

CHAPTER 1

ADVANCED HEART FAILURE

EPIDEMIOLOGY

Epidemiological Scope

Epidemiological Transition. In less industrialized countries, the epidemiological transition is associated with a reduced risk of mortality from communicable diseases and an increased risk of death from cardiovascular diseases, including heart failure (Redfield, 2002; Cappuccio, 2004). Improved management of acute coronary syndromes and improved longevity of the population have resulted in a growing number of patients with heart failure. In industrialized countries, the prevalence and incidence of heart failure are estimated to be around 1.5% and 0.15% of the population, respectively (Hunt *et al.*, 2005; Deng, 2002). An estimated 10% of persons with heart failure are in advanced stages. In the United States and Europe alone, with >700 million inhabitants and >7 million patients with heart failure, the prevalence of advanced heart failure — constituting between 1%–10% of the heart failure population — is estimated to total between 70 000 and 700 000 patients (Deng, 2005).

Evolution of Treatment Options. Correspondingly, the evolution of treatment options for advanced heart failure patients over the last few decades has been impressive. It includes medical treatment (angiotensin-converting enzyme inhibitors, beta-blockade), defibrillator therapy, heart transplantation, and most recently mechanical circulatory support devices (MCSDs). The comparison of outcomes between different therapies for advanced heart failure is challenging. For example, heart transplantation has never been tested in a randomized clinical trial because of the obvious survival advantage in the 1970s in comparison to medical therapy, which has been questioned during the last decade. Therefore, the clinical decision-making

algorithm is subject to continuing debate and consensus processes, as exemplified by the recent guideline development initiative of the International Society for Heart and Lung Transplantation (Mehra *et al.*, 2006).

Classification and Staged Therapy of Advanced Heart Failure

Definition. The terminology of chronic heart failure in its advanced stages is not very precise. The terms “advanced”, “severe”, “congestive”, “refractory”, and “end-stage” heart failure are used in largely interchangeable ways. End-stage heart failure reflects the impaired prognosis associated with it, and has been incorporated into the recent staging system for heart failure (Hunt *et al.*, 2001; Hunt *et al.*, 2005). However, the term advanced heart failure will be used in this book to express the more recent insight into the partial reversibility of the heart failure remodeling process.

Classification. The New York Heart Association (NYHA) classification of heart failure has been complemented by a staging system of heart failure (Hunt *et al.*, 2001; Hunt *et al.*, 2005). This staging system has the advantages of including asymptomatic stages (risk factors, structural heart disease) and reflecting the progressive nature of the heart failure syndrome. It bears a resemblance with the classification of tumors, a similarly malignant group of conditions (Fig. 1).

Prognosis of Advanced Heart Failure

Epidemiological Data. The contemporary incidence and prognosis of heart failure are not well known. To describe the survival of a population-based cohort of patients with incident, i.e. new-onset heart failure and the clinical features associated with mortality, an observational study was conducted in a population of 151 000 served by 82 general practitioners in west London. New cases of heart failure were identified by daily surveillance of acute hospital admissions to the local district general hospital, and by general practitioner referral of all suspected new cases of heart failure to a rapid access clinic. All patients with suspected heart failure underwent clinical assessment; and chest radiography, ECG, and echocardiogram were

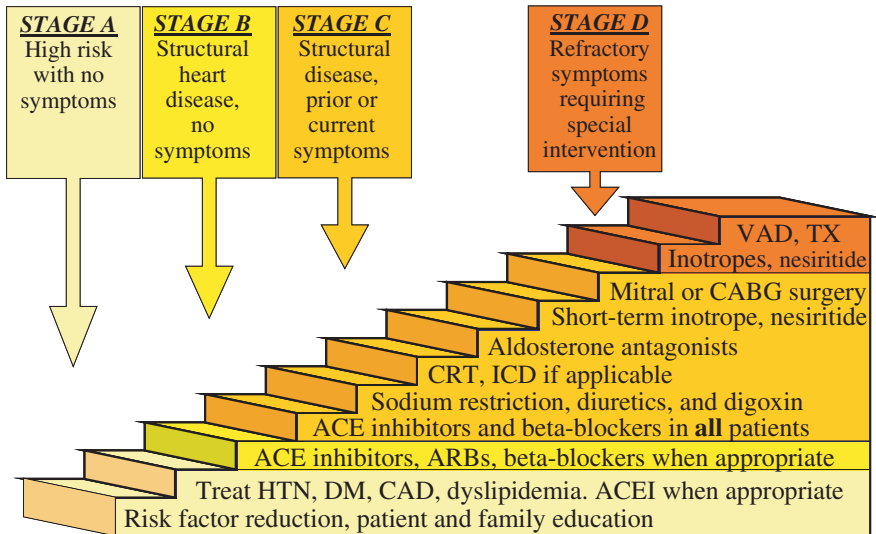


Fig. 1. Staging of heart failure and associated interventions (adapted from Hunt *et al.*, 2005).

performed. A panel of three cardiologists reviewed all the data and determined whether the definition of heart failure had been met. Patients were subsequently managed by the general practitioner in consultation with the local cardiologist or admitting physician. Death, overall and from cardiovascular causes, served as the main outcome measure.

There were 90 deaths (83 cardiovascular deaths) in the cohort of 220 patients with incident heart failure over a median follow-up of 16 months. Survival was 81% at 1 month, 75% at 3 months, 70% at 6 months, 62% at 12 months, and 57% at 18 months. Lower systolic blood pressure, higher serum creatinine concentration, and greater extent of crackles on auscultation of the lungs were independently predictive of cardiovascular mortality (all $p < 0.001$). The authors concluded that mortality is high in the first few weeks after diagnosis for patients with new heart failure, and that simple clinical features can identify patients at especially high risk of death (Cowie *et al.*, 2000).

Response to Therapy and Prognosis. Class IV symptoms predict high mortality rates, but the outcome is not known for patients who improve

to establish freedom from congestion. Revised estimates at 1 month could facilitate decisions regarding transplantation and other high-risk interventions. A UCLA/Harvard study determined whether evidence of congestion after 4 to 6 weeks of heart failure management predicted the outcome for patients hospitalized with chronic New York Heart Association class IV symptoms. At 4 to 6 weeks after hospital discharge, 146 patients were evaluated for congestion by five criteria (orthopnea, jugular venous distention, edema, weight gain, and new increase in baseline diuretics). Heart failure management included inpatient therapy tailored to relieve congestion, followed by adjustments to maintain fluid balance during the next 4 weeks.

Freedom from congestion was demonstrated at 4 to 6 weeks in 80 (54%) patients, who subsequently had 87% 2-year survival compared with 67% in 40 patients with 1 or 2 criteria of congestion and 41% in 26 patients with 3 to 5 criteria. The Cox proportional hazards model identified left ventricular dimension, pulmonary wedge pressure on therapy, and freedom from congestion as independent predictors of survival. The persistence of orthopnea predicted 38% 2-year survival (without urgent transplantation) versus 77% in 113 patients without orthopnea. Serum sodium was lower and blood urea nitrogen and heart rate were higher when orthopnea persisted. The authors concluded that the ability to maintain freedom from congestion identifies a population with good survival despite previous class IV symptoms. At 4 to 6 weeks of heart failure management, patients with persistent congestion may be considered for high-risk intervention (Lucas *et al.*, 2000).

MANAGEMENT OVERVIEW

Ted L
(born 1943)

**Living with
heart failure:
preoperative
perspective**

My Early Years

I was born with a congenital heart disease that kept me from keeping up with my little playmates. But as I reached my high school years, I began to outgrow the problem and went on to enjoy college intramural sports and upon graduation skiing, squash, sky diving, and golf.

After graduating from Rollins College, I went to Wall Street to make my fame and fortune. I spent 20 hectic years in a bond-trading room, jumping up and down,

yelling “buy!” “sell!” “you’re done!” Then, I spent 16 years working as a financial planner with individuals and their corporations to develop a plan to cover all of life’s contingencies.

During this time, in 1973, I met Trina Richner and within 5 weeks we were engaged. Since I had not seen a heart specialist in 20 years, I thought it best to get an updated diagnosis for my future bride and myself. Dr Steve Scheidt at New York Presbyterian Hospital–Cornell Medical Center was recommended to me, and I spent several days undergoing diagnostic tests. His conclusion: I had a form of cardiomyopathy called idiopathic hypertrophic subaortic stenosis — an enlarged heart muscle. But since I was asymptomatic, there was little I needed to do. I had annual checkups with him for the next 20 odd years.

My Medical Journey

In the early 1990s, I experienced my first heart problem: dizzy spells and skipped heart beats. Over the next decade, my cardiologist mixed and matched various medications as the problems grew progressively worse. By early 2003, I knew I was really in trouble as I was having difficulty walking a New York City block, having to stop four or five times to catch my breath. I developed the typical symptoms of a person with chronic heart failure. I had shortness of breath and edema that was particularly obvious when one looked at my ankles. Dr Steve Scheidt came to the conclusion that I should have a consultation with a leading heart specialist in cardiomyopathy, Dr Barry Maron at the Minneapolis Heart Institute. In May 2003, I spent a day undergoing tests with his team of six, and late in the afternoon we convened in his office to hear the results.

Let me read a few sentences from a recent correspondence of his.

Dear Ted ... I often think about the day of our consultation and how awkward I felt about hitting you with such bad news that I know you didn’t expect ... and using such severe medical terms as “end-stage hypertrophic cardiomyopathy” to emphasize the

point that you needed to move fast . . . which you did . . . fortunately. Best Regards, Barry Maron.

I only had one question for Dr Maron: “The words ‘end-stage’ don’t sound good to me. Just what are you telling me?” “Ted, you have 6 months to a year to live with that heart of yours.”

Within a week upon return, I was interviewed by members of the Columbia Presbyterian Hospital’s heart transplant team. I was told that I would make a good transplant candidate, but at that moment I was too healthy to be put on the heart transplant list. They would be most happy to follow my case. In 5 days, I went from “go home, move fast, you are dying and need a heart transplant” to “you’re too healthy to be put on the list.” Go figure!

At first I got mad, then I got angry and went into denial. But reality finally came upon me, and I began to ask God “why me?” Hadn’t I spent the last 20 years as an active member of my church being as good a Christian as I could? I was even helping my community by serving on my cooperative building’s Board of Trustees.

I also began to question my own body. Why had my body suddenly deserted me? For my entire life, my heart, mind, and body had all gone along together. If something bad happened to me, my body took care of it. Now, it was going off in a different direction and I had no control over it.

I began an emotional journey that has continued to this day. Once I began to learn about organ transplantation, I found that one out of three persons die while waiting for a new heart. Would I live long enough to get a new heart? I felt sorry for myself. Would the new heart take if I got one? How would it work? How long would it last? I thought a lot about my wife. If I died, was I leaving her in good financial shape? Who would she turn to for help? We had to make plans together.

One day, I came to the sudden realization that for me to live someone else had to die. I had been praying for God

to get me a new heart from the beginning, but I couldn't imagine asking God to have someone else die so that I could live. I came around to the realization that if God wanted me to live, then he had a plan for me. What was it? If I was to get a new heart, what did he want me to do with it? That began a dialog between us that has continued right up to the present.

Dr Maron was right. My heart deteriorated rapidly to the point where I was having trouble walking from my bedroom to my kitchen by March 2004. Due to chronic heart failure, my body filled with 30 pounds of fluid surrounding my heart, lungs, and other bodily functions. It was most pronounced to the casual observer in my very swollen ankles.

Clinical Presentation and Pathophysiology of Heart Failure

The introduction of newer modes of therapy into medical practice, and into the management of heart failure in particular, requires continuous evaluation of evidence according to established criteria. The distinction between evidence based on randomized clinical trials, all-or-none studies, outcomes research, cohort studies, case-control studies, case series, and investigational procedures allows differentiating between different levels of enthusiasm for clinical recommendations (http://www.cebm.net/levels_of_evidence.asp).

Definition. Chronic heart failure is defined as a clinical syndrome in which, secondary to impaired function of the heart, a performance commensurate with the metabolic needs of the body cannot be maintained or can only be maintained at the expense of elevated filling pressures of the left and right ventricles (Braunwald, 1992).

Compensatory Mechanisms. In increasing stages of heart failure, the adrenergic system, renin-angiotensin system, antidiuretic hormone system, and atrial natriuretic peptide system are chronically activated. These

chronic neurohormonal changes lead to compensatory elevation of afterload, preload, heart rate, contractility, and cardiac hypertrophy. The New York Heart Association functional class IV is characterized by a flattening and rightward shift of the cardiac function curve to the point where reduced cardiac output does not fulfill the metabolic requirements of the body, capillary wedge pressure reaches a level at which pulmonary edema ensues, or both happen (Braunwald, 2002).

Maladaptive Nature of Chronic Neurohormonal Activation. The discovery that neurohormonal mechanisms can exert a detrimental effect in individuals with advanced heart failure brings up the question of their evolutionary role. These mechanisms evolved for situations that coincide with acute volume losses in otherwise healthy persons. Of highest priority in these situations would be the maintenance of an adequate cardiac output, peripheral vascular resistance, and arterial perfusion pressure as well as consecutive regulation of blood volume. A temporary activation of the described neurohormonal mechanisms with intact cardiac function presumably does not initiate the vicious cycle encountered in heart failure. While an evolutionary optimization of acute cardiovascular regulation must be assumed, there is no need for optimization of regulatory mechanisms in chronic heart failure because it usually manifests beyond the reproductive age (Braunwald, 1992).

Specific Underlying Disease Conditions in Heart Failure

Cardiomyopathy WHO Classification. The 1995 World Health Organization classification of cardiomyopathies distinguishes between the following:

- dilated cardiomyopathies (ischemic and nonischemic);
- hypertrophic cardiomyopathies;
- restrictive cardiomyopathies;
- arrhythmogenic right ventricular cardiomyopathies;
- specific cardiomyopathies; and
- unclassified cardiomyopathies (Richardson *et al.*, 1996).

Giant Cell Myocarditis. Among the unclassified cardiomyopathies is myocarditis. Among the group of myocarditis, the entity of giant cell myocarditis is the rarest but most devastating disease that usually affects young, otherwise healthy individuals. Associations with thymoma, inflammatory bowel disease, and a variety of autoimmune disorders have been reported. The rate of death or heart transplantation is approximately 70% at 1 year. Data from a Lewis rat model and from observational human studies suggest that giant cell myocarditis is mediated by T lymphocytes, and may respond to treatment aimed at attenuating T-cell function.

Recent findings from the Giant Cell Myocarditis Registry, a clinical and pathological database from 63 cases of giant cell myocarditis gathered from 36 medical centers, include the following: the sensitivity of endomyocardial biopsy for giant cell myocarditis for patients who undergo transplantation or autopsy is 82% to 85%. Registry subjects who received cyclosporine in combination with steroid, azathioprine, or muromonab-CD3 have prolonged transplant-free survival (12.6 months vs. 3.0 months for no immunosuppression). Posttransplantation survival is approximately 71% at 5 years, despite a 25% rate of giant cell infiltration in the donor heart. To confirm and extend these findings, randomized trials of immunosuppression included muromonab-CD3, cyclosporine, and steroids (Cooper *et al.*, 1997; Cooper, 2000).

Other Forms of Myocarditis/Heart Muscle Disease. There has been controversy over the extent to which patients with unclassified dilated cardiomyopathies should undergo diagnostic endomyocardial biopsy testing. In a series of 100 consecutive patients, the pathological diagnostic information obtained was judged to be useful to the clinician in 54 patients and not useful in 46 patients. In 74 patients with congestive heart failure of unknown etiology and a dilated heart, useful pathological diagnoses included myocarditis, vasculitis, doxorubicin cardiomyopathy, and congestive cardiomyopathy. In most of the patients with biopsy findings of myocarditis, there were no other clinical or laboratory findings indicating the presence of this disease, and the diagnosis of myocarditis would have been overlooked without a biopsy. In 26 patients in whom there was clinical evidence of constrictive or restrictive cardiovascular physiological characteristics, useful biopsy diagnoses included radiation-induced

cardiomyopathy, endomyocardial fibrosis, amyloidosis, or no myocardial disease; in the patients without myocardial disease, thoracotomies were performed for constrictive pericarditis. Transvenous endomyocardial biopsy can provide clinically useful information in the evaluation of diseases of the myocardium. The Dallas classification of myocarditis is based on EMB findings (Aretz *et al.*, 1987).

Risk Stratification in Advanced Heart Failure

Risk stratification of patients with end-stage congestive heart failure is a critical component of the selection process for the best treatment; for example, if the choice between optimal medical therapy, heart transplantation, or chronic mechanical circulatory support has to be made. Accurate identification of individuals most likely to survive without a transplant would facilitate more efficient use of scarce donor organs.

Heart Failure Survival Score (HFSS). In a landmark collaboration between the University of Pennsylvania and Columbia University from 1987 to 1995, multivariable proportional hazards survival models were developed with the use of data on 80 clinical characteristics from 268 ambulatory patients with advanced heart failure (derivation sample). Invasive and noninvasive models (with and without catheterization-derived data) were constructed. A prognostic score was determined for each patient from each model. Stratum-specific likelihood ratios were used to develop three prognostic-score risk groups. The models were prospectively validated on 199 similar patients (validation sample) by calculation of the area under the receiver operating characteristic curve for 1-year event-free survival, the censored c-index for event-free survival, and comparison of event-free survival curves for prognostic-score risk strata. Outcome events were defined as urgent transplant or death without transplant.

