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CONSENSUS CONFERENCE REPORT

Mechanical Cardiac Support 2000: Current Applications and Future Trial Design

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Bethesda, Maryland

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of Thoracic Surgeons, and the American Society of Transplant Surgeons.* Additionally, participants included members of these agencies: Food and Drug Administration, National Institutes of Health, and the American Society for Artificial Internal Organs.

TABLE OF CONTENTS

IMPACT STATEMENT

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

The participants concluded that important differences between devices and drugs may warrant novel study designs characterized by innovation and flexibility. While the randomized clinical trial remains the most powerful tool for unambiguous comparison of interventions, variations may include timed graduation from control to investigational therapies, assignment influenced by patient risk or patient preferences and criteria for an optional crossover to compassionate device use. A major impact would result from a national outcomes database for advanced heart failure that identifies high-risk populations with

*The recommendations set forth in this report are those of the conference participants and do not necessarily reflect the official position of the American College of Cardiology. The full text document will be published in the *Journal of the American College of Cardiology*, and the executive summary will be published in *Circulation*, the *Journal of Heart and Lung Transplantation*, and the *Journal of Thoracic and Cardiovascular Surgery*. This document is available on the World Wide Web site of the American College of Cardiology (www.acc.org). Reprints of this document are available for $5.00 each by calling 800-253-4636 (U.S. only) or by writing the Resource Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20814.

JACC Vol. 37, No. 1, 2001
January 2001:340–70

the greatest potential for benefit from newer therapies and thus facilitates the design of devices and device trials. A separate registry with industry of outcomes after device placement would help to identify "breakthrough" device therapies and facilitate the refinement and acceptance of this new technology. As represented in this conference, progress in mechanical circulatory support will be accelerated by the continued coordination of scientists, engineers, industry, clinical investigators and regulatory and payment agencies in prospective partnership.

INTRODUCTION

Over the past five years, mechanical circulatory support devices have evolved from the earlier investigational stages to become standard therapy for bridging to transplantation, in some cases extending beyond original indications. As the first randomized controlled trial of mechanical circulatory support, the Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure (REMATCH) trial began in 1998 and has undergone regular protocol modifications resulting from experiences gained with the patient population and the devices themselves. In 1999, an expert review panel for the National Heart, Lung and Blood Institute (NHLBI) recommended continued support for the development of total artificial heart programs. Refinement of currently available left ventricular (LV) devices continues steadily, and many new types of support devices are in or approaching clinical trials. Ethical and practical issues have emerged regarding the design and funding of these future clinical trials. Challenges for optimal application are being compounded as the separation between indications for recovery, bridge to transplantation and permanent use is becoming less distinct.

As in the original conference on trial design for mechanical circulatory support led by Pae in 1995, the goals of investigators, governmental agencies and industry remain the establishment of clinical trials that are "scientifically sound, clinically meaningful and achievable in a finite time frame at reasonable expense." With the rapid increase in experience with populations of advanced heart failure, broader clinical application of available devices and the promise of new technology for future support, members of the steering group for the NHLBI, the Food and Drug Administration (FDA), the American College of Cardiology Committee on End-Stage Heart Failure and the International Society for Heart and Lung Transplantation sought broad representation from professional societies and industry to address the issues involved in trial design for mechanical circulatory support looking ahead from 2000.

The professional societies with significant interest in this field were invited to co-sponsor this conference and to select delegates to participate in the discussion and writing of the draft document. The writing groups established the basis of their conclusions for discussion and subsequent revision by all participants during the conference at the Heart House in Bethesda, Maryland, to which representatives of industry were also invited. The published document represents the consensus of the participants, as approved by the Steering Committee, and does not imply formal acceptance by any of the societies represented. New developments will render the specifics of this document obsolete, but it is hoped that the fundamental considerations established here will help to guide trial design and clinical decisions for the near future.

EXECUTIVE SUMMARY

Present Status of Devices for Heart Failure

Current use of mechanical circulatory support devices is dominated by the indications of post-cardiotomy shock and bridging to cardiac transplantation. In the U.S., about 6,000 patients a year receive support devices after cardiac surgery, with hospital survival of 20% to 40%. Sustained improvement of native heart function after support also occurs in 5% to 15% of transplant candidates, with greater frequency of recovery in patients with fulminant myocarditis. Bridging to cardiac transplantation occurs in 300 to 400 patients yearly in the U.S., with an overall discharge rate of 50% to 70% from device implantation through transplantation.

Limitations in our current conception of device indications need to be recognized. First, the need for biventricular versus univentricular support is difficult to determine. Second, the ultimate utility of a total artificial heart versus ventricular assist device(s) (VAD) has not been established. Third, the intended duration of mechanical support is a moving target. The time and type of device utilization is influenced by external factors such as the time to myocardial recovery, donor organ availability, the potential of outpatient therapy and the unpredictability of adverse events associated with new technology. Thus, even within the field of currently used devices, evolving indications mandate flexible guidelines for utilization.

Development of Drugs and Surgical Devices for Advanced Heart Failure

Observation provided the basis for early therapies of heart failure, many of which have subsequently been abandoned. A systematic approach to testing pharmacologic therapies in heart failure has arisen only within the last 20 years. The basis of evidence supporting the current medical therapy with angiotensin-converting enzyme inhibitors and beta-adrenergic receptor antagonists has arisen from double-blind, randomized controlled trials in hundreds to thousands of patients with mild to moderate heart failure. Except for digoxin, oral inotropic agents have been shown in controlled trials to increase mortality, despite sound theoretical rationale. The template of the double-blind, randomized control trial has emerged as the gold standard for evaluating new pharmacologic therapies. It has not been applied to urgent therapies such as diuretics for relief of pulmonary edema and intravenous inotropic agents for cardiogenic shock (CS), during which placebo therapies might be regarded as unacceptable.

Many surgical approaches have been introduced for heart failure. The coronary artery surgery trial demonstrated benefit in patients with reduced left ventricular ejection fractions (LVEFs) but did not target patients with symptomatic heart failure. Requiring five years to complete enrollment, the trial of revascularization for acute CS demonstrated benefit in patients <75 years of age. Revascularization, valve surgery and other remodeling techniques are being employed for some patients with more severe chronic heart failure (HF). The inability to provide comparable placebo therapy, strong patient preferences regarding invasive procedures, and the front-loaded risk of operative procedures have complicated the evaluation of these new approaches.

