (P <.001). Conversely, 71% of the VE LVAS-treated patients (198/280) survived: 67% (188/280) ultimately received a heart transplant, and 4% (10/280) had the device removed electively. One-year post-transplant survival of VE LVAS-treated patients was significantly better than that of the comparison group (84% patients were alive vs 63% p=.0197).

Authors' conclusions: The HeartMate VE LVAS provides adequate hemodynamic support, has an acceptably low incidence of adverse effects, and improves survival in heart transplant candidates both inside and outside the hospital. The studies of the HeartMate LVAS (both pneumatic and electric) for Food and Drug Administration approval are the only studies with a valid control group to show a survival benefit for cardiac transplantation.

CMS Comments: Performance of the LVAD outside of the hospital was one of the key points of this study and patients receiving the device consented to release from the hospital following implantation, if qualified. Qualifications included achieving a NYHA class of I or II. 115 of 228 potentially eligible patients achieved full outpatient status, while using an LVAD as a bridge to transplant. Forty-five additional patients were able to leave the hospital for day trips, but were not fully released. For the cohort of fully and partially released patients (n=160), 138 ultimately received a transplant, ten elected to have the LVAD removed without transplant and twelve died while awaiting transplant. Five of the explanted patients achieved myocardial recovery; four were explanted due to infection and one due to pump malfunction.

ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult – 2002 [TAB 12]

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Endorsed by the Heart Failure Society of America

Introduction: In formulating this document, the writing committee decided to take a new approach to the classification of heart failure (HF) that emphasized both the evolution and progression of the disease. In doing so, they identified four stages of HF.

Stage A identifies the patient who is at high risk for developing HF but has no structural disorder of the heart; stage B refers to a patient with a structural disorder of the heart but who has never developed symptoms of HF; stage C denotes the patient with past or current symptoms of HF associated with underlying structural heart disease; and stage D designates the patient with end-stage disease who requires specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care. Only the latter 2 stages, of course, qualify for the traditional clinical diagnosis of HF for diagnostic or coding purposes. This classification recognizes that there are established risk factors and structural prerequisites for the development of HF and that therapeutic interventions performed even before the appearance of left ventricular dysfunction or symptoms can reduce the morbidity and mortality of HF. This classification system is intended to complement but not to replace the New York Heart Association (NYHA) functional classification, which primarily gauges the severity of symptoms in patients who are in stage C or D.

It has been recognized for many years, however, that the NYHA functional classification reflects a subjective assessment by a physician and changes frequently over short periods of time and that the treatments used do not differ significantly across the classes. Therefore, the committee believed that a staging system was needed that would reliably and objectively identify patients in the course of their disease and would be linked to treatments that were uniquely appropriate at each stage of their illness. According to this new approach, patients would be expected to advance from one stage to the next unless progression of the disease was slowed or stopped by treatment. The purpose of this new classification scheme is to add a useful dimension to thinking about HF similar to that achieved by staging systems for other disorders (e.g., those used in the classification of cancer).

All recommendations provided in this document follow the format of previous ACC/AHA guidelines:

Class I: Conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful.

The recommendations listed in this document are evidence based whenever possible. Pertinent medical literature in the English language was identified through a series of computerized literature searches (including Medline and EMBASE) and a manual search of selected articles. References selected and published in this document are representative but not all-inclusive.

The levels of evidence on which these recommendations are based were ranked as level A if the data were derived from multiple randomized clinical trials, level B when data were derived from a single randomized trial or nonrandomized studies, and level C when the consensus opinion of experts was the primary source of recommendation. The strength of evidence does not necessarily reflect the strength of a recommendation. A treatment may be considered controversial although it has been evaluated in controlled clinical trials; conversely, a strong recommendation may be based on years of clinical experience and be supported only by historical data or by no data at all.

The ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult were approved for publication by the governing bodies of the ACC and AHA. These guidelines will be reviewed annually after publication and will be considered current unless the ACC/AHA Task Force on Practice Guidelines revises or withdraws them from circulation.

Recommendations for Patients With Refractory End-Stage HF (Stage D):

Class I

1. Meticulous identification and control of fluid retention. (*Level of Evidence: B*)

2. Referral for cardiac transplantation in eligible patients. (*Level of Evidence: B*)

3. Referral to an HF program with expertise in the management of refractory HF. (*Level of Evidence: A*)

4. Measures listed as class I recommendations for patients in stages A, B, and C. (*Levels of Evidence: A, B, and C as appropriate*).

Class IIb

1. Pulmonary artery catheter placement to guide therapy in patients with persistently severe symptoms. (*Level of Evidence: C*)

2. Mitral valve repair or replacement for severe secondary mitral regurgitation. (*Level of Evidence: C*)

3. Continuous intravenous infusion of a positive inotropic agent for palliation of symptoms. (*Level of Evidence: C*)

Class III

1. Partial left ventriculectomy. (*Level of Evidence: C*)

2. Routine intermittent infusions of positive inotropic agents. (*Level of Evidence: B*)

CMS Comments: The definition of the Stage D heart failure patient seems to be a good description of the patient for whom the LVAD may be used for destination therapy Unfortunately, these staging definitions do not appear to have attained wide usage in the two years since this document was published. At the time the guidelines were prepared, REMATCH had not been completed and no recommendations regarding the role of LVADs as destination therapy for end-stage heart failure are made. The authors state: "Cardiac transplantation is currently the only established surgical approach to the treatment of refractory HF…" There is a useful table of the indications for cardiac transplant on page 30. There is also a section on the end of life considerations (pp 38-39) related specifically to heart failure.

Listing Criteria for Cardiac Transplantation [TAB 13]

Report of one of a series of American Society of Transplant Physicians—National Institutes of Health conferences for purposes of developing guidelines for inclusion on a transplantation list. A discussion of the relative indications for surgery, necessary testing to make the determination and effects of such factors as pulmonary hypertension, age, psychosocial and other comorbid conditions, which should be considered when determining the need for transplantation. Although this is a 1998 document it is a relatively concise treatment of the major issues that need to be considered.

CMS Policy Regarding Heart Transplantation, CIM policy 35-87 [TAB 14]

Federal Register Notice: Criteria for Medicare Coverage of Heart Transplants: 52 FR 10935, April 6, 1987 [TAB 15]

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Listing Criteria for Cardiac Transplantation: Results of an American Society of Transplant Physicians-National Institutes of Health Conference (Transplantation. 66(7):947-51) **[Tab 13]**

CMS Policy Regarding Heart Transplantation, CIM policy 35-87 **[Tab 14]**

Criteria for Medicare Coverage of Heart Transplants, 52 FR 10935, April 6, 1987 (Section pertaining to criteria for Medicare coverage of heart transplants) **[Tab 15]**