The noninvasive model performed well in both samples, and increased performance was not attained by the addition of catheterization-derived variables. Prognostic-score risk groups derived from the noninvasive model in the derivation sample effectively stratified the risk of an outcome event in both samples (1-year event-free survival for derivation and validation samples, respectively: low risk, 93% and 88%; medium risk, 72% and 60%;

high risk, 43% and 35%). The authors concluded that the selection of candidates for cardiac transplantation may be improved by use of this noninvasive risk stratification model (Aaronson *et al.*, 1997). The beauty of this score resides not only in its powerful predictive value, but also in its easy bedside implementation by the equation $HFSS = [(0.69 \times CAD: YES = 1; NO = 0) + (0.022 \times HR) + (-0.046 \times LVEF) + (-0.026 \times mBP) + (0.61 \times IVCD: YES = 1; NO = 0) + (-0.055 \times VO_2) + (-0.047 \times Na)]$.

Heart failure has an annual mortality rate ranging from 5% to 75%. The purpose of the Seattle Heart Failure Model study was to develop and validate a multivariate risk model to predict 1-, 2-, and 3-year survival in heart failure patients with the use of easily obtainable characteristics relating to clinical status, therapy (pharmacological as well as device), and laboratory parameters. The Seattle Heart Failure Model was derived in a cohort of 1125 heart failure patients with the use of a multivariate Cox model. For medications and devices not available in the derivation database, hazard ratios were estimated from published literature. The model was prospectively validated in five additional cohorts totaling 9942 heart failure patients and 17 307 person-years of follow-up.

The accuracy of the model was excellent, with respective predicted versus actual 1-year survival rates of 73.4% vs. 74.3% in the derivation cohort and 90.5% vs. 88.5%, 86.5% vs. 86.5%, 83.8% vs. 83.3%, 90.9% vs. 91.0%, and 89.6% vs. 86.7% in the five validation cohorts. For the lowest score, the 2-year survival was 92.8% compared with 88.7%, 77.8%, 58.1%, 29.5%, and 10.8% for scores of 0, 1, 2, 3, and 4, respectively. The overall receiver operating characteristic area under the curve was 0.729 (95% CI, 0.714 to 0.744). The model also allowed estimation of the benefit of adding medications or devices to an individual patient's therapeutic regimen. The authors concluded that the Seattle Heart Failure Model provides an accurate estimate of 1-, 2-, and 3-year survival with the use of easily obtained clinical, pharmacological, device, and laboratory characteristics (Levy *et al.*, 2002).

Behavioral Interventions in Advanced Heart Failure

Randomized Clinical Trials. The management of patients with heart failure, independent of the specific types of interventions anticipated, improves

with multidisciplinary, patient-oriented, flexible care (Fonarow *et al.*, 1997; Shah *et al.*, 1998; Philbin, 1999). Since behavioral factors, such as poor compliance with treatment, frequently contribute to exacerbations of heart failure, a prospective randomized trial of the effect of a nurse-directed multidisciplinary intervention on rates of readmission within 90 days of hospital discharge, quality of life, and costs of care for high-risk patients 70 years of age or older who were hospitalized with congestive heart failure was conducted by Rich *et al.* (1995). The intervention consisted of comprehensive education of the patient and family, a prescribed diet, social service consultation and planning for an early discharge, a review of medications, and intensive follow-up.

Survival for 90 days without readmission, the primary outcome measure, was achieved in 91 of the 142 patients in the treatment group, as compared with 75 of the 140 patients in the control group who received conventional care ($P = 0.09$). There were 94 readmissions in the control group and 53 in the treatment group (risk ratio, 0.56; $P = 0.02$). The number of readmissions for heart failure was reduced by 56.2% in the treatment group (54 vs. 24, $P = 0.04$), whereas the number of readmissions for other causes was reduced by 28.5% (40 vs. 29, P not significant). In the control group, 23 (16.4%) patients had more than one readmission, as compared with 9 (6.3%) patients in the treatment group (risk ratio, 0.39; $P = 0.01$). In a subgroup of 126 patients, quality-of-life scores at 90 days improved more from baseline for patients in the treatment group ($P = 0.001$). Because of the reduction in hospital admissions, the overall cost of care was \$460 less per patient in the treatment group. It was concluded that a nurse-directed, multidisciplinary intervention can improve quality of life and reduce hospital admission and medical costs for elderly patients with congestive heart failure (Rich *et al.*, 1995).

Pharmacological Treatment

Randomized Clinical Trials of Renin-Angiotensin System Blockade.

The first randomized prospective medical trial demonstrating a survival benefit from medical treatment in advanced heart failure was the CONSENSUS I trial (Swedberg, 1987). A total of 256 patients in NYHA class

IV heart failure were randomized to either enalapril or placebo. While the 1-year placebo mortality rate was 64%, it was reduced to 46% in the enalapril group. At 10-year follow-up, five patients, all in the enalapril group, were long-term survivors ($P = 0.004$). This study is unique in that it was the first heart failure trial not only in unselected NYHA class IV patients, but also in examining extended survival (Swedberg *et al.*, 1999).

In the RALES trial, 1663 patients who had severe heart failure and a left ventricular ejection fraction of $<35\%$, and who were being treated with an angiotensin-converting enzyme inhibitor, a loop diuretic, and in most cases digoxin, were randomly assigned to receive 25 mg of spironolactone daily or placebo. After a mean follow-up period of 24 months, there was a 46% mortality rate in the placebo group and a 35% mortality rate in the spironolactone group (Pitt *et al.*, 1999). The angiotensin II type 1 receptor blocker valsartan significantly reduced the combined endpoint of mortality and morbidity, and improved clinical signs and symptoms in patients with heart failure. However, the *post hoc* observation of an adverse effect on mortality and morbidity in the subgroup receiving valsartan, an ACE inhibitor, and a beta-blocker raised concern about the potential safety of this specific combination (Cohn and Tognoni, 2001).

To determine whether the angiotensin receptor blocker (ARB) candesartan decreases cardiovascular mortality, morbidity, and all-cause mortality in patients with CHF and depressed LVEF, a prespecified analysis of the combined Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM) low-LVEF trials was performed. CHARM is a randomized, double-blind, placebo-controlled, multicenter, international trial program. The New York Heart Association (NYHA) class II through IV CHF patients with an LVEF of $\leq 40\%$ were randomized to candesartan or placebo in two complementary parallel trials (CHARM-Alternative, for patients who could not tolerate ACE inhibitors; and CHARM-Added, for patients who were receiving ACE inhibitors).

Mortality and morbidity were determined in 4576 low-LVEF patients (2289 on candesartan and 2287 on placebo), titrated as tolerated to a target dose of 32 mg once daily, and observed for 2 to 4 years (median, 40 months). The primary outcome (time to first event by intention to treat) was cardiovascular death or CHF hospitalization for each trial, with all-cause mortality a secondary endpoint in the pooled analysis of the low-LVEF

trials. Of the 2289 patients in the candesartan group, 817 (35.7%) experienced cardiovascular death or CHF hospitalization as compared with 944 (41.3%) in the placebo group (HR, 0.82; 95% CI, 0.74 to 0.90; $P < 0.001$), with reduced risk for both cardiovascular deaths [521 (22.8%) vs. 599 (26.2%); HR, 0.84 (95% CI, 0.75 to 0.95); $P = 0.005$] and CHF hospitalizations [516 (22.5%) vs. 642 (28.1%); HR, 0.76 (95% CI, 0.68 to 0.85); $P < 0.001$]. It is important to note that all-cause mortality was also significantly reduced by candesartan [642 (28.0%) vs. 708 (31.0%); HR, 0.88 (95% CI, 0.79 to 0.98); $P = 0.018$]. No significant heterogeneity for the beneficial effects of candesartan was found across pre-specified and subsequently identified subgroups, including treatment with ACE inhibitors, beta-blockers, an aldosterone antagonist, or their combinations. The study drug was discontinued because of adverse effects exhibited by 23.1% of patients in the candesartan group and 18.8% in the placebo group, such as increased creatinine (7.1% vs. 3.5%, respectively), hypotension (4.2% vs. 2.1%), and hyperkalemia (2.8% vs. 0.5%) (all $P < 0.001$).

The authors concluded that candesartan significantly reduces all-cause mortality, cardiovascular death, and heart failure hospitalizations in patients with CHF and LVEF of $\leq 40\%$ when added to standard therapies including ACE inhibitors, beta-blockers, and an aldosterone antagonist. Routine monitoring of blood pressure, serum creatinine, and serum potassium is warranted (Young *et al.*, 2004). The accompanying editorial concluded that angiotensin II receptor blockers are now a reasonable alternative to angiotensin-converting enzyme (ACE) inhibitors as first-line agents for HF. Angiotensin II receptor blockers or ACE inhibitors are useful to prevent HF in selected stage A and B patients (Fig. 1), and candesartan can improve outcomes in patients with impaired cardiac function who are intolerant of ACE inhibitors (Young *et al.*, 2004).

Randomized Clinical Trials of Adrenergic System Blockade. The MERIT Study Group (1999) investigated whether metoprolol controlled release/extended release (CR/XL) once daily, in addition to standard therapy, would lower mortality in patients with decreased ejection fraction and symptoms of heart failure. The MERIT Study Group enrolled 3991

patients with chronic heart failure in New York Heart Association (NYHA) functional class II–IV and with ejection fraction of 0.40 or less, stabilized with optimum standard therapy, in a double-blind randomized controlled study. Randomization was preceded by a 2-week single-blind placebo run-in period. Of the 3991 patients, 1990 were randomly assigned metoprolol CR/XL 12.5 mg (NYHA III–IV) or 25.0 mg once daily (NYHA II), and 2001 were assigned placebo. The target dose was 200 mg once daily, and doses were uptitrated over 8 weeks. The primary endpoint was all-cause mortality, analyzed by intention to treat. The study was stopped early on the recommendation of the independent safety committee. The mean follow-up time was 1 year.

All-cause mortality was lower in the metoprolol CR/XL group than in the placebo group [145 (7.2% per patient-year of follow-up) vs. 217 deaths (11.0%), relative risk 0.66 (95% CI 0.53–0.81); $p = 0.00009$ or adjusted for interim analyses $p = 0.0062$]. There were fewer sudden deaths in the metoprolol CR/XL group than in the placebo group [79 vs. 132, relative risk 0.59 (95% CI 0.45–0.78); $p = 0.0002$], and fewer deaths from worsening heart failure [30 vs. 58, relative risk 0.51 (95% CI 0.33–0.79); $p = 0.0023$]. The authors concluded that metoprolol CR/XL once daily, in addition to optimum standard therapy, improves survival. The drug was well tolerated (MERIT, 1999).

The CIBIS-II Study Group (1999) investigated the efficacy of bisoprolol, a beta1-selective adrenoceptor blocker, in decreasing all-cause mortality in chronic heart failure. In a multicenter double-blind randomized placebo-controlled trial in Europe, they enrolled 2647 symptomatic patients in New York Heart Association class III or IV with a left ventricular ejection fraction of 35% or less that were receiving standard therapy with diuretics and angiotensin-converting enzyme inhibitors. They randomly assigned patients bisoprolol 1.25 mg ($n = 1327$) or placebo ($n = 1320$) daily, the drug being progressively increased to a maximum of 10 mg per day. Patients were followed up for a mean of 1.3 years. Analysis was by intention to treat. CIBIS-II was stopped early, after the second interim analysis, because bisoprolol showed a significant mortality benefit.

All-cause mortality was significantly lower with bisoprolol than with placebo [156 (11.8%) vs. 228 (17.3%) deaths, with a hazard ratio of 0.66

(95% CI 0.54–0.81, $p < 0.0001$)]. There were significantly fewer sudden deaths among patients on bisoprolol than in those on placebo [48 (3.6%) vs. 83 (6.3%) deaths, with a hazard ratio of 0.56 (95% CI 0.39–0.80, $p = 0.0011$)]. Treatment effects were independent of the severity or cause of heart failure. The authors concluded that beta-blocker therapy has benefits for survival in stable heart failure patients (CIBIS-II, 1999).

The COPERNICUS trial demonstrated beneficial effects on mortality in NYHA class IV patients with chronic heart failure. In this trial, the placebo 1-year mortality rate of 19.6% was reduced to 11% by carvedilol. All subgroups, including those with the most advanced heart failure, showed the same beneficial direction of effect (Packer *et al.*, 2001). The Carvedilol or Metoprolol European Trial (COMET) reported a significant survival benefit for carvedilol — a beta1-, beta2-, and alpha1-blocker — vs. metoprolol tartrate — a beta1-selective blocker — in patients with mild-to-severe chronic heart failure (Poole-Wilson *et al.*, 2003).

Randomized Clinical Trials of Positive Inotropes/Vasodilators. Trials using positive inotropes such as vesnarinone (Feldman *et al.*, 1993; Cohn *et al.*, 1998), xamoterol (Ryden, 1990), ibopamine (Hampton *et al.*, 1997) and milrinone (Packer *et al.*, 1991) or vasodilators such as epoprostenol did not demonstrate a survival benefit; in fact, they showed an adverse mortality effect (Califf *et al.*, 1997). Over the past few years, a large clinical development program with the phosphodiesterase III inhibitor enoximone has yielded promising preliminary results during periods of concomitant cardioprotection with beta-blockers and ICDs. The phase II results of the Oral Enoximone in Intravenous Inotrope-Dependent Subjects (EMOTE) study showed promise (Lowe *et al.*, 2005).

However, the phase III Studies of Oral Enoximone Therapy in Advanced Heart Failure (ESSENTIAL) trials demonstrated a lack of statistically significant differences in all predefined endpoints (Cleland *et al.*, 2005). Time to all-cause mortality and time to first cardiovascular hospitalization were similar in the enoximone and placebo study groups (hazard ratios 0.97 and 0.98, respectively). Interestingly, both all-cause mortality and mortality or cardiovascular hospitalization rates were lower with enoximone in the last one-half of follow-up (beyond 16.4 months)

(5.4% with enoximone vs. 8.8% with placebo, $p = 0.045$; and 12.5% with enoximone vs. 17.4% with placebo, $p = 0.09$). Furthermore, patients with LVEF $<20\%$ had greater improvement in 6-min walk test distance in the enoximone group. High hopes are also being placed on the results of two phase III trials of another inodilator drug, levosimendan: “Survival in Patients with Acute Heart Failure in Need of Intravenous Inotropic Support” (SURVIVE) and “Second Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy vs. Survival in the Short Term Treatment of Decompensated Heart Failure” (REVIVE-II) (Cleland *et al.*, 2006).

Randomized Clinical Trials of Antiarrhythmics in Ventricular Tachyarrhythmias. Sudden death accounts for one third to one half of the deaths in patients with heart failure. With respect to antiarrhythmic treatment, class I antiarrhythmic drugs have been disappointing. Amiodarone and beta-blockers are the only interventions that have not been shown to increase mortality risks in patients with congestive heart failure. The GESICA trial evaluated the effect of low-dose amiodarone on 2-year mortality in patients with severe heart failure. This prospective multicenter trial included 516 patients on optimal standard treatment for heart failure. Patients were randomized to 300 mg/day amiodarone (260 patients) or to standard treatment (256 patients). Intention-to-treat analysis showed 87 deaths in the amiodarone group (33.5%) compared with 106 in the control group (41.4%) ($p = 0.024$) (Doval *et al.*, 1994).

The CHF-STAT investigators used a double-blind, placebo-controlled protocol, in which 674 patients with symptoms of congestive heart failure, cardiac enlargement, 10 or more premature ventricular contractions per hour, and a left ventricular ejection fraction of 40% or less were randomly assigned to receive amiodarone (336 patients) or placebo (338 patients). There was no significant difference in overall mortality between the two treatment groups ($P = 0.6$). The 2-year actuarial survival rate was 69.4% for the patients in the amiodarone group and 70.8% for those in the placebo group. There was a trend toward a reduction in overall mortality among the patients with nonischemic cardiomyopathy who received amiodarone (Singh *et al.*, 1995). Recent studies using beta-adrenergic blockers in patients with reduced systolic function and heart failure symptoms have

shown significant reductions in overall mortality rates, with a combined relative risk reduction for sudden death of 38% (Teerlink and Massie, 2000).

Resynchronization

Randomized Clinical Trials. A growing body of evidence suggests that the use of implantable devices to resynchronize ventricular contraction may be a beneficial adjunct in the treatment of chronic heart failure. One third of patients with chronic heart failure have electrocardiographic evidence of a major intraventricular conduction delay, which may worsen left ventricular systolic dysfunction through asynchronous ventricular contraction. Uncontrolled studies suggest that multisite biventricular pacing improves hemodynamics and well-being by reducing ventricular asynchrony.

The MUSTIC trial assessed the clinical efficacy and safety of this new therapy. Sixty-seven patients with severe heart failure (New York Heart Association class III) due to chronic left ventricular systolic dysfunction, with normal sinus rhythm and a QRS-interval duration of more than 150 ms, received transvenous atrioventricular pacemakers (with leads in one atrium and each ventricle). This single-blind, randomized, controlled cross-over study compared the responses of the patients during two periods: a 3-month period of inactive pacing (ventricular inhibited pacing at a basic rate of 40 bpm), and a 3-month period of active (atrioventricular) pacing. The mean distance walked in 6 min was 22% greater with active pacing (399 ± 100 m vs. 326 ± 134 m, $P < 0.001$), the quality-of-life score improved by 32% ($P < 0.001$), peak oxygen uptake increased by 8% ($P < 0.03$), hospitalizations decreased by two thirds ($P < 0.05$), and active pacing was preferred by 85% of the patients ($P < 0.001$) (Cazeau *et al.*, 2001).