Fundamental differences between drugs and devices. As therapies for heart failure advance beyond drugs into procedures and devices, fundamental differences emerge in the evaluation of efficacy. By contrast with drug development, progress with devices is more incremental, with experience leading to progressive device modifications. The impact of devices is more transparent, in part because the most obvious risks are front-loaded compared with those from new drugs. It is harder for the effects of devices to be masked or mimicked by the natural history of heart failure. Practical considerations relate to the higher order of magnitude of expense per patient in a trial, which can be prohibitive for companies without major revenue from previous products. The clinically meaningful benefit, however, is projected to be larger than the benefit of new drugs, such that estimated sample sizes are in hundreds rather than thousands of subjects. The experience and skill necessary to achieve optimal outcomes restrict center participation in trials and limit the generalizability of results. A crucial difference between drugs and devices is the inability to blind patients or physicians to therapy, a limitation with both ethical and practical implications for clinical trials.

The sum of evidence guiding therapy with drugs is dominated by evidence from large trials completed prior to drug approval. Once it is approved, it is difficult to identify use and attribute effects of any particular drug because of variable prescription, adherence and combination with other medications. For this reason, post-marketing surveillance provides limited information regarding drugs for heart failure, except for non-cardiovascular side effects. By contrast, the very complexity and undisguised impact of devices render their use and outcomes easier to track, as long as appropriate registries are maintained. The cumulative body of evidence guiding the ultimate use of devices may be drawn more from information gained after initial approval.

Target Populations and End Points for Mechanical Circulatory Support

Target populations for mechanical circulatory support can be defined by the expected natural history of heart failure. Patients with CS have an in-hospital mortality of >50% but also carry high risk for patient-related operative complications. Ambulatory patients without resting symptoms on standard oral therapy often survive for two years or longer. Despite various approaches to risk stratification, it remains hard to specify an intermediate-risk population. For patients receiving outpatient intravenous inotropic therapy, the six-month mortality is currently in the range of 50%. However, without objective indications for and restrictions on this therapy, it may encroach on the population with less advanced disease. Another target population might be cardiac transplant patients with triple vessel coronary artery disease (CAD) and decreased ejection fraction, with <50% one-year survival, but mechanical devices in the post-transplant population may be complicated by previous surgery and immunosuppression. The target population for trials should be defined widely to include patients with the best natural history compatible with the degree of certainty that a given device will provide an improvement. This would be greatly facilitated by a multicenter registry of advanced heart failure. After approval, ongoing re-evaluation of a successful device should reflect the observed trend for downshifting risks, in which procedures with proven benefit in a high-risk population become generalized to patients with less risk of post-operative complications but potentially less benefit.

End points for clinical trials will be chosen according to the severity of disease in the population selected. For patients with the most severe disease, early survival will be a fundamental end point. A combination of early survival and functional end points may be most appropriate for trials allowing eventual device placement in patients randomized to medical therapy. As the risk of death becomes imminent, measurements of functional capacity, quality of life and survival adjusted for patient preferences become increasingly relevant. At all levels, measures of efficacy will need to be supplemented by measures of cost-effectiveness. It should be emphasized, however, that cost-effectiveness for a successful device is likely to improve after approval, as experience is gained and costs are decreased.

The Spectrum Including "Breakthrough" Devices

In the future, initial studies could identify a therapy with such an obvious impact on survival that it would be considered a "breakthrough" for a population with otherwise high early mortality (Fig. 1). In retrospect, cardiac transplantation was considered a breakthrough that has been widely accepted without a controlled study. Most new therapies do not enter the breakthrough realm during preliminary testing but fall somewhere else along the spectrum before approval. Outside of breakthroughs, there may be some therapies that are not yet approved but are considered by experienced clinicians to be so effective that waiting for a controlled trial would not be ethical. The best way to bridge this gap to expedite approval from regulatory agencies has not yet been determined for any of the life-threatening diseases. The focus of this conference is not on the approval process but on designing trials of devices for

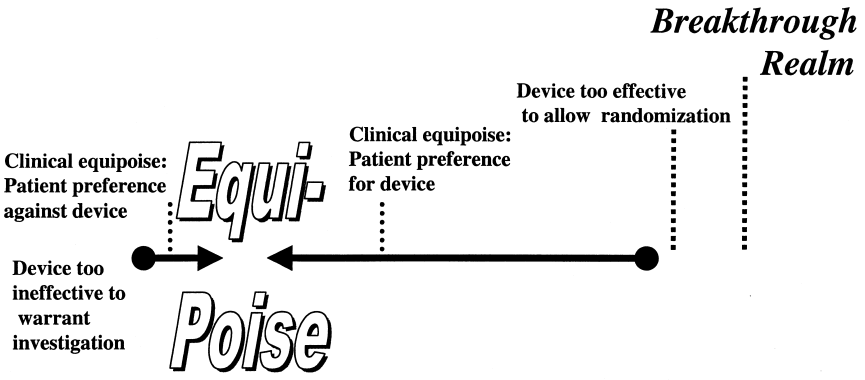

Figure 1. Line depicting the relationship between equipoise and efficacy of a new therapy, as perceived after initial clinical testing. It is possible that the early experience could be so dramatic that both the scientific and regulatory community regard it as a "breakthrough" therapy that should be approved without further investigation for the defined population. Initial experience could also demonstrate sufficient success that the scientific community is convinced of efficacy, while the regulatory agencies require further information. This gap might be bridged by continued clinical investigation at limited sites, with prospective definition of a non-randomized cohort for comparison. In the majority of cases, initial testing does not establish efficacy, and clinical equipoise can be maintained for the performance of randomized controlled trials. It is anticipated that patient preference regarding new therapies will most often lie to the right of clinical equipoise, complicating trials of therapies that cannot be blinded. The asymmetry of the line to the right of equipoise reflects the enthusiasm necessary to drive any therapy through clinical evaluation.

which there is reasonable doubt regarding efficacy. Even for devices in the breakthrough realm for end-stage disease, the design of trials would remain relevant for extension to those populations with lesser severity of illness, in whom the benefit of the device could not be assumed.

Trial Design for Mechanical Circulatory Support

All new devices are required by the Medical Device Amendments Act to be "safe and effective," as shown through "well-controlled scientific studies" or "valid scientific evidence." Because mechanical circulatory support devices fall into the highest of three risk categories, the sponsor must conduct clinical trials before the FDA grants a premarketing approval (PMA) decision. Multiple challenges characterize the performance of these trials for mechanical support devices. Because device innovation, exemplified by left ventricular assist devices (LVADs), is incremental and iterative, it is difficult to determine when a device should come to clinical trial and which aspects of development should be "frozen" while modification continues throughout the investigational and post-marketing stages. There is little precedent for trial design when a high severity of illness limits the duration of observation and humanistic concerns dictate consideration of alternate therapies outside protocol. Other life-threatening illnesses, such as cancer and AIDS, have led to consideration of research designs to minimize ethical conflicts and shorten the PMA processes while shifting more emphasis to rigorous post-marketing studies.

The randomized controlled trial (RCT) remains widely regarded as the most powerful and sensitive tool for comparing therapeutic interventions and the most persuasive force for the acceptance of new technology. Many of the differences between drugs and devices, as detailed in the preceding text, complicate the translation of RCTs from pharmaceutical trials to trials of mechanical support devices.

Ethics of randomized controlled trials for mechanical circulatory support. Special emphasis was placed by this conference on consideration of the ethics of RCTs for mechanical support devices. A fundamental tenet of the ethical RCT is that equipoise exists for the treatment being tested; it would thus not be ethical to do an RCT of a device already determined from initial testing to be in the breakthrough realm for the population being considered. Theoretical equipoise, in which available data and investigator preference are exactly balanced, may in fact never be located for the individual clinician. Clinical equipoise, in which genuine debate and uncertainty exist among the clinical community, is more feasible and relevant. Although it was initially challenged for the REMATCH trial, the position of equipoise was strengthened by the analysis of pilot data from the pilot trial for REMATCH (PRE-MATCH), in which no clear survival benefit from the LVAD could be seen at three months.

After randomization has taken place, the patient and his physician are aware of the selected therapy, unlike participation in the placebo arm of a double-blinded drug trial. The combination of life-threatening disease and unblinded therapy raises ethical issues beyond that of physician equipoise at the start of the trial. The visible impact of the device may threaten maintenance of equipoise for investigators following patients during the course of a trial. Responding as individuals to unfiltered information, patients are less likely to be in positions of equipoise even before randomization. Patients consenting to new trials are likely to be already biased toward the procedure and thus may perceive randomization to the control arm as a loss of hope, with potentially deleterious impacts on individual outcomes.

Practical issues of randomized controlled trials for mechanical circulatory support. Patient preference for specific therapies perceived to be life-saving may limit enrollment, particularly when a similar therapy is perceived to be

offered by other routes. From a methodologic aspect, randomization does not eliminate evaluation bias when all parties know the treatment received. Patient dissatisfaction regarding treatment choice threatens compliance with follow-up and increases the likelihood of off-protocol therapy that could compromise the trial results, as was seen in early trials of AZT for AIDS.

The cost of initiating a randomized trial for a new device greatly exceeds that of continuing to report uncontrolled experience. For this effort to be undertaken, the ultimate value in terms of acceptance as an effective device must be consistently endorsed. Financial impediments have profoundly impaired the conduct of clinical trials of devices, for which there have been substantial unreimbursed costs. These disincentives to enrollment increase the duration and overall cost of the study, delaying the time to potential recovery of development costs. Government support for reimbursement of routine Medicare treatment costs and "conditional coverage" of treatment costs in recognized scientifically-designed trials are strongly endorsed by this conference.

Despite a number of obstacles, an RCT of classical design is nearing completion to determine the impact of an implantable mechanical circulatory support device as destination therapy compared with optimal medical therapy. If the REMATCH trial proves a survival benefit for devices in this population, similar devices may be tested against this benchmark. Regardless of the outcome of this trial, both the lessons learned during its conduct and the ultimate results will have a profound influence on the design of future trials.

Modifications of the randomized controlled trial for mechanical cardiac support. It should be recognized that the gold standard methodology for evaluating the impact of a treatment on outcome remains the randomized, double-blinded, placebo-controlled trial. It should also be recognized, however, that surgical interventions in advanced illness may not appropriately lend themselves to all aspects, such as blinding, of this methodological gold standard. With increasing appreciation for the unique aspects of mechanical circulatory support for advanced heart failure, variations in the design of randomized trials merit consideration.

The aspects of randomization and a control arm can be retained in a non-blinded trial with an option to receive active device therapy as "compassionate use" after the achievement of a predefined time or intermediate end points. (Because only the original cohorts would be compared, this does not represent a true crossover design.) This feature may encourage recruitment and retention, while re-aligning incentives for the patient and physician to continue full efforts after randomization to a control arm. Models for randomized trials that allow some degree of patient preference could improve recruitment and patient satisfaction while providing more information on outcomes for patients not desiring device therapy. The degree to which patient preference should influence the choice of therapy remains a major ethical issue for this and other life-threatening conditions. From a more practical standpoint, it is not clear to what extent the advantages of design modifications would outweigh the increase in sample size that would be required.

Comparison of non-randomized cohorts. In the absence of a randomized control group, there are no large historical groups that could be considered for comparison. Contemporary cohort studies offer better information than observational reports without comparison, but they are compromised by a major bias in favor of new treatments. Data provided by a cohort analysis of the bridge-to-transplant experience indicated a major benefit from the device for that indication. While this cohort data were often cited to suggest that a randomized trial of therapy in non-transplant candidates was not ethical, its relevance to this different population was questioned when the small randomized pilot trial indicated no major difference in early outcomes between the device and optimal medical therapy.

Alternatively, to generate prospective control groups, cohorts could be defined by an obligatory control period prior to enrollment that could provide short-to-intermediate-term information, after which, however, subjects entering surgery might be either better or worse than at initial evaluation. Comparison of patients preferring surgery to patients preferring medical therapy would require an extensive adjustment for baseline factors influencing outcome, not all of which can be identified. For non-randomized cohorts, it is not possible to adjust for all of the factors that lead to the provision of a therapy to one patient and not another. A different approach to outcomes adjusted for severity of illness is being investigated for therapy of breast cancer, in which therapy is allocated only to the patients at highest risk, whose outcome is then compared with that projected from a less compromised population on standard therapy, according to a mathematical model. This technique and all of the regression models used to control for cohort differences would require a deeper knowledge of risk profiles and outcomes for advanced heart failure than that which currently exists.

Vital Role of Registries

The absence of broad-based data and the magnitude of mortality, morbidity and resource utilization argue strongly for the creation of a registry of advanced heart failure. Such a multicenter registry would advance both risk stratification for outcome prediction and the development of a multivariate regression model to help adjust for differences between cohorts. Greater confidence in our ability to identify high-risk populations would sharpen trial design and accelerate recognition of devices in the breakthrough realm. Design of RCTs would be streamlined by better selection of target populations and better prediction of event rates.