In the MIRACLE trial, the first parallel-group randomized evaluation of the efficacy of cardiac resynchronization in patients with NYHA class III–IV heart failure and a QRS duration of >130 ms, 266 patients received the Medtronic InSync device and were then randomized to resynchronization vs. no resynchronization for 6 months while background medication was maintained. The clinical composite score was defined as the

primary endpoint, which characterized patients as improved (if they showed improvement in NYHA class or patient global assessment), unchanged, or worse (if they died, had worsening heart failure leading to hospitalization or discontinuation of treatment, or had worse NYHA class or global assessment). More patients improved (63% vs. 38%) and fewer patients deteriorated (22% vs. 29%) in the group with the activated device as compared to the control group (Packer and Abraham, 2001).

The Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial was a randomized, open-label, three-arm study of patients with New York Heart Association class III or IV heart failure, an ejection fraction of 35% or less, and a QRS duration of >120 ms. The COMPANION study objectives were to determine whether optimal pharmacological therapy used with (1) ventricular resynchronization therapy alone or (2) ventricular resynchronization therapy combined with cardioverter-defibrillator capability is superior to optimal pharmacological therapy alone in reducing combined all-cause mortality and in modifying other endpoints (Bristow *et al.*, 2000). A total of 1520 patients who had advanced heart failure (New York Heart Association class III or IV) due to ischemic or nonischemic cardiomyopathies and a QRS interval of at least 120ms were randomly assigned in a 1:2:2 ratio to receive optimal pharmacological therapy (diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, and spironolactone) alone or in combination with cardiac resynchronization therapy with either a pacemaker or a pacemaker/defibrillator. The primary composite endpoint was the time to death from or hospitalization for any cause.

Compared to optimal pharmacological therapy alone, cardiac resynchronization therapy with a pacemaker decreased the risk of the primary endpoint (hazard ratio, 0.81; $P = 0.014$), as did cardiac resynchronization therapy with a pacemaker/defibrillator (hazard ratio, 0.80; $P = 0.01$). The risk of the combined endpoint of death from or hospitalization for heart failure was reduced by 34% in the pacemaker group ($P < 0.002$) and by 40% in the pacemaker/defibrillator group ($P < 0.001$ for the comparison with the pharmacological therapy group). A pacemaker reduced the risk of the secondary endpoint of death from any cause by 24% ($P = 0.059$), and a pacemaker/defibrillator reduced the risk by 36% ($P = 0.003$). The authors

concluded that for patients with advanced heart failure and a prolonged QRS interval, cardiac resynchronization therapy decreases the combined risk of death from any cause or first hospitalization and, when combined with an implantable defibrillator, significantly reduces mortality (Bristow *et al.*, 2004).

In the Cardiac Resynchronization Heart Failure (CARE-HF) study, patients with New York Heart Association class III or IV heart failure due to left ventricular systolic dysfunction and cardiac dyssynchrony who were receiving standard pharmacological therapy were randomly assigned to receive medical therapy alone or with cardiac resynchronization. The primary endpoint was the time to death from any cause or an unplanned hospitalization for a major cardiovascular event. The principal secondary endpoint was death from any cause. A total of 813 patients were enrolled and followed for a mean of 29.4 months. The primary endpoint was reached by 159 patients in the cardiac resynchronization group, as compared with 224 patients in the medical therapy group (39% vs. 55%; hazard ratio, 0.63; 95% CI, 0.51 to 0.77; $P < 0.001$). There were 82 deaths in the cardiac resynchronization group, as compared with 120 in the medical therapy group (20% vs. 30%; hazard ratio, 0.64; 95% CI, 0.48 to 0.85; $P < 0.002$). Compared with medical therapy, cardiac resynchronization reduced the interventricular mechanical delay, the end-systolic volume index, and the area of the mitral regurgitant jet; increased the left ventricular ejection fraction; and improved symptoms and the quality of life ($P < 0.01$ for all comparisons).

The authors concluded that in patients with heart failure and cardiac dyssynchrony, cardiac resynchronization improves symptoms and the quality of life and reduces complications and the risk of death. These benefits are in addition to those afforded by standard pharmacological therapy. The implantation of a cardiac resynchronization device should be routinely considered in such patients. The beneficial effects of CRT in this group of patients were impressive, considering that these patients were receiving optimal medical therapy with diuretics, beta-blockers, spironolactone, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker at the time of enrollment. The results showed that for every nine devices implanted, one death and three hospital stays were prevented (Cleland *et al.*, 2005).

Defibrillator

Randomized Clinical Trials. The publication of the Sudden Cardiac Death Heart Failure Trial (SCD-HeFT) in January 2005 provided a definite answer to the question of comparative survival benefit by defibrillator vs. amiodarone in patients with NYHA class II or III heart failure and an ejection fraction of <35%. The SCD-HeFT investigators randomly assigned 2521 patients with New York Heart Association (NYHA) class II or III CHF and a left ventricular ejection fraction (LVEF) of 35% or less to conventional therapy for CHF plus placebo (847 patients), conventional therapy plus amiodarone (845 patients), or conventional therapy plus a conservatively programmed, shock-only, single-lead ICD (829 patients). Placebo and amiodarone were administered in a double-blind fashion. The primary endpoint was death from any cause. The median LVEF in patients was 25%; 70% were in NYHA class II, and 30% were in class III CHF. The cause of CHF was ischemic in 52% of patients and nonischemic in 48% of patients. The median follow-up was 45.5 months.

There were 244 (29%) deaths in the placebo group, 240 (28%) in the amiodarone group, and 182 (22%) in the ICD group. Compared with placebo, amiodarone was associated with a similar risk of death (hazard ratio, 1.06; 97.5% CI, 0.86 to 1.30; $P = 0.53$), and ICD therapy was associated with a decreased risk of death of 23% (hazard ratio, 0.77; 97.5% CI, 0.62 to 0.96; $P = 0.007$) and an absolute decrease in mortality of 7.2% after 5 years in the overall population. Results did not vary according to either ischemic or nonischemic causes of CHF, but they did vary according to the NYHA class. The authors concluded that in patients with NYHA class II or III CHF and LVEF of 35% or less, amiodarone has no favorable effect on survival, whereas single-lead, shock-only ICD therapy reduces overall mortality by 23%. This study concluded a long debate over the potential benefit of amiodarone in heart failure and the role of the defibrillator (Bardy *et al.*, 2005).

With these results in place, the implantable cardioverter-defibrillator (ICD) has to be considered the major therapeutic tool to prevent sudden arrhythmic death in these patients. Before SCD-HeFT, the Multicenter Automatic Defibrillator Implantation Trial (MADIT) studied whether prophylactic therapy with an implanted cardioverter-defibrillator, as compared

with conventional medical therapy, would improve survival in a high-risk group of patients with nonsustained ventricular tachycardia, previous myocardial infarction, and left ventricular dysfunction (estimated 2-year mortality rate of 30%). Over the course of 5 years, 196 patients in New York Heart Association functional class I, II, or III with prior myocardial infarction, a left ventricular ejection fraction of $<35\%$ (a documented episode of asymptomatic nonsustained ventricular tachycardia), and inducible, nonsuppressible ventricular tachyarrhythmia on electrophysiological study were randomly assigned to receive an implanted defibrillator ($n = 95$) or conventional medical therapy ($n = 101$). During an average follow-up of 27 months, there were 15 deaths in the defibrillator group and 39 deaths in the conventional therapy group ($P = 0.009$). There was no evidence that amiodarone, beta-blockers, or any other antiarrhythmic therapy had a significant influence on the observed hazard ratio. It was concluded that in patients with a prior myocardial infarction who are at high risk for ventricular tachyarrhythmia, prophylactic therapy with an implanted defibrillator leads to improved survival as compared with conventional medical therapy (Moss *et al.*, 1996).

The AVID investigators (1997) conducted a randomized comparison of defibrillator and antiarrhythmic drugs in patients who had been resuscitated from near-fatal ventricular fibrillation or who had undergone cardioversion from sustained ventricular tachycardia. Patients with ventricular tachycardia also had syncope or other serious cardiac symptoms, along with a left ventricular ejection fraction of 0.40 or less. One group of patients had cardioverter-defibrillator implantation ($n = 507$); the other received class III antiarrhythmic drugs ($n = 509$). Overall survival was greater with the implantable defibrillator, with unadjusted estimates of 89.3% as compared with 82.3% in the antiarrhythmic drug group at 1 year, 81.6% vs. 74.7% at 2 years, and 75.4% vs. 64.1% at 3 years ($P < 0.02$) (AVID, 1997).

In the MUSTT trial, the hypothesis tested was that electrophysiologically guided antiarrhythmic therapy would reduce the risk of sudden death among patients with coronary artery disease, a left ventricular ejection fraction of $<40\%$, and asymptomatic, nonsustained ventricular tachycardia. Patients in whom sustained ventricular tachyarrhythmias were induced by programmed stimulation were randomly assigned to receive either antiarrhythmic therapy, including drugs and implantable defibrillators

as indicated by the inducibility during electrophysiological testing, or no intervention if noninducible. Angiotensin-converting enzyme inhibitors and beta-adrenergic blocking agents were administered as tolerated. A total of 704 patients with inducible, sustained ventricular tachyarrhythmias were randomly assigned to different treatment groups. Five-year Kaplan–Meier estimates of the incidence of the primary endpoint of cardiac arrest or death from arrhythmia were 25% among patients receiving electrophysiologically guided therapy and 32% among those assigned to no antiarrhythmic therapy. Neither the rate of cardiac arrest or death from arrhythmia nor the overall mortality rate was lower among the patients assigned to electrophysiologically guided therapy and treated with antiarrhythmic drugs than among the patients assigned to no antiarrhythmic therapy (Buxton *et al.*, 1999).

A follow-up study to MADIT, MADIT II demonstrated a 30% all-cause mortality risk reduction from defibrillator implantation in over 1200 patients from 76 institutions with ischemic heart disease and an ejection fraction of <30%. It examined the prophylactic benefit in coronary artery disease patients with a left ventricular ejection fraction of <30% who had at least one myocardial infarction, but required no further risk stratification. Invasive electrophysiological testing for risk stratification was not required. MADIT II applied a sequential design trial that compared ICD vs. no ICD therapy. Programmed electrical stimulation to test the inducibility of ventricular tachycardia was performed during ICD implantation, and various noninvasive risk markers were tested after randomization. The primary endpoint was total mortality, and secondary objectives were quality-of-life issues as well as the cost-effectiveness ratio. Over the course of 4 years, the MADIT II investigators enrolled 1232 patients with a prior myocardial infarction and a left ventricular ejection fraction of 0.30 or less. Patients were randomly assigned in a 3:2 ratio to receive an implantable defibrillator (742 patients) or conventional medical therapy (490 patients). The clinical characteristics at baseline and the prevalence of medication use at the time of the last follow-up visit were similar in the two treatment groups.

During an average follow-up of 20 months, the mortality rates were 19.8% in the conventional therapy group and 14.2% in the defibrillator group. The hazard ratio for the risk of death from any cause in the defibrillator group as compared with the conventional therapy group was

0.69 (95% CI, 0.51 to 0.93; $P = 0.016$). The effect of defibrillator therapy on survival was similar in subgroup analyses stratified according to age, sex, ejection fraction, New York Heart Association class, and the QRS interval. The investigators concluded that in patients with a prior myocardial infarction and advanced left ventricular dysfunction, prophylactic implantation of a defibrillator improves survival (Moss *et al.*, 2002).

On the other hand, there was no evidence of improved survival among patients with coronary heart disease, a depressed left ventricular ejection fraction, and an abnormal signal-averaged electrocardiogram, in whom a defibrillator was implanted prophylactically at the time of elective coronary bypass surgery (Bigger, 1997). The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) randomized 674 patients who had recently suffered a myocardial infarction (6 to 40 days after myocardial infarction), had a left ventricular ejection fraction of $\leq 35\%$, and had impaired cardiac autonomic function (decreased heart rate variability or elevated average heart rate as determined by 24-h ambulatory monitoring) to receive either ICD implantation or no ICD therapy. A percutaneous coronary intervention on the infarct-related artery was performed in only 36% of study patients. During a follow-up period of 30 ± 13 months, there was no significant difference in overall mortality between the two treatment groups. However, annual mortality rates were low in both groups: 7.5% for ICD-treated patients and 6.9% for control patients. These results suggested that the prophylactic use of ICD placement within the first month after acute myocardial infarction remains of unproven benefit (Hohnloser *et al.*, 2004).

Despite a steady decline in the risk of death from pump failure, many patients remain at high risk for sudden cardiac death. The incidence of sudden cardiac death in the US alone has been estimated at 184 000 to over 400 000 cases annually. During the past decade, substantial advances have been made in the use of device-based therapy for this population. The role of the implantable cardioverter-defibrillator (ICD) in routine heart failure management continues to evolve (Cesario and Dec, 2006). Implantable cardioverter-defibrillator therapy should not be used for patients with advanced heart failure symptoms (NYHA functional class IV) that remain refractory to optimal medical therapy for whom cardiac transplantation is

not an option. However, some of these patients may still be considered for cardiac resynchronization therapy with ICD backup capability. Sweeney *et al.* have shown little improvement in survival after ICD implantation for these patients, most of whom died of progressive pump failure (Sweeney *et al.*, 1995). Furthermore, ICD treatment is contraindicated in the presence of medically intractable ventricular tachycardia or ventricular fibrillation. Implantable cardioverter-defibrillator therapy remains unproven for patients with substantially impaired systolic function and coronary artery disease, who lack evidence of sustained or nonsustained ventricular tachycardia and are scheduled to undergo coronary revascularization.

Coronary Artery Bypass Surgery

Randomized Clinical Trials. High-risk revascularization may constitute the treatment of choice in the subgroup of advanced heart failure patients with ischemic cardiomyopathy, an ejection fraction of $<35\%$, viable myocardium, and vessels suitable for grafting. To address this issue, the NIH-sponsored Surgical Treatment for Ischemic Heart Failure (STICH) trial with 2800 patients aims to answer two key questions of therapeutic strategy in the management of patients with symptomatic heart failure, left ventricular dysfunction, and coronary artery disease amenable to CABG: (1) Does surgical coronary revascularization in addition to aggressive medical HF management confer long-term mortality, morbidity, quality of life, or cost benefits beyond aggressive medical management alone? (2) Does surgical ventricular shape restoration in combination with CABG improve the outcome compared to coronary revascularization alone or medical therapy alone (Joyce *et al.*, 2003)?

Non-RCT Evidence. To assess the effect of CABG on future risk of death in patients with LV dysfunction and heart failure, mortality and modes of death in 5410 patients with ischemic LV dysfunction who were enrolled in the Studies Of Left Ventricular Dysfunction (SOLVD) trials were retrospectively evaluated. Outcomes of patients with ($n = 1870$; 35%) vs. without ($n = 3540$) a history of prior CABG were compared, and stratification by baseline ejection fraction values (<0.25 , $0.25\text{--}0.30$, and >0.30)

was performed. Prior CABG was associated with a 25% reduction in risk of death and a 46% reduction in risk of sudden death independent of EF and severity of heart failure symptoms. It was concluded that in patients with ischemic LV dysfunction, prior CABG is associated with a significant independent reduction in mortality (Veenhuyzen *et al.*, 2001). Different trials have suggested the benefit of revascularization in advanced heart failure if angina (Winkel and Piccione, 1997) or hibernation (Di Carli *et al.*, 1995; Hausmann *et al.*, 1997; Elefteriades *et al.*, 1993; Olson *et al.*, 1993; Mickelborough *et al.*, 1995) is present. If no viable myocardium is present, the prospect of improvement with revascularization is reduced; thus, cardiac transplantation should be considered for appropriate candidates (Dreyfus *et al.*, 1993; Kron *et al.*, 1989; Lansman *et al.*, 1993; Tjan *et al.*, 2000).

Mitral Valve Surgery

Non-RCT Evidence. Severe mitral regurgitation is a frequent complication of end-stage cardiomyopathy that contributes to heart failure and predicts poor survival. The group at the University of Michigan, Ann Arbor, studied the intermediate-term outcome of mitral reconstruction in 48 patients who had cardiomyopathy with severe mitral regurgitation (63 ± 6 years, EF $16\% \pm 3\%$, maximal drug therapy, New York Heart Association class III–IV, refractory 4+ mitral regurgitation). All 48 had undersized flexible annuloplasty rings inserted, 7 had coronary bypass grafts for incidental disease, 11 had prior bypass grafts, and 11 also had tricuspid valve repair. One operative death occurred as a result of right ventricular failure. Postoperative transesophageal echocardiography revealed mild mitral regurgitation in 7 patients and no mitral regurgitation in 41. There were 10 late deaths, 2 to 47 months after mitral valve reconstruction. The 1- and 2-year actuarial survival rates were 82% and 71%. At a mean follow-up of 22 months, the number of hospitalizations for heart failure had decreased, and one patient had heart transplantation. Significantly, the New York Heart Association class improved from 3.9 ± 0.3 before the operation to 2.0 ± 0.6 after the operation. Twenty-four months after the operation, left ventricular volume and sphericity decreased, whereas ejection fraction and cardiac output repeatedly increased (Bolling *et al.*, 1998).