There is now broad consensus that responsible progress in the field of mechanical circulatory support requires the establishment and maintenance of a mandatory registry that

JACC Vol. 37, No. 1, 2001
January 2001:340–70

includes all implantable devices, both before and after approval. It should be possible to require specific baseline data collection on patients with mechanical assist devices after device approval if that stipulation is formally linked to the initial approval. By contrast to pharmaceutical therapies, which are easier to study before approval and harder to track afterward, mechanical circulatory support devices may, with appropriate registry documentation, be supported by a weight of evidence distributed differently between pre- and post-approval experiences.

The Near Future

The lessons learned through the use of current technology have led to formative strategies regarding the timing of implantation, rehabilitative potential and discharge management in patients supported with circulatory assist devices. However, limitations of systems requiring external power sources connected through percutaneous drivelines have led to the development of numerous systems that are as completely implanted in the body as possible. This has resulted in developments along two broad approaches. The first is a refinement of implantable pulsatile systems, including the Abiomed and Penn State/3M total artificial hearts, the Thoratec IVAD, the Novacor II, the World Heart Heartsaver VAD and the Arrow LionHeart VAD. The majority of these systems utilize transcutaneous power transmission and either an integral or component volume compensatory mechanism. A second thrust utilizes a completely new concept of axial flow technology for chronic support and includes the Nimbus/TCI HeartMate II, Intracorporeal Ventricular Assist System (IVAS), the Jarvik 2000 IVAS and the DeBakey/Micromed IVAS. These systems also depend on transcutaneous power transmission but eliminate the need for volume compensation. The AB-180 Circulatory Support System, the HeartMate III LVAD and the CorAide are devices based on centrifugal principles. In many ways our limited understanding of the impact of this latter group of devices may dictate newer study design principles.

Although there are no specific standards for the preclinical evaluation of newer mechanical circulatory support systems, guidelines do exist. A Preliminary Draft Guidance for Ventricular Assist Devices and Total Artificial Hearts issued by the FDA in December 1987 needs to be updated. The joint paper developed by the American Society for Artificial Organs (ASAIO) and the Society of Thoracic Surgeons (STS) addresses only reliability concerns for long-term devices and does not address emerging technology for which a comprehensive standard with criteria for preclinical testing is still needed. The revision of these guidelines becomes even more important as distinctions between short-, intermediate- and long-term support become increasingly blurred during clinical application. An interdisciplinary effort needs to address the development of a comprehensive standard for the pre-clinical evaluation of blood pumps, taking into account the uniqueness of each system and its intended use, yet remaining sufficiently flexible to incorporate new clinical experience.

As the field moves ahead, it has become clear that no one trial design or set of standards will be ideal or appropriate for all of these devices, populations and stages of development. This document represents both consensus and controversy from leading scientists, clinical investigators, representatives of industry and regulatory agencies. One of the most important achievements of this conference may be the recognition that the pace of real progress in mechanical circulatory support will be accelerated by ongoing collaboration.

[END OF EXECUTIVE SUMMARY]

I. CURRENT STATUS OF MECHANICAL CARDIAC SUPPORT

A variety of devices are available to patients depending on the indications for support (1). In Table 1, the devices that have been used in more than 100 patients in the U.S. are listed, along with the chief characteristics that determine present use. Currently, specific device use is governed by the FDA.

Devices for circulatory support are currently used in three broad categories: 1) acute CS with support <1 month; 2) more prolonged support from 30 days to >1 year; and 3) permanent support as an alternative to transplantation (2). The acute, short-term group includes patients who have cardiac failure after cardiac operations, myocardial infarction (MI) shock or acute cardiomyopathy due to myocarditis or other causes, with a potential likelihood of recovery. In the intermediate or long-term group are those who are suitable for transplantation but deteriorate before a heart becomes available and require mechanical support prior to transplantation. A small percentage of these patients with chronic HF regain ventricular function and are able to have the devices removed without requiring transplantation. The third group of patients has irreversible cardiac failure that might require circulatory support, but they are not good candidates for cardiac transplantation. Therefore, if devices are inserted, they must be considered permanent or "destination therapy" and are currently investigational.

The acute heart failure patients are still comprised primarily of those requiring support after cardiac operations and represent about 1.5% of the 400,000 patients who undergo cardiac operations in the U.S. each year. Post-cardiotomy patients may require support for a variety of problems, often relating to the sequelae of perioperative MI, valve disease or problems of myocardial preservation. Several devices are available to support post-cardiotomy shock patients. The simplest device is extracorporeal membrane oxygenation (ECMO), a cardiopulmonary bypass system with venoarterial cannulation placed either through the femoral or intrathoracic vessels. These systems are limited by their short-term usefulness of <1 week and by problems

Table 1. Current Status of Mechanical Cardiac Support Devices

Types of Devices	ECMO	Centrifugal	Abiomed	Thoratec	Novacor	HeartMate	Cardiowest
FDA approved indications	N/A	N/A	Post-cardiotomy recovery	Post-cardiotomy recovery and bridge	Bridge	Bridge	Bridge*
Position	External	External	External	External	Internal	Internal	Internal
Ventricular support	Cardiopulmonary	Left, right or both	Left, right or both	Left, right or both	Left only	Left only	Left and right
Patient size	Small-large	Small-large	Small-large	Medium-large	Large	Large	Large
Average duration	Short	Short	Intermediate	Intermediate to long	Long	Long	Long
Power source	Electric	Electric	Pneumatic	Pneumatic	Electric	Electric or pneumatic	Pneumatic
Cannulation site	Arterial and venous	Arterial, atrial or ventricular	Arterial, atrial or ventricular	Arterial, atrial or ventricular	Ventricular	Ventricular	N/A
Native ventricle	Remains	Remains	Remains	Remains	Remains	Remains	Removed
Anti-coagulation	Yes	Yes	Yes	Yes	Yes	No	Yes
Patient ambulation	No	No	Yes, restricted	Yes	Yes	Yes	Yes
Wearable	No	No	No	No	Yes	Yes	No
Patient discharge	No	No	No	No	Yes	Yes-electric, yes-pneumatic*	No
Device cost	$	$	$$	$$ to $$$$	$$$$	$$$$	N/A

*Investigational device exemption (IDE). ECMO = extracorporeal membrane oxygenation; FDA = Food and Drug Administration.

with bleeding and coagulation. The systems have been improved recently by heparin coating of the circuits, which may reduce the incidence of thromboembolism as well as the bleeding caused by anticoagulation. However, these systems do not always provide adequate LV decompression, a primary determinant of recovery. Often the ECMO system, the centrifugal or the Abiomed VADs are used as systems for acute resuscitation to salvage severely ill patients, who are subsequently determined to be transplant candidates and are converted to a bridge to transplant device (Thoratec, Cardiowest, Novacor and HeartMate), thus creating a "bridge to a bridge." Four centrifugal pumps are currently available and provide the advantage of biventricular support, but they also present problems of anticoagulation (3). Two VADs, the Abiomed (4) and the Thoratec (5), offer the advantages of pulsatility, specially integrated cannulas for a variety of cannulation options, and more sophisticated control systems. The Thoratec VAD allows for ambulation and management out of an ICU setting. Currently, none of these systems allows for hospital discharge of patients in the U.S. However, clinical trials with a portable driver (Thoratec) are ongoing, and the driver is approved for use in other countries.

Outcomes of post-cardiotomy support are similar regardless of the device employed (1) and relate primarily to age of recipient, timing of insertion and degree of completed MI (3,4). Survival rates range from 20% to 40% with complications of bleeding (25% to 45%), renal failure (20% to 30%), multiorgan failure (20% to 25%), thromboembolism (4% to 20%), neurological deficit (5% to 20%) and infections (35% to 60%), of which only 5% to 10% are actually device related. A small group of patients in the post-cardiotomy group undergo support for a period of time without recovery of cardiac function and become candidates for cardiac transplantation. With the Thoratec VAD, the only device approved for both post-cardiotomy support and bridge to transplantation, there were 34 patients who underwent bridge to transplantation after a recent cardiac operation. Seventy-one percent were transplanted and 53% were actually discharged from the hospital. By comparison, of 536 patients primarily implanted with Thoratec VADs as a bridge to transplantation, 328 or 61% were transplanted, and of those, 284 survived (87% of those transplanted), with an overall survival rate of 53%. However, it is important to note that in the post-cardiotomy group, only 75% of those transplanted survived, while in the primary VAD bridge-to-transplant group, 87% of those transplanted survived.

Post-MI support represents about 10% of all patients treated with VADs. This application has not been widely employed, because of the wide range of co-morbidities encountered by such patients, many of whom succumb before surgery can be performed. Of those implanted with VADs after acute MI with CS, the majority have been considered unsuitable for coronary revascularization. However, the VAD in this population, either post-cardiotomy or after failed medical management, may serve either as a bridge to transplant or bridge to recovery, providing an emerging potential application. Recent experiences when LVADs were implanted within 14 days after acute MI have shown a survival rate of 74% to transplantation or explantation (6). This experience suggests that VAD implantation for post-MI CS may be able to reduce the mortality of 65% to 80% currently associated with medical management.

Acute dilated cardiomyopathy has a variety of etiologies,

JACC Vol. 37, No. 1, 2001
January 2001:340–70

the most common of which is myocarditis (7). This has been an indication for LVAD implantation in about 15% of all patients on VADs. The outcomes are quite variable, but the potential for recovery is increased in younger patients, patients who have had shorter periods of heart failure and patients who have improved more rapidly after LVAD implantation (8). Intermediate or long-term device support (30 days to >1 year) has been employed largely for candidates for cardiac transplantation whose condition deteriorates before hearts become available. Of approximately 2,400 cardiac transplants performed in the U.S. in 1997, 15% of those patients required circulatory support devices to be bridged to transplantation. The types of devices used to bridge patients include extracorporeal VADs, implantable wearable LVADs and implantable biventricular replacement devices. The most important evolution in this group of patients has been the ability to discharge them from the hospital with implantable wearable LVADs. However, these LVADs do not provide for right ventricular (RV) support. If severe right heart failure occurs, another device must be implanted for the RV. Consequently, patients with severe concomitant RV failure have usually been implanted with extracorporeal VADs or implantable biventricular replacement devices. Approximately 10% to 15% of all patients implanted with wearable VADs have required right heart support with another device.

Of the more than 3,000 patients who have been implanted with circulatory support devices as a bridge to transplantation, approximately 60% to 70% actually received a transplant. Of those who received a transplant, 85% to 90% survived to be discharged from the hospital (9–11). Among those implanted as a bridge to transplantation, approximately 5% recovered ventricular function and survived without cardiac transplantation. Approximately 25% of patients from one series of more than 100 patients implanted with VADs for bridge to transplantation recovered ventricular function, and of those survivors, 14 retained good cardiac function while the others later died or required cardiac transplantation (8).

During the last year, at least 50% of patients receiving implantable wearable LVADs have been able to be discharged from the hospital, and patients have been supported from periods of a few weeks to >4 years. Although patients discharged from the hospital may require readmission for problems of infection, anticoagulation or bleeding, the cost of caring for these patients has been significantly reduced by the out-of-hospital option. Currently, that option is available only with the implantable wearable LVADs and is not available with the extracorporeal LVADs or the implantable biventricular replacement devices. However, this option has potentially important economic implications.

Complications occurring during bridge to transplantation are well documented in individual series, but unfortunately a reliable common registry is not currently available to determine outcomes. From individual series, it is reported that bleeding requiring reoperation occurs in 5% to 30%, infections occur in 40%, and device-related infections occur in only 5% to 30%. Thromboembolism has been reported in 5% to 25% of patients, with a stroke rate of 2.7% to 25%. Elevated panel reactive antibodies (PRA) may complicate the LVAD bridge to transplantation. These are presumed to be due to anti-HLA antibodies induced by blood products, cross-reactive antibodies to the device itself or antiphospholipid antibodies due to exposure to fibrin glue (topical bovine thrombin) or perioperative blood transfusions. The consequent elevation of PRAs cause "positive" donor-specific crossmatches that may delay transplantation. In one large series (12) with the TCI HeartMate device, PRA elevation to greater than 10% occurred in 66% of patients post-LVAD but persisted in only 22% at the time of transplantation. However, several patients required immunosuppressive therapy and plasmapheresis to reduce the PRA.