Left Ventricular Geometry Restoration

Non-RCT Evidence. To evaluate the safety and efficacy of surgical anterior ventricular endocardial restoration (SAVER), which excludes non-contracting segments in the dilated remodeled ventricle after anterior myocardial infarction, an international group of cardiologists and surgeons from 11 centers investigated the role of SAVER in patients after anterior myocardial infarction. From January 1998 to July 1999, a total of 439 patients underwent the procedure and were followed for 18 months. Early outcomes of the procedure and risk factors were investigated. Concomitant procedures included coronary artery bypass grafting in 89% of patients, mitral valve repair in 22%, and MV replacement in 4%. The hospital mortality rate was 6.6%, and few patients required mechanical support devices such as intra-aortic balloon counterpulsation (7.7%), left ventricular assist device (0.5%), or extracorporeal membrane oxygenation (1.3%). Postoperatively, the ejection fraction increased from $29\% \pm 10.4\%$ to $39\% \pm 12.4\%$, and the left ventricular end-systolic volume index decreased from $109 \pm 71 \text{ mL/m}^2$ to $69 \pm 42 \text{ mL/m}^2$ ($p < 0.005$). At 18 months, the survival rate was 89.2%. Time-related survival at 18 months was 84% in the overall group and 88% among the 421 patients who had coronary artery bypass grafting or MV repair (Athanasuleas *et al.*, 2001; Athanasuleas *et al.*, 2004).

The echocardiographic changes and functional outcome from mitral valve repair, combined with partial left ventriculectomy (the Batista procedure), were investigated by the Cleveland Clinic. From May 1996 to August 1997, the operation was performed on 57 patients, primarily (95%) transplant candidates with idiopathic dilated cardiomyopathy. All were NYHA class IV (36.8% had improved to class III by the time of surgery) on medical therapy, including 40% hospitalized on inotropes and three patients on intra-aortic balloon pumps. The mean cardiac index was $2.1 \pm 0.6 \text{ L/min/m}^2$ with a wedge pressure of $24 \pm 8 \text{ mm Hg}$. There were two in-hospital mortalities (3.5%). At 3 months, there were significant persistent changes in LV end-diastolic diameter ($8.1 \pm 1.0 \text{ cm}$ to $6.3 \pm 0.9 \text{ cm}$) and ejection fraction ($13.6\% \pm 6\%$ to $23\% \pm 7.7\%$). Subjective improvement included a mean change in NYHA functional class from 3.7 to 2.2, and objective changes included improvement in peak oxygen consumption from

10.6 ± 4 mL/kg/min to 15.4 ± 4.5 mL/kg/min. The actuarial survival rate at 1 year was 82.1%; and freedom from death, relisting for transplantation, and need for LVAD support were 58% (McCarthy *et al.*, 2000).

Most recently, the Reconstructive Endoventricular Surgery, Returning Torsion Original Radius Elliptical Shape to the Left Ventricle (RESTORE) study group tested how surgical ventricular restoration affects early and late survival in a registry of 1198 postanterior infarction congestive heart failure patients treated by the international RESTORE team. They applied surgical ventricular restoration to 1198 postinfarction patients between 1998 and 2003. Early and late outcomes were examined, and risk factors were identified. Concomitant procedures included coronary artery bypass grafting in 95% of patients, mitral valve repair in 22%, and mitral valve replacement in 1%.

Overall 30-day mortality after SVR was 5.3% (8.7% with mitral repair vs. 4.0% without repair; $p < 0.001$). Perioperative mechanical support was uncommon (<9%). Global systolic function improved postoperatively. Ejection fraction (EF) increased from 29.6% ± 11.0% preoperatively to 39.5% ± 12.3% postoperatively ($p < 0.001$). The left ventricular end-systolic volume index (LVESVI) decreased from 80.4 ± 51.4 mL/m² preoperatively to 56.6 ± 34.3 mL/m² postoperatively ($p < 0.001$). Overall 5-year survival was 68.6% ± 2.8%. Logistic regression analysis identified EF of ≤30%, LVESVI of ≥80 mL/m², advanced New York Heart Association (NYHA) functional class, and age of ≥75 years as risk factors for death. Five-year freedom from hospital readmission for CHF was 78%. Preoperatively, 67% of patients were NYHA functional class III or IV; and postoperatively, 85% were class I or II. Based on these results, the group concluded that surgical ventricular restoration improves ventricular function and is a highly effective therapy in the treatment of ischemic cardiomyopathy with an excellent 5-year outcome (Athanasuleas *et al.*, 2004).

Cardiac Transplantation

Non-RCT Evidence. In the context of contemporary medical and surgical therapy, there is growing recognition that the relative role of cardiac transplantation may need to be redefined (Stevenson *et al.*, 1991; Levine *et al.*, 1996; Kao *et al.*, 1994; Frigerio *et al.*, 1997; St. John Kolar, 2000).

Based on the assumption that its goal is to prolong life (Hunt *et al.*, 1976) while improving its quality (O'Brien *et al.*, 1987; Marzo *et al.*, 1992; Grady *et al.*, 1998) and in the absence of randomized clinical trial proof of its benefit, data from early studies, recent observational cohort studies (Hosenpud *et al.*, 1999; Hosenpud *et al.*, 2001), and more recent effective therapies in advanced heart failure have to be reassessed to characterize patients with those clinical profiles who may now be considered “too well” for cardiac transplantation (Hunt, 2000).

These profiles likely include patients with low risk according to the Heart Failure Survival Score (Aaronson and Mancini, 1999; Deng *et al.*, 2000); peak $\text{VO}_2 > 14\text{--}18$ mL/kg/min without other indications; left ventricular EF $< 20\%$ alone, history of NYHA class III/IV symptoms alone; history of ventricular arrhythmias alone; patients with advanced heart failure in whom angiotensin-converting enzyme inhibitor, beta-blockade, or spironolactone therapy has not been attempted; and patients who have not been subjected to a structured cardiac transplantation evaluation in a designated cardiac transplantation center.

Advanced Heart Failure Treatment Algorithm

Defining Clinical Profiles of Patients Too Well for Transplantation.

Referral to a designated cardiac transplantation center for evaluation usually takes place when the treating cardiologist/internist has exhausted all lifestyle and medical options without success, in the setting of decompensation and progression of advanced heart failure, a phase known to be associated with a high risk of death. A structured management algorithm (Fig. 2) needs to be applied in order to recompensate the patient, initiate neurohormonal blockade and lifestyle changes, or — if recompensation cannot be achieved — evaluate cardiac transplantation with the option of mechanical circulatory support device (MCSD) bridging. All patients who can be recompensated and who tolerate neurohormonal blockade should be considered too well for cardiac transplantation at that time. This definition is facilitated by an allocation algorithm based on medical urgency and not on waiting time, because the team does not need to make an extrapolation of the likely clinical course of the patient over the next 6–12 months. The

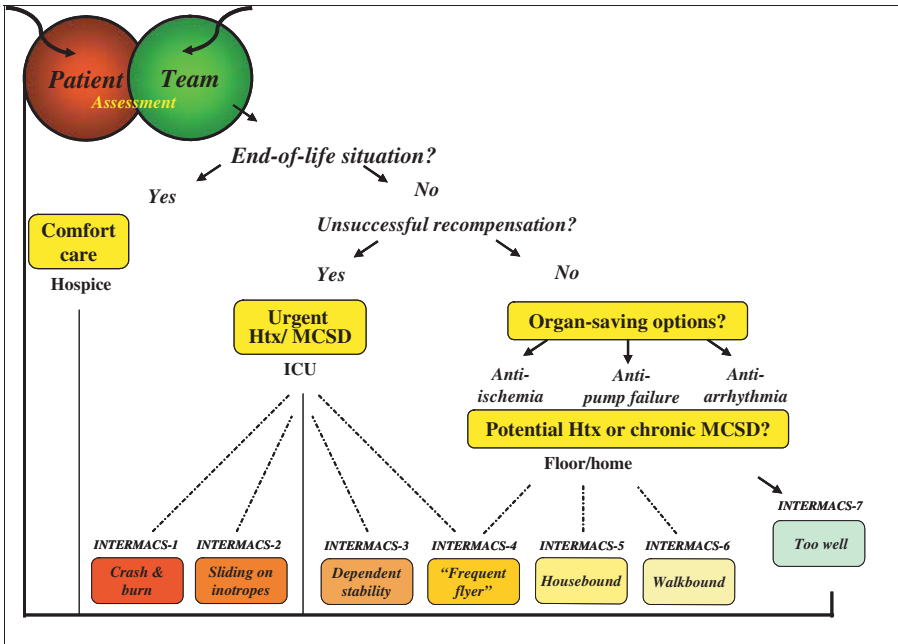


Fig. 2. The selection algorithm starts with the encounter between patient and team, and is followed by a stepwise evaluation of important issues including the following: (1) Is an end-of-life situation present? (2) Can the patient be recompensated? (3) After neuro-hormonal blockade initiation, are there organ-saving options including revascularization, contractility enhancement, and antiarrhythmia therapy? (4) Is the patient a suitable candidate for heart replacement options, including mechanical circulatory support and heart transplantation?

evaluation may serve to designate a patient as a “potential transplant candidate”, who could be placed on a national “potential transplant candidate list”. This algorithm combines the psychological benefit for the patient of being accepted by the program with ongoing access to a diversity of advanced heart failure treatment modalities, not committing to transplantation as the only therapeutic option (Deng *et al.*, 2002).

If the initial evaluation reveals hemodynamic instability (therefore, completing cardiac transplant evaluation and listing), follow-up may still lead to stabilization without transplantation, thus enabling delisting in individual cases. If at initial evaluation, refractory hemodynamic instability is accompanied by advanced multiorgan dysfunction, then comfort care has to be

considered. The initial assessment is not a complete cardiac transplantation evaluation, but rather an approach to address the following main questions: How severe is the heart failure condition? Are there reversible causes? Are there risk factors limiting the overall prognosis?

The recompensation phase, either with or without right heart catheter monitoring, aims to acutely optimize volume status, contractility, afterload, heart rate, gas exchange, urine output, and potentially reversible precipitating factors. The neurohormonal blockade, initiated after recompensation is accomplished, aims at downtitration of the maladaptive activation of the neurohormonal systems by administration of angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists.

In the COPERNICUS trial, a subgroup of more advanced heart failure patients was included, and classified as recent or recurrent cardiac decompensation or severely depressed cardiac function, characterized by the presence of pulmonary rales, ascites, or edema at randomization; three or more hospitalizations for heart failure within the previous year; the need for intravenous positive inotropic agents or an intravenous vasodilator drug within 14 days; or an ejection fraction of $<15\%$. In patients who were likely to receive a cardiac transplant and had symptomatic hypotension or severe renal dysfunction, it was recommended that, rather than starting carvedilol during acute decompensation, measures should first be taken to stabilize their clinical condition (particularly with respect to their volume status) and then initiate adrenergic blockade. It was pointed out that expertise in the care of patients with advanced heart failure is important in this management process (Packer *et al.*, 1999).

The EFICAT trial examined the question of whether or not patients considered as transplantation candidates and thus excluded from participation in the COPERNICUS trial could be safely administered carvedilol. The primary endpoint was the absolute change from baseline to latest available LV ejection fraction measurement determined by radionuclide ventriculography between carvedilol and placebo. The trial prospectively randomized 118 patients with CHF of ischemic ($n = 44$) or nonischemic ($n = 74$) etiology, a mean age of 53.3 ± 9.8 years, and a mean LVEF at baseline of $19.9\% \pm 6.6\%$. The mean absolute change of LVEF from baseline was $6.0\% \pm 9.3\%$ in the carvedilol group vs. $0.7\% \pm 7.1\%$ in the placebo-treated patients ($p < 0.008$). Serious adverse events were experienced by

33/60 patients (13 deaths) on placebo and 29/58 patients (9 deaths) on carvedilol. It was concluded that carvedilol is an efficacious and safe drug in euvoletic patients considered for the cardiac transplantation waiting list (Angermann *et al.*, 2001).

Structured Prognostication Algorithm in a Designated Transplant Center as Prerequisite. Beyond recompensation and neurohormonal blockade, prognostication is an integral part of the management algorithm (Fig. 2). Based on the groundbreaking work of Mancini and coworkers (Mancini *et al.*, 1991), the UCLA team assessed the role of peak oxygen uptake in the re-evaluation of candidates awaiting heart transplantation. All ambulatory transplant candidates with an initial peak oxygen uptake of <14 mL/kg per min were identified. Of 107 such patients listed, 68 survived without early deterioration or transplantation to undergo repeat exercise. In 38 of these 68 patients, peak oxygen uptake increased by ≥ 2 mL/kg per min to a level of ≥ 12 mL/kg per min after 6 ± 5 months, together with an increase in anaerobic threshold, peak oxygen pulse, and exercise heart rate reserve, and a decrease in heart rate at rest. Increased peak oxygen uptake was accompanied by stable clinical status without congestion in 31 of 38 patients, and these 31 were taken off the active waiting list. At 2 years, their actuarial survival rate was 100% and the survival rate without relisting for transplantation was 85%. The authors concluded that an algorithm with scheduled re-evaluation of exercise capacity and clinical status allows identification of patients who are “too well” during follow-up. They estimated that 29% of ambulatory transplant candidates can be removed from the waiting list with excellent early survival despite low peak oxygen uptake on initial testing, thus allowing to defer transplantation in favor of more compromised candidates (Stevenson *et al.*, 1995).

In order to refine risk stratification in ambulatory cardiac transplantation candidates and estimate their survival probability without transplantation (and thus the potential benefit from transplantation), the group at the University of Pennsylvania and Columbia University developed the first independently validated prognostication tool, entailing a high-risk, medium-risk, and low-risk stratum. Event-free (death or urgent transplantation) survival rates at 1 year for the low-, medium-, and high-risk HFSS strata were $93\% \pm 2\%$, $72\% \pm 5\%$, and $43\% \pm 7\%$, respectively. Event-free survival

rates for the medium- and high-risk strata were much worse than expected after cardiac transplantation; the low-risk stratum had an event-free survival rate that was better than with transplantation. Based on this excellent prognostication tool, patients with HFSS low risk would be considered too well for cardiac transplantation (Aaronson *et al.*, 1997). Risk stratification of hospital-bound cardiac transplantation candidates who are inotrope- or left ventricular assist device-dependent can be improved by the inclusion of further parameters (Smits *et al.*, 2003b).

Clinical Profiles of Patients Too Well for Transplantation. In summary, according to the available evidence summarized above, patients with the following clinical profiles should be considered too well for cardiac transplantation (Deng *et al.*, 2002):

- patients with low-risk HFSS;
- patients with a peak $\text{VO}_2 > 14\text{--}18$ mL/kg/min without other indications;
- patients with a left ventricular EF $< 20\%$ alone;
- patients with a history of NYHA class III/IV symptoms alone;
- patients with a history of ventricular arrhythmias alone;
- patients with advanced heart failure (class IV symptoms, ejection fraction $< 25\%$) in whom angiotensin-converting enzyme inhibitor, beta-blockade, or spironolactone therapy has not been attempted; and
- patients who have not been subjected to a structured cardiac transplantation evaluation in a designated cardiac transplantation center.

Implications for Listing and Allocation Rules. To formalize the staged approach towards cardiac transplantation listing, a national potential transplant candidate list based on a systematic screening process in a designated transplant center should be considered. This would facilitate placement on the (urgency-driven) waiting list should deterioration subsequently occur. The potential transplant candidate list would emphasize to the patient the temporary nature of the evaluation process, which is often not adequately appreciated in current transplant practice.

In response to a debate on the fairness of the organ allocation system in the US, the US Department of Health and Human Services published a regulation termed the “Organ Procurement and Transplantation Network:

Final Rule” (Federal Register, 1998) to assure that the allocation of scarce organs will be based on common medical criteria, not accidents of geography. The stated principles favor the establishment of more effective federal oversight, increase of public access to information, implementation of consistent medical listing criteria, emphasis on medical need, and reduction of geographic disparities in waiting times. In line with these data, allocation systems are moving towards a system that favors medical urgency over waiting time (Gibbons *et al.*, 2000). Within this framework, patients who are in a less urgent medical condition with respect to their heart failure severity should be considered too well for cardiac transplantation.

DEFINITION OF MECHANICAL CIRCULATORY SUPPORT

General Definition

Mechanical circulatory support devices (MCSs) are defined as mechanical pumps assisting or replacing the left, right, or both ventricles of the heart to pump blood. While the term left ventricular assist device (LVAD) or left ventricular assist system (LVAS) indicates left ventricular support, the broader term MCS has been adopted to include left ventricular, right ventricular, and biventricular devices, the latter including biventricular assist devices as well as complete heart replacement devices.

Specific Forms

Over the last two decades, mechanical circulatory support devices (MCSs) have been developed at a rapid pace with the goal of supporting patients with advanced heart failure as a bridge to cardiac transplantation (BTT), a bridge to recovery (BTR), and an alternative to transplantation (ATT). Their clinical impact is rapidly increasing after the publication of the first randomized trial demonstrating their positive impact on survival and quality of life (Rose *et al.*, 2001). The current generation of devices provides a differentiated spectrum of circulatory support, ranging from short to intermediate and long-term duration. Also, partial left ventricular support, more complete left ventricular support, right ventricular support, and biventricular support options can be tailored to the hemodynamic needs

of the patient. On a technical level, the device positions range from paracorporeal pumps (intracorporeal pumps with transcutaneous drivelines) to completely implantable systems.