The final group of patients, who are not yet well defined, are patients who have apparently irreversible cardiac failure but are not good candidates for cardiac transplantation. Enrollment is almost completed in the randomized, controlled REMATCH trial, in which the TCI HeartMate vented electric LVAD is compared with optimal medical therapy in patients who are not candidates for cardiac transplantation (13). The FDA has recently given permission for Novacor to begin a similar study of the permanent implantation as "destination therapy" for patients with severe cardiac failure who are not candidates for cardiac transplantation. Unlike the REMATCH trial, the Novacor study will not include a randomized control group. The obvious impediments to the success of such long-term device therapy are the risks of infection related to externalized energy sources, the threat of thromboembolic events and mechanical failure. Although we do not have data from the current studies to address these questions, it is apparent that the long-term result will depend on solving these problems. If these trials can demonstrate efficacy, it will be appropriate to consider this therapy for similar patients among the 50,000 to 100,000 patients in the U.S. who have been estimated to potentially benefit from this technology (14).

II. EVOLUTION OF THERAPIES FOR HEART FAILURE

A. Medical Therapies for Heart Failure

The evolution of therapy for heart failure presently includes many strategies never tested by properly controlled clinical trials (Table 2). Many treatments have been abandoned without formal testing after unrewarding anecdotal experience. Over two millennia ago, treatment for what was once termed "dropsy" was aimed at restoring a balance of fundamental elements and complementary humors (15,16). A historical overview of more modern therapies (17) reveals that in 1683, Thomas Sydenham recommended bleeding, purges, blistering, garlic and wine. A century later, William Withering provided a precise description of the benefits of

Table 2. Development of Therapies for Advanced Heart Failure

Pharmacologic Therapies
Herbal remedies (cathartics, purgatives, natural diuretics, foxglove)
Pharmaceutical compounds
- **Digitalis glycosides
- *Diuretics
- *Nitrovasodilators (**for combination)
- Hydralazine (**for combination)
- Neg**: Flosequinan
- Neg**: Epoprostenol
- **Angiotensin-converting enzyme inhibitors
- **Angiotensin receptor blockers
- **Aldosterone antagonists
- Neg**: Catecholamine-related oral inotropic agents
- Neg**: Phosphodiesterase-related oral inotropic agents
- Neg**: Calcium channel blocking agents
- **Beta-adrenergic receptor antagonists

Lifestyle Interventions
- Sodium restriction
- Alcohol restriction
- *Exercise training

Device Therapies
- Southey tubes to drain peripheral edema
- (*)Implantable cardioverter defibrillators
- A-V interval pacing
- (*)Biventricular pacing

Surgical Therapies
- Thyroidectomy
- Pericardiectomy
- Valvular heart surgery
- *Coronary revascularization
- Cardiac remodeling
- Aneurysmorrhaphy/aneurysmectomy
- (*)Infarct reduction
- Ventricular reduction surgery
- Cardiac transplantation
  - Orthotopic
  - Heterotopic
- Ventricular assist devices
  - Post-cardiotomy
  - Bridge to recovery from cardiomyopathy
  - Bridge to transplant
  - (*)Destination therapy

*Limited trial evidence; **substantial trial evidence; Neg** = substantial evidence of harm or lack of benefit; (*)Trial in progress. It should be noted that harm or lack of benefit can often be identified without controlled trials.

foxglove in the Shropshire maid's cure for dropsy. Catharsis and venesection continued through the nineteenth century, with amyl nitrate, mercurial diuretics and digitalis glycosides becoming available in the early part of the twentieth century.

While the laboratory experience was developing that allowed human cardiac transplantation to proceed, medical therapy for heart failure included only digitalis, thiazide diuretics (introduced in 1962) and furosemide (introduced in 1965). Controlled trials of withdrawing or administering digoxin did not take place until 1993 (18,19) and 1997 (20), and there were no trials of diuretics except as substudies of two trials testing other drugs (21,22). The quest to establish a basis of evidence from which to prescribe effective therapies for specified populations has been relatively recent (23). The concept of vasodilators for heart failure was introduced by the acute use of nitroprusside in 1974, followed by hydralazine in 1977. The first large randomized clinical trial in heart failure with mortality end points was not completed until 1986 (24), demonstrating improved survival with the hydralazine-isosorbide dinitrate combination. With the release of captopril in 1980 and enalapril in 1984, multiple large, randomized, placebo-controlled trials established angiotensin-converting enzyme inhibitors as the cornerstone of therapy, with extensive unforeseen benefits for this drug class occurring beyond that expected only from vasodilation (25–28).

Trials have also demonstrated the lack of sustained clinical benefit from many therapies with sound theoretical rationale. Although acute hemodynamic improvements in heart failure patients were readily demonstrated with dopamine in 1972 and dobutamine in 1974, inotropic agents have not been associated with sustained hemodynamic benefit or mortality reduction during chronic therapy. In fact, mortality is increased in these patients, as suggested by early experiences and confirmed in larger trials (29). Although excess myocyte calcium concentrations have been implicated in progression and death, calcium channel blockers have worsened heart failure and survival in retrospective analyses and prospective trials. Many anti-arrhythmic agents that suppress ventricular arrhythmias were shown in large trials to increase death in patients with heart failure. Amiodarone, the only currently available anti-arrhythmic agent that does not increase mortality in heart failure, may in fact have more benefit for heart failure end points than for sudden death. Beta-adrenergic blocking agents worsen hemodynamics initially but, when tolerated, lead eventually to improved hemodynamics and survival in recent large trials of mild-to-moderate heart failure.

Reviewing the history of introduction, adoption and, in some cases, abandonment of therapies for heart failure, reveals the contribution of large controlled trials in defining the additive impact of our interventions. In the process of establishing a basis of evidence to guide current medical therapy for heart failure, a template has been created for the rigorous testing of medications that can be administered in parallel with placebo therapy. End points of survival, clinical status, cardiovascular function and cost-effectiveness can be evaluated using this template without either patient or physician knowing who has received the new therapy being tested.

However, the randomized placebo-controlled trials have, in general, not included patients desperate for relief from severe heart failure symptoms or hoping to be rescued from imminent death. For example, the rapid impact of intravenous diuretics in treating dyspnea from pulmonary edema in heart failure, and the rapid benefit of inotropic therapy to improve perfusion acutely in CS have not been put to the test of placebo-controlled, randomized trials. The immediate cause-effect response typically observed renders a physician unlikely to substitute placebo therapy in these situations. Even in a less compromised group of hospitalized patients, placebo-controlled trials have either excluded patients with urgent indications for intravenous therapy or

JACC Vol. 37, No. 1, 2001
January 2001:340–70

limited placebo therapy to a short period with early crossover to active treatment.

B. Surgical Therapies for Heart Failure

Early surgical procedures for heart failure included thyroidectomy, pericardiectomy and valve replacement. Subsequent procedures, such as intra-aortic balloon counterpulsation for CS (30), proposed in 1961, and LV aneurysmectomy introduced for chronic HF in 1962 (31), were more systemically studied and reported but without specific control groups against which to compare benefit. As soon as orthotopic cardiac transplantation was performed in humans, it was tried in many centers with poor initial results. In large part through the perseverance of the Stanford team, outcomes steadily improved. Approval by Medicare of heart transplant as standard therapy was based on careful description of outcomes for a cohort of patients assumed to have over 50% six-month mortality without transplantation (estimates based on early waiting list deaths, but not on any control groups). Increasing waiting times for transplantation have led to expanding use of mechanical circulatory support as bridging devices for cardiac transplantation. Comparisons with patient cohorts without bridging devices suggested better survival to transplantation and discharge, but no randomized trials were done before the widespread acceptance of bridging strategies.

With a limited supply of donor hearts, research continued into other surgical options for heart failure. Coronary revascularization and valvular heart surgery, once thought to be contraindicated in the presence of a low ejection fraction, were extended into the heart failure population, where their roles are not yet defined. A variety of cardiac remodeling procedures (aneurysmorrhaphy/aneurysmectomy, infarct exclusion, application of cardiac restraining and ventricular splinting devices) have recently been introduced and reported in small numbers. More systematic evaluations have been recommended (31). In fact, there are developing plans for a national randomized trial in ischemic heart failure to compare medical therapy with surgical therapy, with further randomization of the surgical arm with or without ventricular reconstruction.

Despite the obstacles, large randomized clinical trials have been performed with surgical therapies of advanced cardiac disease. Three landmark trials of coronary artery bypass surgery clarified its role in ameliorating morbidity and mortality from coronary heart disease (32–34). The smaller analyses of patients with three-vessel disease with decreased LVEF demonstrated particular benefit but included few patients with typical heart failure. With enthusiasm generated by uncontrolled experiences of cardiomyoplasty, the Cardiomyoplasty-Skeletal Muscle Assist Randomized Trial (C-SMART) was an ambitious trial (35) that included a non-blinded, control arm of patients without cardiomyoplasty. Due to early problems with patient recruitment and withdrawal to receive active therapy, the protocol was changed to allow crossover to active treatment after one year. After recruitment of only 100 patients over five years because of ongoing problems with both patient recruitment and reimbursement, the trial was terminated, despite a trend for improved outcomes in the surgical group.

Revascularization is commonly employed as standard therapy for CS due to an acute ischemic event. The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock? (SHOCK) trial (36) of revascularization for acute coronary syndromes causing CS was completed in 302 patients only after five years. Survival benefit from revascularization was not apparent at one month but shown by the six-month evaluation for patients under 75 years. At the same time, the Swiss Multicenter Angioplasty for Shock Trial was terminated because of inadequate enrollment (37).

The ongoing REMATCH trial (13) faces the double challenge posed by both a surgical trial and study of a more compromised heart failure population than was ever enrolled in a controlled trial. Candidate criteria were originally designed to include patients with an expected 25% two-year survival. Considering previous information from cohort experiences suggesting a large benefit from "bridging" in transplant candidates, concern was raised that this trial was unethical because it denied patients a life-saving therapy. In fact, the 21-patient pilot trial prior to REMATCH demonstrated a three-month mortality of almost 30% without apparent difference between the medical and surgical arms. Attempting to find a population with intermediate risk, the inclusion criteria for REMATCH were subsequently expanded to require 60 rather than 90 days of severe symptoms and either dependence on intravenous inotropic agents or a peak oxygen consumption <14 ml/kg/min, compared with the previous limit of 12 ml/kg/min. Enrollment in the trial has been limited by issues of reimbursement for the surgical procedures, difficulty in regional recruitment at designated centers and reluctance of patients and families as well as physicians to accept randomization in the setting of a life-threatening illness for which a new therapy might be life-saving. Still, it is anticipated that the completion of this trial in 2001 will provide new benchmarks for both the medical and device arms of future trials.

C. Downshifting of Risk for New Surgical Therapies

The recognized success of new surgical procedures for advanced disease may be followed in some cases by a cycle of improving results and expanding population definition. The evolution of such therapy contrasts with the development of pharmacologic and exercise interventions, which have usually been initiated in patients with mild disease, validated in trials of moderate disease and ultimately extended to patients with severe disease who would have been excluded from the landmark trials (38). Surgical therapies for heart failure carry front-loaded risk that is easier to absorb for patients expecting high early mortality. As survival and improved function are realized by these desper-

ate patients, the procedure is then sought by patients at earlier stages of the disease. These patients are more likely than the initial subjects to obtain good results from the procedure. With the downshifting of risk, however, the actual benefit, calculated as the difference between outcome with the procedure and outcome without the procedure, may become less significant. An appropriate example of "downshifting" the risk is the evolution of cardiac transplantation (39–41). Candidates were originally expected to have "less than six months to live," at which time survival with transplantation was 60% to 70% at one year. The current one-year survival rate after heart transplant is 80% to 85%, with a 10-year survival rate of about 50%. For ambulatory heart failure patients not requiring intravenous inotropic agents, the survival without transplantation has also improved to 60% to 70% without death or urgent transplantation at one year in many studies, leaving a smaller margin of early benefit. The positive impact of heart transplant remains striking, however, for patients in critical status or dependent on inotropic infusion. After initial experiences, risk can shift up as well, as has happened for candidates developing organ failure while awaiting transplantation, such that procedures may be extended to patients who are more severely ill than their predecessors. As new surgical therapies for heart failure are introduced and accepted into broadening populations, it remains crucial to monitor the target populations and ensure that the benefits expected from earlier experience are being derived.

III. TARGET POPULATIONS AND END POINTS FOR MECHANICAL CIRCULATORY SUPPORT

A. Indications for Device Support

The appropriate population for a trial of mechanical circulatory support is comprised of the patients whose current quality of life and prognosis are measurably worse than expected outcomes for the device being tested. The population should be defined as broadly as possible to maximize generalization of the results. Although the specific entry criteria will vary for each device and indication, there are general categories of patients who can be considered along a scale of disease severity (Table 3). As the severity of disease increases, there is greater certainty regarding imminent death, and less certainty is required regarding the device performance and patient outcome after device implantation. In general, however, increasing disease severity also increases the risk of adverse outcomes attributable more to the patient than to the device. At lesser grades of severity, when death is not imminent, details regarding the expected function and quality of life with mechanical circulatory support become more critical. In one study, a majority of patients anticipating continued heart failure symptoms at rest expressed willingness to trade >50% of their remaining time, or take >50% risk of death, for a chance to return to more normal function (42).