EVOLUTION OF MECHANICAL CIRCULATORY SUPPORT

**Ted L
(born 1943)**

**The heart
pump**

The Heart Pump

On April 1, 2004, I was rushed to Columbia Presbyterian Hospital and almost checked out before I checked in. I was one very sick fellow. Dr Donna Mancini, the head of the heart transplant unit, and Dr Yoshifumi Naka, one of the specialists in heart surgery, told my wife that I was too sick for a transplant and that the only course of action was to implant a heart assist device in my chest: an LVAD (left ventricular assist device). It would take over for my heart's main pumping chamber, the left ventricle. Dr Naka did this on April 13, 2004.

The LVAD was implanted in my chest and was very obvious to anyone within 15 feet of me. First, it was physically intimidating. It was just under the skin of my chest and weighed 5 pounds. It was 5 inches in diameter, 2 inches thick, and had an external tube coming out of my chest for the electrical wires to the motor and as an exhaust for the pump. Most notable was the sound and feel of the pump. With each heartbeat, it went "wish, wish, wish". Besides hearing the exhaust, I could hear and feel the pump with each beat of my heart. What fantastic state-of-the-art equipment! Each day, the nurses meticulously cleansed the opening and put new bandages over the wound to make sure that I did not get infected. I became amazed at just how hard the heart works every moment of every day.

Once I recovered and had completed my physical therapy, the doctors discharged me on May 26, 2004 — 56 days after arriving. Over the next 14 months, with the help of the heart pump, I recovered all my bodily functions and went on to get myself in the best physical shape I had been in for a decade or so. I worked out 3 days a week

at the Cornell Cardiac Fitness Center on stationary bicycles, treadmills, and rowing machines. I kept this up until the day I got my call for a new heart. I basically got myself into better shape than I had been in the previous 10–15 years through exercise, carefully sticking to the prescribed diet, and keeping myself mentally and physically active.

Before leaving the hospital, both my wife and I were trained in the use of the LVAD. Trina became an expert in cleansing and changing my bandages, and she followed my exercises and dietary activities each day. I began calling my wife Dr L. When I first came home and was just recuperating around the apartment, the set of batteries would run the pump for about 7 1/2 hours, but as I became more active this dropped to about 5 hours. When I was going to bed at night, I used a 25-foot extension cord from my power unit that limited my movements to the bed, the chair, and the bathroom. The power unit charged my four sets of batteries each night while I slept.

It is quite an experience to carry an implanted 5-pound pump, two external batteries weighing 10 pounds, and a computer regulating the pump and sending messages about the state of its operation. I also had to carry with me a beeper for instant communications with the hospital and a cell phone to call anyone.

Since the pump continually needed new batteries and could possibly malfunction, I carried an extra set of batteries, an extra computer, and a hand pump. The LVAD, if necessary, could be operated with a hand pump should something happen to the electrical system; however, that would be the ultimate emergency.

The biggest concern was that the batteries would run out of juice before I could get home and get to my backup batteries. Most people leave home each morning with the idea that if plans change, they will adapt. But if I was stuck somewhere and was unable to get home to replace and recharge my batteries, I would be in severe trouble, having to rely on the hand pump.

Learning how to take a shower properly became a challenge. No water could ever get into the exhaust tube, or the electrical motor could short-circuit and stop. Not good, as they say. After cutting up plastic shower curtains and using tape, my wife and I realized that it wouldn't work. The tape always came loose. After much trial and error, I settled on large sheets of tegaderm bandages — totally adhesive-backed and water-repellent. Before you knew it, I was enjoying 20-minute showers without any concern.

I will never forget the first time my wife and I went to the opera. We found our places, the lights went dim, and all noises stopped, with one exception: my heart pump kept going “wish, wish, wish”. People to the left, right, behind, and in front of us began to wonder what that irritating noise was. One fellow turned around and said, “Would you turn off whatever it is that's making the noise?”

In the summer of 2004, there were bomb scares by terrorists at several buildings in New York City. One was my favorite haunt, the Citicorp Center building, because the Barnes & Noble bookstore was located there — my home away from home while I was on the LVAD. Two policemen were stationed at every door, and you should have seen their reaction to my equipment. Carrying two black boxes in a shoulder holster and a black box on my belt got their attention. Eventually, they came to know me and asked how I was coming along. They became quite interested in the heart pump, as they had never heard of such a thing.

The highlight of my life on the LVAD came at a charitable dance at Mt. Sinai Hospital. My wife's firm had taken a table and we were invited to attend. I told Trina that I would try to get out on the dance floor, but was not sure how long I would last. We started with a waltz, but before you knew it the band was doing more upbeat rhythms. We began jitterbugging and I was able to keep up. Meanwhile, back at the table, my wife's associates began asking themselves, “Tell me again, who is it that is waiting for a heart transplant?”

Many people have asked me how I withstood the waiting, never knowing when the call would come. My answer to that was this: I set a schedule each day and stuck to it, just as if I were in college and had classes to attend. I filled each day reading books, studying about medications and transplantation, took courses on geopolitics, went to New York University School of Continuing and Professional Studies for a certificate in foundation management, volunteered at the New York Organ Donor Network, and made sure to meet and talk to friends about my heart pump.

Early History

Early descriptions of mechanical support of the human circulation are documented at least back to the early 19th century. The experimental application of mechanical support in animal models was reported in the 1930s. Major interest in mechanical support of the human circulation would await the advent of open heart surgery in the 1950s (Kirklin, 2006). The basic pump design has changed little over this development period, but the power delivery and control have moved from large bedside consoles to wearable components, enabling patient autonomy in an outpatient setting (Schmid *et al.*, 1999). This has brought about substantial improvements in patients' quality of life (Dew *et al.*, 1999) and reductions in resource use (Gelijns *et al.*, 1997).

Smaller, inexpensive, and less obtrusive blood pumps are undergoing development, and some are being tested in clinical trials (Katsumata and Westaby, 1998; Wieselthaler *et al.*, 2000; Goldstein *et al.*, 2005). However, while the potential benefits are encouraging, these designs still have to prove their durability, reliability, and physiological suitability for chronic applications (DeBakey, 2005). An excellent monograph with overviews of the current MCS-D-device types was recently published by the International Society of Heart and Lung Transplantation (Frazier and Kirklin, 2006). Other excellent monographs on MCS-Ds have been published over the last decade (Goldstein and Oz, 2000; Rose and Stevenson, 1998).

Recent Regulatory Approval Processes in the US

Following the initiative by the US National Heart, Lung, and Blood Institute in the 1970s to develop long-term artificial heart devices (Hogness and VanAntwerp, 1991), two electrically powered pumps emerged from this initiative and completed trials sponsored by the Food and Drug Administration for evaluating safety and efficacy. In 1998, they received certification for commercial application: the HeartMate® VE (ThermoCardio Systems, Woburn, MA) (Poirier, 1999) and the Novacor® N100 PC (World Heart Corporation, Oakland, CA) (Portner *et al.*, 1989; Robbins and Oyer, 1999). In September 2006, the ABIOCOR total artificial heart (Abiomed, Inc., Danvers, MA) received Humanitarian Device Exemption (HDE) from the FDA.

INDIVIDUAL MECHANICAL CIRCULATORY SUPPORT DEVICES (see Appendix 2 for contacts)

**Eric G
(born 1950)**

**Description of
HeartMate I
device**

It sounds simple and I suppose it is. Then, there's the reality: the realization that for my immediate (and possibly longer-term) future, I have a leash. In my chest is a titanium drum about 4 inches in diameter and about 2 inches thick. It's attached via tubing to my heart and my aorta. Then, there's that tube sticking up out of my belly that connects to an air vent and the controller unit, which in turn connects to the power for this device. During the day, I have batteries that have to be charged and ready 24/7. Even to walk down the block to see my neighbors, I need a hand pump just in case the batteries die, a cable breaks, or a controller fails; if I don't manually pump the device in these scary scenarios, I will die. The controller is the brain behind the pump's ability to keep me alive. It is directly and securely attached to the tube that is sticking out of my belly. It is always with me. On the positive side, it isn't terribly large (perhaps 4.5" × 5" × 1") and it weighs practically nothing. The controller requires two power connections.

In order to maximize living with an LVAD, the developers gave the unit two ways to be powered. During the day, the unit uses two rechargeable batteries. Remove one or the other without replacing it quickly, and an alarm will sound: the system will admonish you. There are two power sources, even though one might be strong enough; there's no "safety" with just one power source. The first time you hear the alarm, you will panic, although you know what it means (change the battery a little faster). Really, is it just the battery or have I accidentally ended my life? Just the battery, whew.

At night, my leash is electric. A power base unit (PBU) is plugged into the wall. It has two cords that plug into the two cords on my controller. By changing one battery to AC and then the second battery to the AC, a continuity of power is maintained and no alarms sound. I have a range of about 20 feet at my disposal. Luckily, we worked out how to include both the bed and the bath inside that length.

But wait, there is no battery! What if the power fails tonight? Storms can happen at any time, a tree could fall and snap the power lines; through no fault of my own, I would be dead. However, the base unit has a safety battery built in. If the unit stops improperly, alarms sound and an internal battery that isn't obvious from the outside takes over, thus giving me precious minutes to reattach batteries. The rechargeable batteries last only 4–6 hours; even with several sets, the batteries last for just 20–24 hours. Therefore, as another safety measure, there's a massive battery pack (almost the weight of a car battery) that is good for 24 hours.

Characteristics of currently available MCSDs are summarized in Table 1.

Thoratec

Company History. Thoratec® Corporation (www.thoratec.com) was founded in California in March 1976. The company currently markets the

Table 1. Characteristics of currently available MCSDs.

Type	Ventricle	Flow	Pump position	Implant #
AbioCor	Total heart	Pulsatile	Intrathoracic	> 10
Abiomed BVS 5000	Left & right	Pulsatile	Paracorporeal	> 3000
Abiomed AB 5000	Left & right	Pulsatile	Intracorporeal	> 30
BerlinHeart INCOR	Left	Nonpulsatile	Intra-abdominal	> 250
BerlinHeart EXCOR	Left & right	Pulsatile	Paracorporeal	> 30
CardioWest	Total heart	Pulsatile	Intrathoracic	> 200
CorAide (Arrow)	Left	Nonpulsatile	Intra-abdominal	> 2
DuraHeart (Terumo)	Left	Nonpulsatile	Intra-abdominal	Preclinical
EVAHEART	Left	Nonpulsatile	Intra-abdominal	Preclinical
HeartWare	Left	Nonpulsatile	Intra-abdominal	1
Jarvik 2000	Left	Nonpulsatile	Intra-abdominal	> 100
LionHeart	Left	Pulsatile	Intra-abdominal	> 25
MEDOS	Left & right	Pulsatile	Paracorporeal	> 200
MicroMed DeBakey	Left	Nonpulsatile	Intra-abdominal	> 380
Thoratec HeartMate I	Left	Pulsatile	Intra-abdominal	> 4100
Thoratec HeartMate II	Left	Nonpulsatile	Intra-abdominal	> 50
Thoratec HeartMate III	Left	Nonpulsatile	Intra-abdominal	Preclinical
Thoratec TLC-II	Left & right	Pulsatile	Paracorporeal	> 2800
Thoratec IVAD	Left & right	Pulsatile	Intra-abdominal	> 30
VentrAssist	Left	Nonpulsatile	Intra-abdominal	> 60
WorldHeart Novacor	Left	Pulsatile	Intra-abdominal	> 1700
WorldHeart Novacor II	Left	Pulsatile	Intra-abdominal	Preclinical
WorldHeart Novacor Rotary	Left	Nonpulsatile	Intra-abdominal	> 1

Thoratec® MCSD and the HeartMate® MCSD in the United States and internationally for use as a bridge to heart transplant. Additionally, the Thoratec MCSD System is marketed for use in the recovery of the heart after open heart surgery, and the HeartMate MCSD is marketed internationally as an alternative to medical therapy. On February 14, 2001, Thoratec completed a merger with Thermo Cardiosystems Inc., originally founded in Massachusetts in 1988.

Thoratec MCSD. The Thoratec® VAD System — now also called the paracorporeal VAD System — is currently (i.e. as of 2006) the only device approved by the US Food and Drug Administration (FDA) that can provide left, right, or biventricular support for both bridge to heart transplant and recovery of the heart after open heart surgery. Thoratec is also pursuing additional indications for the Thoratec MCSD System, and is developing other circulatory support products for patients suffering from heart failure.

As of July 2006, the Thoratec MCS System has been used in more than 2800 patients worldwide, ranging in age from 6 to 77 years and in weight from 37 to 317 pounds (17 to 144kg) (Fig. 3).

Thoratec IVAD. The Thoratec IVAD (implantable ventricular assist device) is now FDA-approved for use in bridge-to-transplantation and postcardiotomy-recovery patients who are unable to be weaned from cardiopulmonary bypass. The IVAD is the only currently approved implantable cardiac assist device that can provide left, right, or biventricular support. It has been approved for use in Europe for over a year. The IVAD's size facilitates BiVAD implants and enables it to accommodate patients, including those who were previously unable to receive an implantable, pulsatile device. The IVAD is based on the Thoratec® VAD System, which has been implanted in over 2800 patients worldwide.

In developing the IVAD, Thoratec obtained extensive surgeon input to deliver an implantable VAD and surgical accessories designed to facilitate implantation ease. With the use of the IVAD “sizer”, the IVAD pocket is created. The reusable “sizer” can be used not only to help determine the proper pocket size and position for the IVAD, but also to assist in selecting the appropriately sized cannulae for the patient. Flared cannula ends and an adapted valve housing design allow IVAD cannulae to slide onto the IVAD pump. The collet system reduces the possibility of using

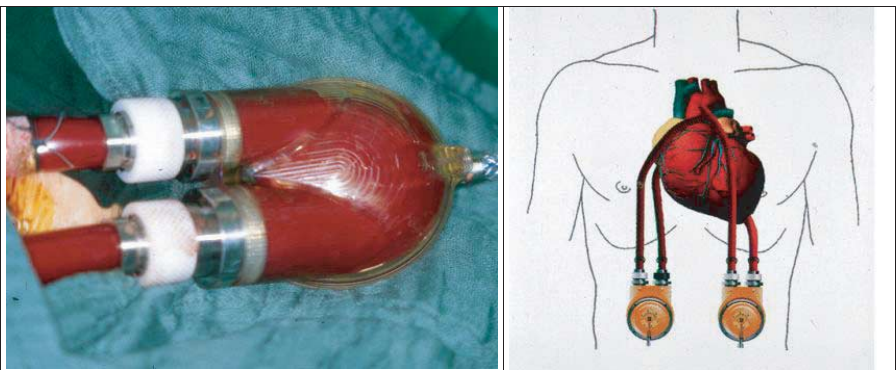


Fig. 3. The Thoratec MCS System.

incompatible components together. The IVAD Cannula Connector Wrench facilitates the securing of the cannula connectors onto the pump. Percutaneous line tunneling is facilitated with the IVAD Percutaneous Line Tuner. The tuner is used for creating the subcutaneous tunneling path and for passing the pump's percutaneous line through the abdomen and out the exit site. In order to accommodate a wide range of patient sizes, two percutaneous line tunnelers of different lengths and curvatures are available.

As of September 2003, a total of 30 patients with advanced heart failure have been supported with the Thoratec IVAD for bridge-to-transplantation or postcardiotomy ventricular failure in Europe and the United States. Sixty-eight percent were successfully treated through transplantation or ventricular recovery, with many of these patients discharged to their homes through the use of the TLC-II® Portable VAD Driver. The initial IVAD results indicate that the device can successfully treat a wide array of patients with a low incidence of many serious, adverse events that are commonly associated with VAD use, such as embolic stroke and systemic infection (Fig. 4).

HeartMate I MCSD. The HeartMate I MCSD is an implantable heart assist device that is designed to perform substantially all or part of the pumping function of the left ventricle of the natural heart for patients suffering from cardiovascular disease. Two systems have been commercialized



Fig. 4. The Thoratec IVAD.

for patients requiring cardiac support: an implantable pneumatic MCS (HeartMate® IP) that is powered by an external electrically driven air pump, and an electric MCS (HeartMate® VE) that is driven by an implanted electric motor and powered by a lightweight battery pack worn by the patient.

In 1994, the FDA granted approval for the commercial sale of the HeartMate IP for use as a bridge to transplant. The HeartMate VE was granted the same approval by the FDA in September 1998. With these approvals, both systems became available for sale to cardiac centers throughout the United States. In August 1998, the HeartMate IP received Canadian approval, permitting the sale of both the air-driven and electric versions throughout Canada. The HeartMate IP received the European Conformity Mark in April 1994, and the HeartMate VE received the same marking in August 1995. In late 1995, the FDA approved the protocol for conducting clinical trials of the HeartMate VE MCS as an alternative to medical therapy in the REMATCH trial; and in May 1998, the first patient was implanted with it as part of this trial. The HeartMate VE MCS is being used in Europe as both a bridge to transplant and as an alternative to medical therapy.

As of July 2006, over 4100 patients worldwide have been supported with the HeartMate MCS. The use of the HeartMate as a destination therapy was approved by the FDA in November 2002. The overall costs for use of the HeartMate as a destination therapy are estimated to be similar to the costs for a heart transplant, or about \$160 000. The HeartMate will probably be used much like dialysis treatment to support patients with kidney failure, supplementing the heart as needed on a long-term basis (Fig. 5).

HeartMate II. HeartMate II is a second-generation MCS that features a miniature rotary blood pump with axial bearings. Because of their small size, rotary blood pumps may potentially be used to provide cardiac support in small adults and in children. In 2000, the clinical trial for HeartMate II was initiated, with a team of cardiac surgeons in Israel performing the first human implant. Clinical trials are underway in Europe and the US (Fig. 6).

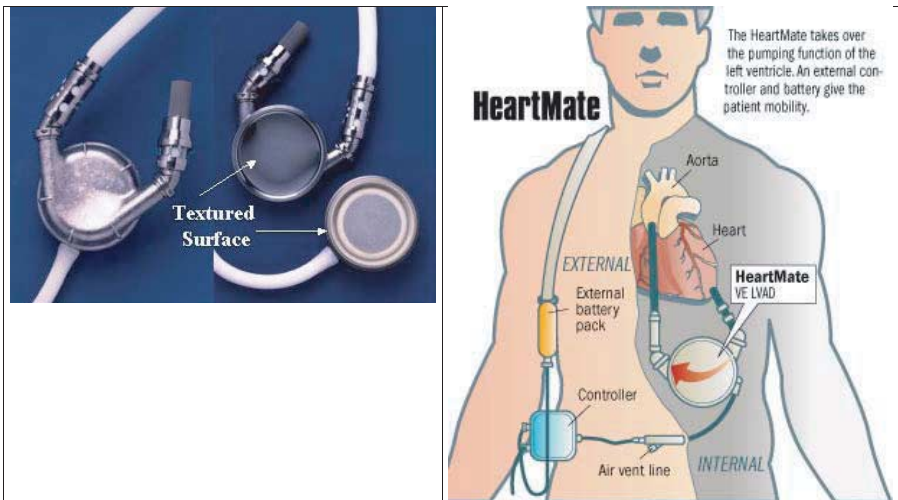


Fig. 5. The HeartMate I MCS.

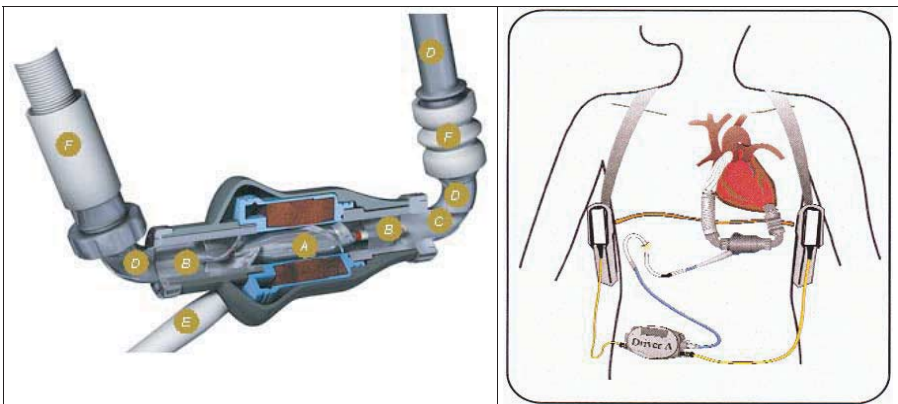


Fig. 6. The HeartMate II MCS.

HeartMate III. Thoratec is developing another advanced HeartMate system, HeartMate® III, designed to meet the needs of a wider range of patients, offer extended durability and longevity, and further improve patients' quality of life. HeartMate III is a third-generation heart assist system featuring a miniature centrifugal pump and state-of-the-art magnetic



Fig. 7. The HeartMate III MCS.

technology. This system is currently being evaluated in an ongoing animal trial (Fig. 7).

WorldHeart

Company History. WorldHeart (www.worldheart.com) is a medical device business initially based on the HeartSaver® MCS and related technologies developed by the Cardiovascular Devices Division of the University of Ottawa Heart Institute. In 1989, the University of Ottawa Heart Institute's Cardiovascular Devices Division (CVD) began conducting research into and developing a fully implantable ventricular assist device capable of prolonging life and maintaining an acceptable quality of life at a reasonable cost. By the end of 1996, CVD had developed its artificial heart — the EMCS — and had proven that this unified system resolved each of these technical barriers.

In May 1996, WorldHeart acquired exclusive worldwide rights to the EMCS and related technologies developed by CVD, with the EMCS providing the basis for WorldHeart's HeartSaver. On June 30, 2000, WorldHeart completed the acquisition of Novacor®, the Oakland, CA, ventricular assist device operation previously owned by Edwards Lifesciences Inc. of Irvine, CA. This acquisition brought together the manufacturing and clinical experience of Novacor in the current generation of pulsatile ventricular assist devices with the next generation of fully implantable pulsatile MCSs, HeartSaver.

HeartSaver MCS D. WorldHeart's initial product was a unique, patented heart assist device fully implantable in the chest alongside the natural heart to provide long-term support of pulsatile blood flow in people suffering from advanced heart failure. The HeartSaver is intended for long-term use; leaves no permanent openings in the skin or tissue; and can be remotely powered, monitored, and controlled using patented transcutaneous energy transfer and proprietary biotelemetry technologies. Recipients are expected to leave the hospital and resume relatively normal day-to-day activities. In 2005, however, World Heart Inc. discontinued the development of the HeartSaver.

Novacor MCS D. The Novacor® MCS D was developed at Stanford University and used in the first successful MCS D bridge to transplant in 1984 (Portner *et al.*, 1989). The pump drive unit is implanted below the diaphragm, anterior to the posterior rectus sheath and connected in parallel to the natural circulation, taking blood from the left ventricle and returning it to the ascending aorta. Since 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; therefore, selection practices between different centers varied greatly, with a large percentage of patients moribund at the time of implantation.

In order to promote an evidence-based perspective in mechanically supported advanced heart failure patients, the Novacor European Registry was initiated in 1997 by clinicians (European Cardiology Advisory Board) active in the use of mechanical circulatory support (Deng *et al.*, 2001a). The Novacor has been in use for more than 15 years, and is considered the industry standard for durability and reliability. As of July 2006, more than 1700 implants have been done at over 90 centers worldwide, out of which 95 patients were supported for >1 year and 2 patients for >4 years. It was the first MCS D technology to be approved in Romania and pass the Drug & Food Council in Japan in June 2001. The Novacor is approved in Europe without restriction, and in the US and Canada for the BTT indication (Fig. 8).

Novacor II MCS D. Evolving from the original Novacor technology, the Novacor II next-generation MCS D currently under development is a

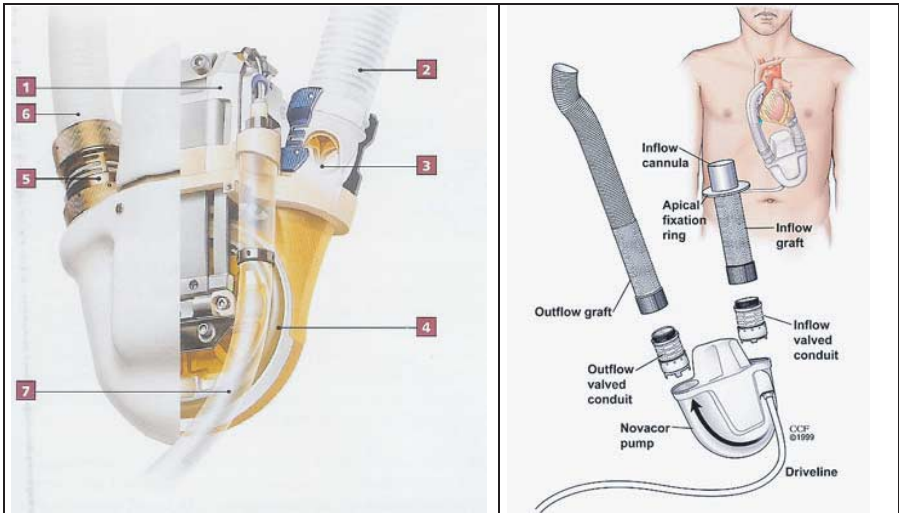


Fig. 8. The Novacor MCS.

miniaturized, bearingless, pulsatile ventricular assist system. Half the size of the first-generation pulsatile system, it retains the physiology pumping mechanism while reducing complexity. It can be fully implantable without the need for a volume compensator. The Novacor II contains no wearing elements (Golding *et al.*, 2006) (Fig. 9).

Novacor Rotary MCS. The Novacor Rotary VAD is a next-generation rotary blood pump intended for destination therapy. With blood-lubricated bearings, the Novacor Rotary VAD is a compact, centrifugal pump with an impeller that is completely magnetically levitated (MagLev™). Full magnetic levitation eliminates wear mechanisms within the pump. It also permits greater clearances and more optimized blood flow around the impeller, while eliminating dependence on the patient's blood for suspension. The Novacor Rotary VAD's levitation technology employs a unique combination of passive and single-axis active control. The Novacor Rotary VAD is not currently available. The clinical feasibility trial began in March 2006.

Like the current Novacor® LVAS, the Novacor Rotary VAD is implanted within the abdomen. Blood enters the pump through an inflow

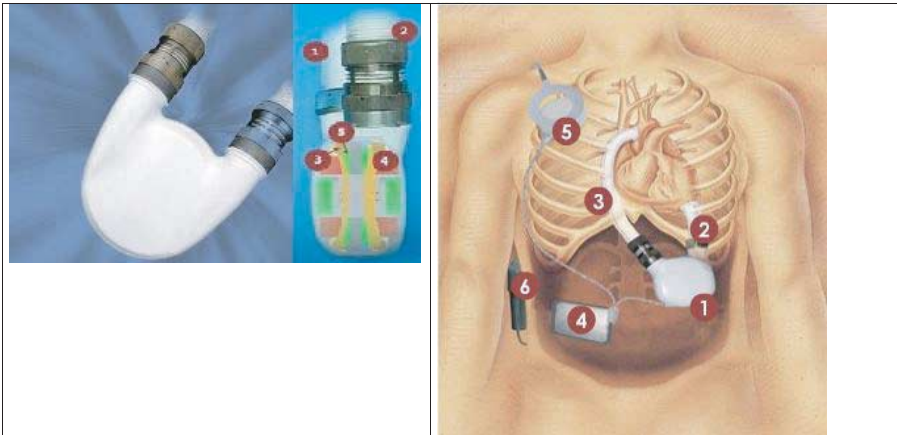


Fig. 9. The Novacor II MCS.

conduit connected to the recipient's left ventricle. The pump then ejects blood through an outflow conduit into the arterial system, thereby supporting the systemic circulation. The physiological control system, currently under development, will allow the device to be self-regulating, automatically adjusting the rotor speed in response to the recipient's changing circulatory requirements. In the initial configuration shown, a percutaneous (through the skin) lead will connect the implanted pump to an external controller and rechargeable power pack. This represents the simplest system with the fewest implanted components. Ultimately, the system could be made available in a fully implantable configuration, in which the controller and a standby battery pack are implanted. A transcutaneous (across the skin) energy transfer system (TETS) would conduct power from an external battery pack to the implanted system (Fig. 10).

MicroMed

Company History. MicroMed originated in 1984 (www.micro-medtech.com). In 1984, Dr Michael DeBakey and Dr George Noon performed heart transplant surgery on NASA–Johnson Space Center engineer David Saucier, following a severe heart attack. Six months later, Saucier returned to work with the desire to apply spacecraft technology to help

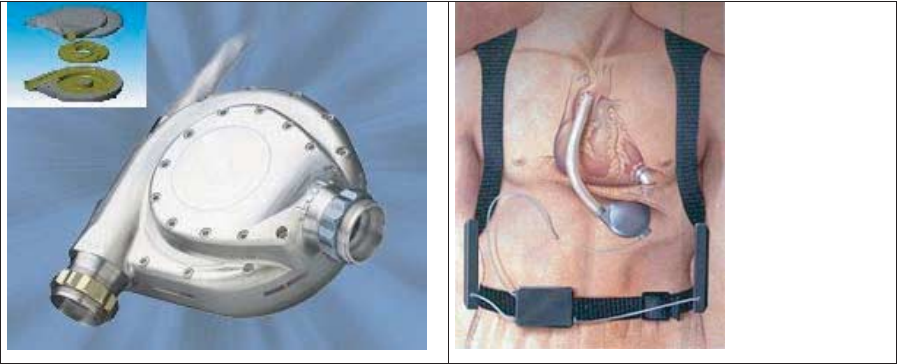


Fig. 10. The Novacor Rotary MCS.

people with diseased hearts. In 1987, informal meetings were initiated to design a low-cost, low-power implantable ventricular assist device. NASA began formal funding of the development of the device 4 years later, bringing space technology to earth-bound applications.

MicroMed DeBakey MCS. The MicroMed DeBakey® MCS is a miniaturized heart pump designed to provide increased blood flow (up to 10 L/min) from the left ventricle of the heart throughout the body for patients with end-stage heart failure. About 1/10 the size of competitive pulsatile MCS products on the market and weighing less than 4 ounces, the MicroMed DeBakey MCS® measures 1" × 3". This smaller size gives treatment hope to those with smaller body types, such as petite women and children, because larger devices cannot be implanted in them. The small size of the device and flexible percutaneous cable also enable lower infection rates. The MicroMed DeBakey MCS® was projected to be 1/3 less expensive than currently marketed pulsatile MCSs, making the process more affordable to a wider group of patients. The device's potential for decreased rates of hemolysis and thromboembolic complications improves its safety. The device only contains one moving part, the inducer/impeller. Third-party studies project that the mechanical durability will last in excess of 5 years. The MicroMed DeBakey MCS® is virtually silent compared to other devices, improving patient comfort while

on the device. Additionally, the portable controller and battery pack enables patient mobility to preserve quality of life.

In 1996, MicroMed received an exclusive license from NASA to use this rotary blood pump for cardiovascular applications. MicroMed then began the development of the critical support systems that would allow the device to be approved by regulatory agencies and to be utilized in life-saving applications in humans. European clinical trials of the MicroMed DeBakey MCS D began in November 1998, and CE Mark certification was awarded in May 2001. US clinical trials began in June 2000; and in April 2001, the FDA expanded the clinical trial parameters to 20 clinical sites and 178 patients. As of July 2006, over 380 patients at 14 heart centers in 7 countries have been implanted with the device (Fig. 11).

Jarvik Heart

Company History. Jarvik Heart, Inc. (www.jarvikheart.com), and the Texas Heart Institute have been developing the Jarvik 2000 for more than 10 years.

Jarvik 2000 MCS D. The Jarvik 2000 continuous flow pump MCS D is a nonpulsatile device developed by Robert Jarvik, one of the pioneers in the development of heart assist technologies. The Jarvik device is much simpler and more compact than pulsatile devices, operating at 25 000 rpm. About the size of a C battery, the Jarvik® 2000 MCS D is a valveless,

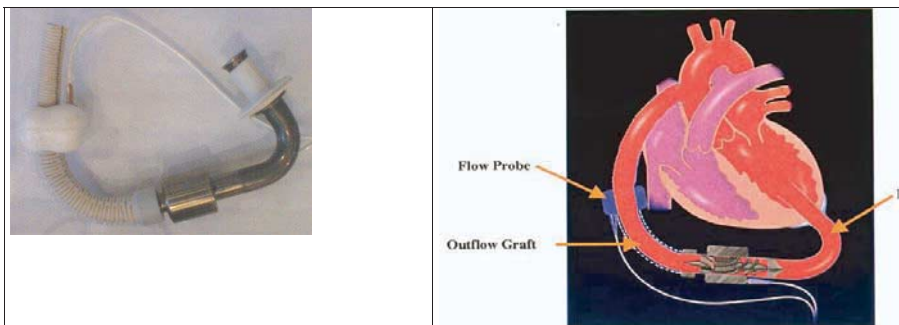


Fig. 11. The MicroMed DeBakey® MCS D.

electrically powered miniature axial flow pump that fits directly into the left ventricle and pushes oxygenated blood throughout the body.

The FDA has granted the Texas Heart Institute and St. Luke's Episcopal Hospital an initial Investigational Device Exemption for the implantation of the Jarvik 2000 as a bridge to transplant in a limited number of patients. While the Jarvik 2000 was initially developed for use as a bridge to transplant, Jarvik is in discussions with the FDA to determine the steps necessary to allow the device to be approved as a destination therapy. As of July 2006, over 100 patients have been implanted with this device (Fig. 12).

Arrow LionHeart

Company History. Arrow International, Inc. manufactures the Arrow LionHeart™ MCSD, the result of an 8-year collaboration between Arrow International (www.arrowintl.com) and the Department of Surgery's Section of Artificial Organs at Pennsylvania State University's Hershey Medical Center. Essential research in the area of sustained mechanical circulatory support that helped to define and develop the Arrow LionHeart™ MCSD has been ongoing at Pennsylvania State University for over 30 years.

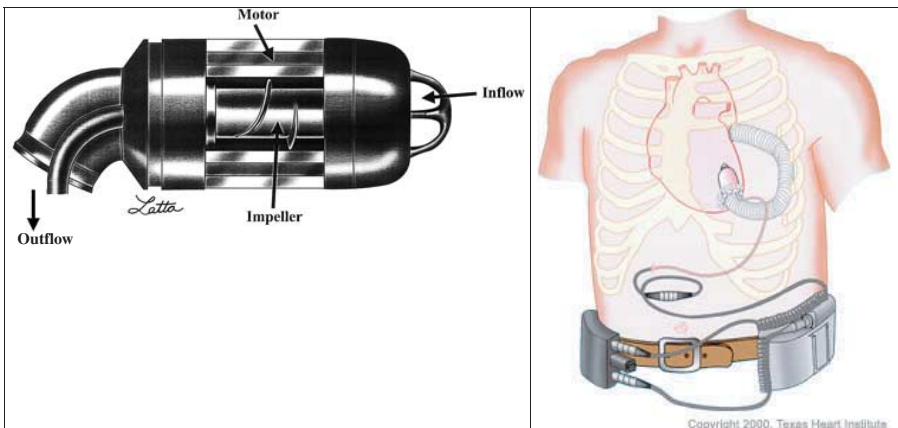


Fig. 12. The Jarvik MCSD.

LionHeart MCSD. The Arrow LionHeart™ MCSD, manufactured by Arrow International, Inc., was designed to be used as a long-term option for patients with progressive, irreversible end-stage (NYHA class IV) congestive heart failure, for whom heart transplantation is not an option. The Arrow LionHeart™ MCSD was not intended as a bridge to transplant or as a bridge to recovery of ventricular function. The LionHeart™ is fully implantable. The MCSD devices that are currently available require percutaneous drivelines and external tethers to a power source. In the Arrow LionHeart™ MCSD, these lines and tethers are eliminated through the use of a transcutaneous energy transmission system. Power is supplied in the Arrow LionHeart™ MCSD through transcutaneous energy, which charges implanted batteries in patients and allows patients to be completely untethered for approximately 20 minutes. This represents a significant advance in mechanical circulatory assist technology. A fully automated control algorithm automatically responds to changes in the recipient's condition.

The Arrow LionHeart™ MCSD optimizes the amount of blood that can be pumped to meet the patient's needs. The modular design of the Arrow LionHeart™ MCSD allows for the exchange of discrete subsystems that require replacement or upgrading over time. The blood pump is electrically powered and is implanted in the preperitoneal space, beneath the left costal margin. The blood pump features a motor, a pusher plate mechanism, a smooth blood sac, and two tilting disk valves for unidirectional flow. The blood pump is connected to the native circulation via inlet and outlet canulae. The motor controller and internal coil control the operation of the blood pump. The blood pump and electronic motor controller are powered by either external sources or rechargeable batteries located in the motor controller. External power is received transcutaneously by the internal coil, and sent to the motor controller and blood pump for continuous operation. The internal coil is placed in the subcutaneous tissue of the chest wall.

The compliance chamber and access port serve as a variable gas volume accumulator. The compliance chamber provides gas to evacuated chambers of the blood pump during its operation. This compliance chamber is periodically replenished via the access port with room air. The compliance chamber is placed in the left pleural space. The access port is passed through the intercostal space and located in the subcutaneous tissue over the left anterior chest wall.

The first human implant of the Arrow LionHeart™ MCS D occurred on October 26, 1999, at the Heart and Diabetes Center in Bad Oeynhausen, Germany. In February 2001, Arrow received an Investigational Device Exemption from the FDA to begin a seven-patient, phase I human clinical trial in the United States for its Arrow LionHeart™ system. The lead investigator for this pilot study is Dr Walter Pae of Penn State's Hershey Medical Center. All seven patients have been enrolled in the initial phase of the study. In December 2001, the FDA approved the addition of seven more phase I implants of the LionHeart™ in the US. These additional implants began in late January or February of 2002, following hospital approvals of amended patient section requirements and screening of potential patients, as part of an ongoing European clinical investigation sponsored by Arrow to demonstrate the safety and performance of the LionHeart™ MCS D for the purpose of obtaining a European Conformity Mark (CE), which was obtained in 2003. As per July 2006, a total of 26 patients have been implanted with the Arrow LionHeart™ MCS D (Fig. 13).

CardioWest

Company History. SynCardia Systems, Inc. (www.syncardia.com), is the manufacturer and distributor of the CardioWest temporary Total Artificial Heart (TAH-t). The CardioWest heart is a descendant of the Jarvik-7-70



Fig. 13. The LionHeart MCS D.

heart, which was developed at the University of Utah by Drs Jarvik, Kolff, Olsen, and others. In 1982, Barney Clark received the first artificial heart as a permanent replacement and survived on the device for 112 days. In 1985, at the University Medical Center, Tucson, AZ, heart surgeon Dr Jack G. Copeland and colleagues became the first in the world to use an artificial heart, the Jarvik-7-100, as a successful bridge to transplantation. The Jarvik 7-70, a smaller TAH, was designed to fit into smaller patients, and quickly became the preferred TAH because of its size and adequate cardiac output. A total of 175 patients were implanted with the Jarvik-7 and Jarvik-7-70 before the FDA withdrew the IDE from its sponsor, Symbion Corp., in January 1990.

In 1991, CardioWest, Inc (Tucson, AZ), was formed by Drs Don Olsen and Jack Copeland to continue the TAH technology and conduct a new FDA IDE trial of the TAH as a bridge-to-transplantation device. In 1998, CE approval was obtained for the CardioWest C-70 TAH-t. In order to commercialize the CardioWest TAH-t and complete the FDA IDE trial, SynCardia Systems, Inc., was formed in 2001 and acquired all assets of CardioWest, Inc., in 2002. In 2004, the CardioWest TAH-t received FDA approval as a bridge-to-transplantation device.

CardioWest TAH-t. The CardioWest TAH-t is a biventricular pulsatile pump that replaces the failing heart and serves as a bridge to transplantation. The CardioWest TAH-t has prosthetic ventricles made of polyurethane and four Medtronic-Hall mechanical valves. Blood and air are separated by a seamless, four-layer, polyurethane diaphragm, which is pushed down by blood during diastole and is displaced forward by compressed air during systole to propel blood out of the ventricles. The TAH-t can provide flows of up to 9.5 L/min or more; typically, it is operated with flows of 6–8 L/min. The Circulatory Support System (CSS) Console, along with the WCOMDU software program, operates the CardioWest TAH-t in the hospital while patients await transplantation. In Europe, SynCardia Systems, Inc., has CE approval to use the Berlin Heart EXCOR TAH-t Portable Driver on TAH-t patients who are stable in the hospital or who are discharged home while awaiting a donor heart. By the end of 2006, the CardioWest TAH-t had been implanted in 635 patients for a total duration of over 100 patient-years. The CardioWest TAH-t is the only FDA-approved artificial heart used as a temporary device for bridge to transplantation (Copeland *et al.*, 2004) (Fig. 14).

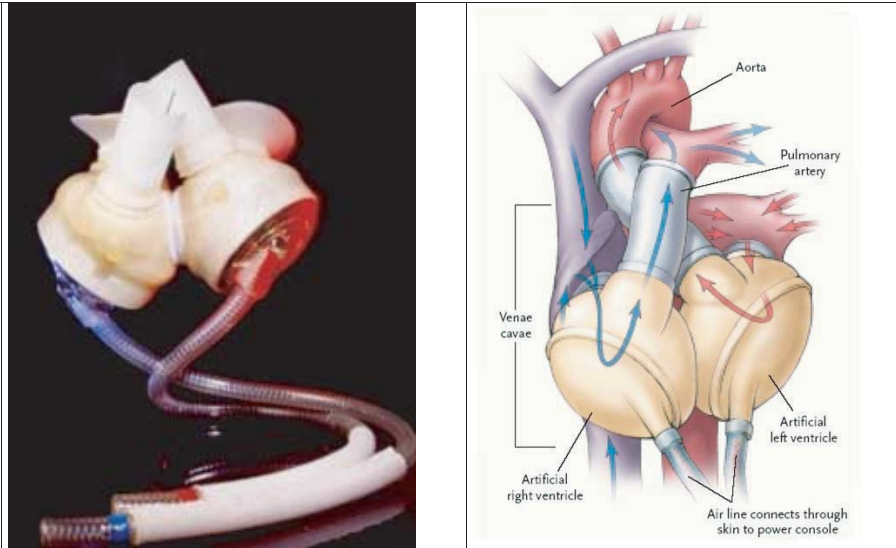


Fig. 14. The CardioWest MCS.

Abiomed

Company History. The cardiac assist and heart replacement products developed by Abiomed (www.abiomed.com) are designed to complement and/or simulate the heart's natural pumping action. Abiomed's first cardiovascular product, the BVS® 5000 Bi-ventricular Support System, is now the most widely used advanced cardiac assist system worldwide. The quest for an artificial heart started with the advent of successful heart surgery to remove shell fragments from soldiers during World War II.

Abiomed BVS 5000. Abiomed's BVS® 5000 cardiac support system provides a patient's failing heart with full circulatory assistance while allowing the heart to rest, heal, and recover its function. The BVS 5000 has been approved in the FDA's rigorous PMA process as a bridge-to-recovery device for the treatment of all patients with potentially reversible heart failure. It is now the most widely used advanced cardiac assist system in the world. It is installed in 600 leading medical centers worldwide. The BVS 5000 is most frequently used in patients whose hearts

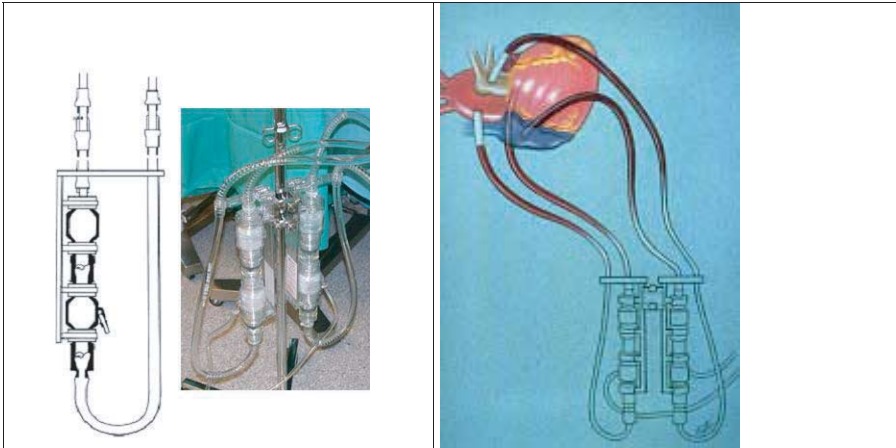


Fig. 15a. The Abiomed BVS 5000 MCS.



Fig. 15b. The Abiomed AB 5000 MCS.

do not immediately recover their function following heart surgery. As of July 2006, more than 3000 systems have been implanted worldwide (Fig. 15a).

Abiomed AB 5000. Abiomed’s AB® 5000 cardiac support system also provides a patient’s failing heart with full circulatory assistance while allowing the heart to rest, heal, and recover its function. The Abiomed

AB 5000 ventricular assist device is a system recently approved by the Food and Drug Administration that consists of a fully automatic, vacuum-assisted console and a paracorporeal, pneumatically driven blood pump. The VAD is designed for short- or intermediate-term use. The console is designed to support the BVS 5000 or AB 5000 blood pumps. The cannulas and implantation are similar to the BVS 5000 system. The Abiomed AB 5000 was designed to be an upgrade to the BVS 5000 in terms of patient mobility, blood pump durability, and overall versatility. As of July 2006, more than 30 systems have been implanted worldwide (Fig. 15b).

AbioCor. The AbioCor™ Implantable Replacement Heart is a fully implantable prosthetic system intended as a substitute for severely diseased human hearts in patients suffering from coronary heart disease or some form of end-stage congestive heart failure. When these patients are at imminent risk of death, the AbioCor is designed to both extend life and provide a reasonable quality of life. After implantation, the device does not require any tubes or wires to pass through the skin. The power to drive the prosthetic heart is transmitted across the intact skin, thus avoiding skin penetration, which may provide opportunities for infection.

The AbioCor Implantable Replacement Heart consists of two blood-pumping chambers. The right pump supplies blood to the lungs, while the left pump provides blood to other vital organs of the body. Each of the two pumps is capable of delivering more than 8 L of blood per min. The replacement heart is about the size of a grapefruit and is quiet. A stethoscope is required to listen to the heart sounds. The pumps and valves are made from Angioflex™, a proprietary Abiomed material. An internal controller regulates the power delivered to the prosthetic heart. Without penetrating the skin, an external unit transmits power to the internal unit. A rechargeable internal battery allows the patient to be completely free of the external power transmission unit for some period of time monitored by the internal system. The AbioCor system is designed to increase or decrease its pump rate in response to bodily needs. The AbioCor also includes an active monitoring system that provides detailed performance feedback, and alarms in the event of irregularities.

As of mid-November 2001, a total of 273 patient-days were accumulated with the AbioCor, with no significant problems observed (except

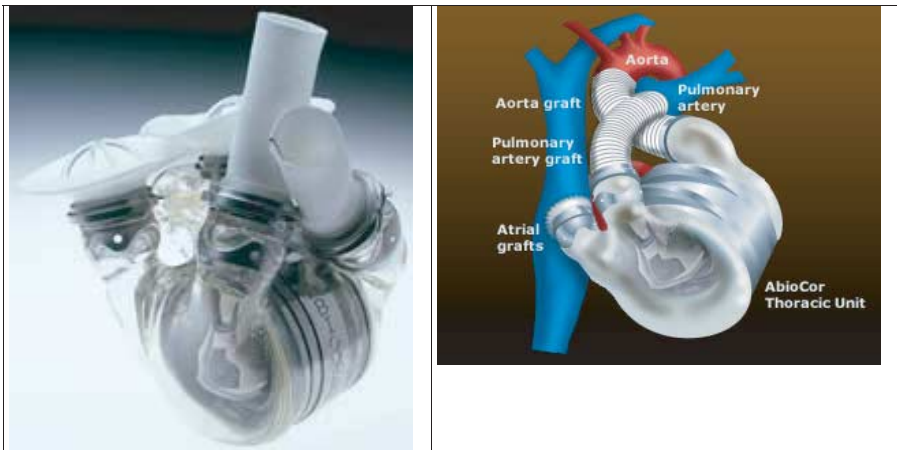


Fig. 16. The AbioCor MCS.

for the incident with the first patient). All patients who received the implants had a 30-day estimated survival of less than 30% prior to receiving their implant. As of July 2006, fourteen patients have received AbioCor implants, and the first patient has had the device in place for over 130 days. As part of the Humanitarian Device Exemption (HDE) program, the US FDA has approved the AbioCor for destination implantation (www.fda.gov/bbs/topics/NEWS/2006/NEW01443) (Fig. 16).

MEDOS

Company History. MEDOS is a German medical device company that has developed a unique multifunctional approach to MCSs (www.medos-ag.de).

MEDOS MCS. The MEDOS MCS System is a mechanical assist device for short- and medium-term heart assist. The MEDOS ventricles were developed according to a construction-size concept. It allows high flexibility with the application of the system as a univentricular and biventricular assist device for the complete patient spectrum, ranging from infant to adult. The MEDOS driving unit was developed especially for

the use of the MEDOS Ventricle, which is the main component of the MEDOS System. This blood pump is known for excellent flow features and biocompatibility, and was developed in line with the latest know-how in construction techniques and hemodynamics. Pressured air or vacuum is created by the MEDOS VAD Driving System, which shifts the position of the double-layered membrane in such a way that the volume on the blood side is rhythmically enlarged or reduced. The three-leaflet valve prosthesis of polyurethane, developed especially for this application, adjusts the bloodstream of the pump; the consequently emerging pulsatile blood flow corresponds to the natural support of the heart.

In order to optimally support patients ranging from infants to heavy-weight adults, the MEDOS Ventricles are available in different sizes: Adult HiFlux (80/72 mL), Adult (80/72 mL and 60/54 mL), Children (25/22.5 mL), and Infants (10/9 mL). The MEDOS VAD Cannulas are especially adjusted to the various pump sizes, and guarantee optimal flow conditions and a high degree of flexibility. As per July 2006, the MEDOS System has been used in more than 350 applications in 84 hospitals worldwide as a bridge to recovery as well as a bridge to transplant in the age



Fig. 17. The MEDOS MCS.

range of 4 days to 76 years and weight range of 3 kg to 135 kg in left ventricular, right ventricular, and biventricular applications (Fig. 17).

Ventricor

Company History. Ventracor is an Australian company producing the mechanical circulatory support device VentrAssist™ Left Ventricular Assist Device (LVAD) (www.ventracor.com).

VentrAssist. The VentrAssist™ is a new third-generation implantable heart device primarily designed as an alternative to heart transplantation for people with cardiac failure. It may also be used for patients waiting for heart transplants as a bridge to transplant or as a bridge to recovery. It is a blood pump that connects to the left ventricle of the diseased heart to help the ailing heart's pumping function and to assist in restoring a better quality of life. VentrAssist™ has only one moving part: a hydrodynamically suspended impeller with a fully redundant backup motor drive, controller, and processor. It has been designed not to have any wearing parts or cause blood damage. It weighs 298 g (10 oz) and measures 60 mm (2.5 inches) in diameter, making it suitable for both children and adults. The implanted parts of the VentrAssist™ device use materials that are fully biocompatible, including titanium alloys with diamond-like carbon coating on blood-contacting surfaces. Its components are light, strong, nontoxic, and highly resistant to degradation within the body.

As per July 2006, Ventracor is the only company with a third-generation LVAD in clinical trials in the USA. In Europe, enrollment targets under the CE Mark Trial have all been met, and Ventracor expects to obtain CE market approval for the commencement of commercial sales in Europe in early 2007. In the US, the Food and Drug Administration (FDA) requires separate clinical trials for bridge to transplant (BTT) and destination therapy (DT). The US Feasibility Trial is aimed at obtaining initial safety data in order to satisfy the regulatory requirements to proceed to the US Bridge to Transplant Pivotal Trial and the US Destination Therapy Trial, which may be run concurrently. Ventracor is currently conducting a five-center, 10-patient US feasibility trial (Fig. 18).

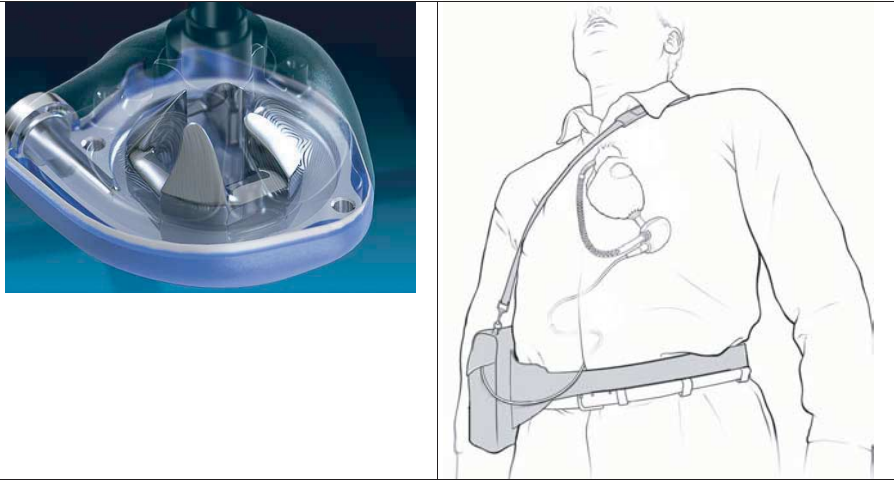


Fig. 18. The Ventracor MCS.

BerlinHeart

Company History. BerlinHeart is a German company producing the MCS BerlinHeart and INCOR (www.berlinheart.com). BerlinHeart AG develops, produces, and trades innovative devices for the mechanical support of the heart. Its products — INCOR®, EXCOR®, and EXCOR® Pediatric — cover the whole range of medical indication for all ages, from the newborn to the adult. As a result, the international BerlinHeart AG is the market leader in Germany and Europe. The claim is to develop trend-setting solutions with the utmost precision and reliability. The short period of innovation and the technological characteristics of its products are unique. Since the foundation of the wholly owned subsidiary BerlinHeart, Inc., in October 2005, the company is also represented in the US.

INCOR® MCS. The INCOR® MCS is an implantable left ventricle assist device. Its global uniqueness lies in the free-floating, active magnetic bearing of the axial impeller. INCOR® has been specially conceived to deal with increasingly long-term applications within the destination therapy framework, so that it is in a position to take over the work of the left ventricle without any wear to the parts and on a permanent basis. Naturally,

INCOR® is also used in bridge-to-transplant and bridge-to-recovery programs. In addition to the implantable pump, the INCOR® system also includes a small external control unit and rechargeable batteries that help the patient to enjoy almost unrestricted mobility. Further external components are a laptop, through which the pump can be started up, monitored, and adjusted; a power supply unit; and a battery charger.

The blood coming from the heart flows into the INCOR® axial flow pump and first passes the inducer, which guides the laminar flow onto the actual impeller. The impeller is suspended by a magnetic bearing and floats free of contact with other parts. It is responsible for the actual pumping, operating at speeds between 5000 and 10000 rotations per min. The stationary diffuser behind the rotor has specially aligned blades, which reduce the rotational effects of the blood flow and add additional pressure to assist the transport of the blood from the outflow cannula to the aorta. The necessary power to drive the pump is supplied through a cable inserted under the skin on the patient's right side. This cable is connected to a small control unit that monitors and regulates the whole system. A main power pack and a backup power pack are attached to the control unit and supply INCOR® with sufficient electrical current. INCOR® generates a steady blood flow which, in combination with the residual activity of the native left ventricle, leads to reduced pulsatility for the patient. The blood contact surfaces of INCOR® are coated with Carmeda® BioActive Surface.

INCOR® is the only axial system worldwide to be equipped with an active magnetic bearing that allows for a freely floating impeller. The INCOR® impeller is axially active and radially passive without producing any actual physical contact. There is no direct mechanical contact between it — as the only movable part in the INCOR® pump — and its static components. This prevents any mechanical friction and, therefore, produces no frictional heat. This means no wear and tear at all to the parts and, consequently, a potentially infinite product life span for the INCOR® heart support system.

The company designed the blades of the internal components using numerical simulations of laser measurements in a fluid dynamics model, which suggests a significant reduction in the rate of hemolysis. The INCOR® motor is extremely efficient (>90%), and therefore has an exceedingly low energy consumption. Any warming of the pump in operation is so minimal that no denaturation of proteins occurs. Both these factors stand in stark contrast to mechanical bearings, which generate at

least local heat (in accordance with the laws of physics) and cause possible thrombal problems through blood protein denaturation. The extremely precise sensors linked to the magnetic bearing supply the patient and the user with a wealth of important data about flow rates and pump performance. These values are also utilized by the pulsatility control. This prevents any suction through the pump in the left ventricle by detecting the residual pulsatility linked with it. The pump then automatically reduces its rotation speed and allows a renewed filling of the ventricle. The originally selected pump performance is then restored slowly and in a controlled way.

Because of its small size, the INCOR® pump is easily implantable. The installation of a separate pump pack is not necessary. An additional special feature is the new snap-in fasteners, which ensure a safe, quick, and uncomplicated connection between pump and cannulas. The silicone sheath prevents an ingrowing of the surrounding tissue. The percutaneous pump cable connects the INCOR® pump with the small external power pack. It is completely encased in silicone. At the place where the cable enters the skin, there is also a polyester velour coating to guarantee safe healing (Fig. 19). INCOR® was first used in clinical studies in June 2002, and received CE mark approval in March 2003. As of January 2007, the INCOR® LVAD has been used in 313 patients in 15 countries.

EXCOR® MCS. The EXCOR® ventricular assist device can be used to support one or both ventricles. The blood pump consists of a transparent



Fig. 19. The INCOR MCS.

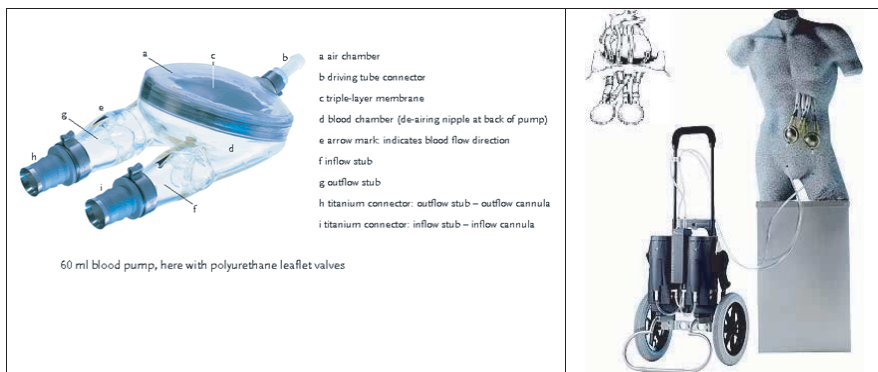


Fig. 20. The EXCOR MCS.

polyurethane housing that is divided into one air chamber and one blood chamber by a three-layer membrane. Graphite between the membranes helps to minimize friction. The membrane on the blood side merges without a seam into the surface of the housing. A specially produced CARMEDA® coating is plated on the slick, flow-optimized blood contact surface. Inflow and outflow sockets, which are made of polyurethane and bear titan connectors for the connection of the cannulas, lead from the blood chamber to the inflow or outflow cannulas. On the air side of the membrane lays the connection for the pneumatic driving tube. Deairing is effected through the deairing socket. Mechanical valves in the sockets ensure an adjusted blood flow. The blood pumps are available with two different types of valves: a tilting disc, which is approved and reliable for long-term applications; and a polyurethane valve, which operates soundless (Fig. 20). EXCOR® was first used in June 1988. As of January 2007, it has been used in 26 countries in 1600 patients, of which 237 were pediatric patients. In North America, it has been used in 74 patients in 26 clinics since 2000.

Terumo

Company History. Terumo Heart, Inc. (Ann Arbor, MI), is a wholly owned US subsidiary of Terumo Corp. (Tokyo, Japan), producing a third-generation centrifugal pump called DuraHeart™ LVAS.

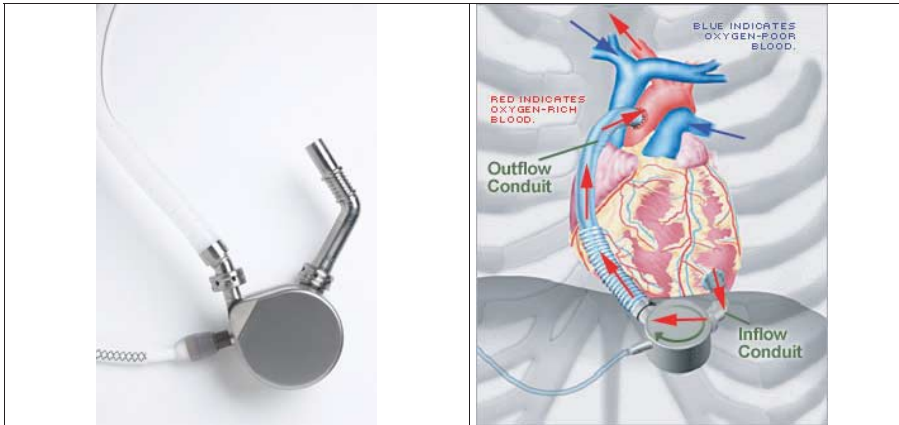


Fig. 21. The DuraHeart MCS.

DuraHeart. DuraHeart™ (Terumo Heart, Inc., Ann Arbor, MI) is a third-generation LVAD comprising a centrifugal blood pump with a magnetically levitated impeller. The pump consists of a titanium blood chamber containing an impeller, and two titanium compartments housing an electromagnetic bearing mechanism and a brushless DC motor. The motor is magnetically coupled to the impeller without a mechanical shaft. The impeller rotates inside the blood chamber without material wear. The blood-contacting surfaces of the pump are modified with a heparin immobilization technique to enhance blood compatibility. The pump was first implanted in Bad Oeynhausen, Germany, for the European multicenter clinical trial. As of January 2007, twenty-nine devices have been implanted with a mean duration of 165 days. Eleven patients were supported for more than 6 months, and 4 for more than 1 year (Golding *et al.*, 2006) (Fig. 21).

CorAide

Company History. Arrow International, in collaboration with the Cleveland Clinic Foundation, produces the CorAide™ MCS (www.arrowintl.com).

Company History. The Arrow CorAide (Cleveland Clinic, Learner Research Institute, Cleveland, OH) is a third-generation centrifugal titanium pump. Problems with rotor balancing and thrombus deposition led

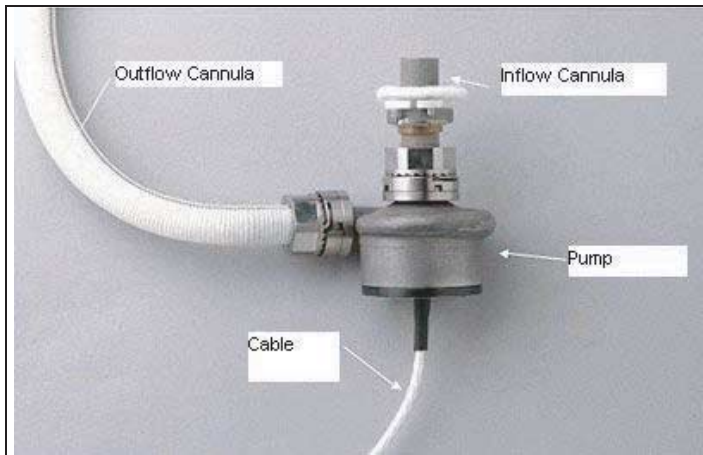


Fig. 22. The CorAide MCS D.

to significant design revision to a more conventional radial design, but with a continuation of the rotor suspension method, the blood-lubricated journal bearing, and the inverted contact-free motor. The Arrow-patented apical cuff clamp allows for positioning and fixation of the apical cannula to optimize flow into the biocompatible coated pump. The first clinical trial was initiated in Europe in 2003; but after the first implanted device was replaced with another bridge device, the clinical trial was suspended. Hemolysis by the journal-bearing clearance dimensions and the effect of that on the critical thickness of the lubricating thin film were the major cause. In February 2005, the European Bridge-to-Transplant Clinical Trial was restarted. As of July 2006, 21 implants have been done; patients were supported for 23–400+ days. (Golding *et al.*, 2006) (Fig. 22).

EvaHeart

Company History. EVAHEART is a Japanese company (www.evaheart-usa.com) producing the EVAHEART Left Ventricular Assist Device MCS D.

EVAHEART MCS D. The EVAHEART Left Ventricular Assist Device is a third-generation centrifugal pump. The pump has a unique thromboresistant coating (2-methacryloyloxyethyl phosphorylcholine) over its

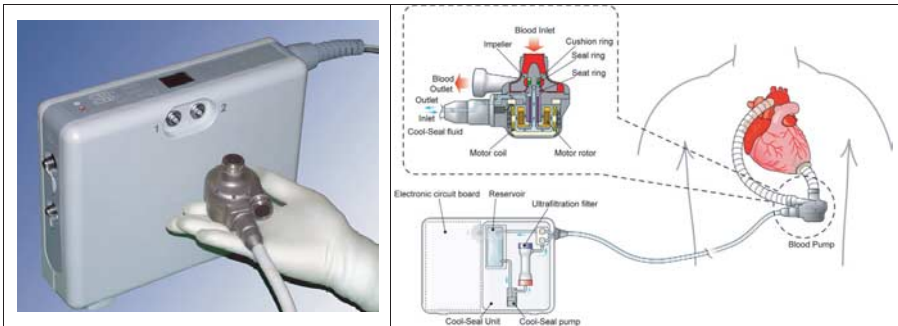


Fig. 23. The EVAHEART MCSD.

blood-contacting surfaces. The impeller is cooled with fluid that is pumped by way of a percutaneous channel from an external device. Electric power to the motor stator creates a rotating magnetic field, which is coupled inactively to the permanent magnet that is bonded to the pump shaft. A pilot bridge-to-transplant clinical trial was initiated in Japan in 2005. Three patients were implanted with the device, and all survived the 98- to 164-day support (Golding *et al.*, 2006) (Fig. 23).

HeartWare

Company History. HeartWare's head office is located in Sydney, Australia. HeartWare's technology is based on a proprietary miniaturization platform, which allows the development of smaller devices that are designed for long-term use and may be implantable by minimally invasive techniques.

Heartware MCSD. HeartWare's left ventricular assist device (HVAD™) system is the company's first product to undergo human implantation. The device can generate up to 10L/min flow, and is designed for use in a wide range of patients because it has a diameter of 4cm and a height of less than 2cm with an integrated inflow conduit. The small size of the HVAD™ pump allows intrapericardial placement, which reduces surgical trauma and facilitates the implant procedure. A unique wide-bladed impeller integrates magnets within the impeller blades, which reduces the pump height and

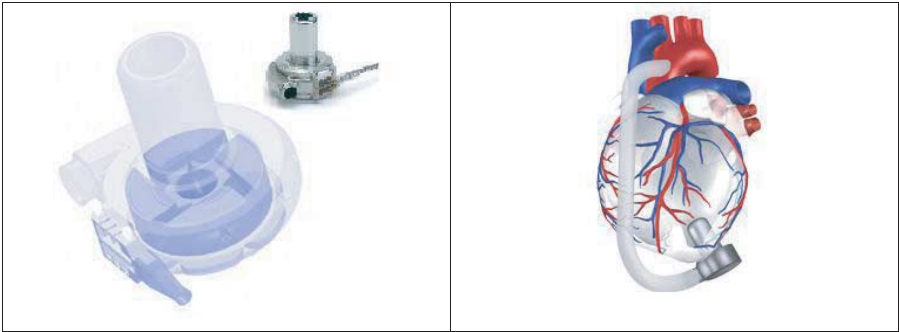


Fig. 24. The HeartWare MCS.

permits the use of redundant motors in the pump housing for added safety. The impeller is the only moving part, and is suspended by a proprietary hybrid magnetic and hydrodynamic bearing system. The HVAD™ pump contains no sensors, mechanical bearings, or points of physical contact within the pump housing. These design features allow the HVAD™ pump to be smaller, quieter, and more durable than otherwise possible.

HeartWare is currently running a combined European and Australian bridge-to-transplant clinical trial aimed at achieving CE mark and TGA approval for the HVAD™ system. Implants are conducted at a minimum of five centers, including Vienna General Hospital (Austria), Royal Perth Hospital (Australia), St Vincent's Hospital (Australia), Harefield Hospital (UK), and Hannover Medical Center (Germany). Trials began in March 2006, when the first implant was conducted at Vienna General Hospital, Austria. As of January 2007, seven patients have undergone implantation of the HVAD™ pump and are awaiting transplantation. HeartWare plans to begin a bridge-to-transplant clinical trial in the United States towards the end of 2007, subject to FDA approval. A destination therapy trial will commence after initiation of the US bridge-to-transplant trial (Fig. 24).