Table 3. Anticipated Survival According to Severity of Advanced Heart Failure

Severity of Heart Failure	≥50% Mortality Expected
Cardiogenic shock	In-hospital
Chronic heart failure with exacerbation into critical low output state	In-hospital
Acute myocardial infarction	In-hospital
Post-cardiotomy shock	In-hospital
Chronic heart failure, dependent on intravenous inotropic therapy	3–6 months
Chronic heart failure, class IV symptoms on oral therapy	12–24 months
Refractory symptoms at rest or minimal exertion	≤12 months
Risk factors such as decreasing sodium, increasing creatinine and/or blood urea nitrogen	
Stabilization as class III	≥24 months
Heart failure, refractory ventricular arrhythmias	Variable, not estimated
Chronic severe post-transplant graft dysfunction with allograft vasculopathy	≤12 months

1. Cardiogenic Shock

a. CRITICAL LOW OUTPUT STATE FROM EXACERBATION OF CHRONIC HEART FAILURE. Most of the current experience with mechanical support as bridging to transplantation derives from the population of patients with chronic HF that decompensates to a critically low output state threatening tissue perfusion and organ viability. In the absence of reversible factors, this state usually leads to death before hospital discharge. When transplantation, and thus bridging to transplantation, is not an option or when current bridging techniques are not applicable, this population could be considered for trials of newer support systems. Early identification of such patients would be desirable for these trials, but it is confounded by difficulty in distinguishing reversibility of organ system dysfunction and by the rapidity of clinical progression. One study evaluated the ability of the Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system to determine optimum timing of VAD implantation in patients with lung rales, S3, peripheral edema, ejection fraction <30%, systolic blood pressure <80 mm Hg, progressive prerenal azotemia, altered level of consciousness, gastrointestinal ischemia or congestion or persistent but reversible pulmonary hypertension (43). By the end of the follow-up period, the VAD patients had survived longer (560 vs. 256 days). Kaplan-Meier analysis of non-VAD patients at low (≤10), medium (11–20) and high (>20) baseline APACHE II scores revealed a decreasing survival with increasing APACHE II scores. Similar outcomes were seen in VAD-treated patients. Patients with low APACHE II scores had similar outcome regardless of whether or not they received VAD support. However, when VAD and non-VAD patients with medium APACHE II scores were compared, VAD-treated patients had better survival, which was confirmed in a model

JACC Vol. 37, No. 1, 2001
January 2001:340–70

after controlling for baseline APACHE II scores. Although this study concluded that the severity of illness measured by APACHE II might be used to time insertion of devices for bridging to transplant, it might also be used to identify patients for urgent destination therapy. However, use of the APACHE II score to predict short-term mortality in patients with primary cardiovascular disease is limited, and it is complicated by variances in interpretation of the scoring system and errors in data capture (44). The use of a modified APACHE II scoring system may improve the accuracy and reproducibility of these methods (45). Extensive prospective evaluations of the APACHE II system (or a modification) are needed to further define the role of this method of risk stratification of potential candidates for mechanical support.

The frequency of CS complicating HF in transplant candidates is difficult to estimate from the 15% of recipients of "bridges" to transplantation, as the increased recognition of the benefits of mechanical support have broadened the application to patients with impending or anticipated circulatory failure. In addition, this population also includes patients bridged for more common causes of CS, such as MI and post-cardiotomy failure.

b. CARDIOGENIC SHOCK AFTER ACUTE MYOCARDIAL INFARCTION. It is estimated that 1.1 million patients suffer an acute MI in the U.S. each year. Of these, approximately one third die prior to presentation (46). In the large multicenter Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial, CS occurred in 7.2% of patients, but it accounted for 58% of all deaths in the entire trial (47). The estimated yearly incidence in the U.S. is 50,000 in the hospital with post-infarction CS. In the SHOCK registry, in-hospital mortality was approximately 60% in patients with post-MI CS (48). Of the patients developing shock, it was present initially in 10.6% and developed after admission in the remaining 89.4%, usually within 48 h (49). In one sub-study of GUSTO a prognostic algorithm predicted with high accuracy the 30-day mortality in patients with CS complicating an acute MI. Increased age was the strongest demographic variable predicting 30-day mortality, and shock at presentation had better outcome than shock presenting later. Clinical predictors focused on findings of peripheral hypoperfusion such as an altered sensorium, cold and clammy skin and oliguria. Significant hemodynamic predictors were a cardiac output <1.5 L/min or a pulmonary arterial wedge pressure >20 mm Hg. A serious limitation of this prognostic algorithm is the lack of consideration of revascularization, found in another GUSTO substudy to reduce the 30-day mortality rate and in the SHOCK trial to reduce six-month mortality (36). Based on these data, a patient with CS after MI, especially if not a candidate for revascularization, could be a candidate for long-term mechanical support.

c. POST-CARDIOTOMY SHOCK. Post-cardiotomy shock is described in approximately 1.5% of the 400,000 patients undergoing cardiac operations each year in the U.S. As discussed above, survival to discharge is in the range of 20% to 40% (1–6). In the minority of patients who proceeded through bridging devices to transplantation, the overall survival rate to discharge was 40% to 60%. Patients who are not candidates for transplantation could be considered for trials of permanent mechanical support, but it should be recognized that the factors rendering them ineligible for transplantation would also affect outcome on devices. The post-surgical state may also predispose to worse outcome because the results of mechanical bridging to transplant have been slightly less favorable in this population than in primary bridging experiences.

2. Heart failure dependent on intravenous inotropic support. The population of patients requiring intravenous inotropic support is increasingly being considered as a potential candidate group for newer heart failure therapies, particularly those that carry significant risk. This population definition is less precise, however, than others based on immediately measurable parameters. Many patients hospitalized for heart failure exacerbations receive brief courses of intravenous inotropic therapy to facilitate diuresis or redesign an effective oral regimen, following which the inotropic therapy is discontinued. Persistent efforts to achieve fluid balance, the substitution or combination of different vasodilators to avoid symptomatic hypotension and severe renal dysfunction, and enrollment in heart failure management programs frequently allow patients previously on intravenous infusions to maintain a reasonable quality of life on oral regimens (50).

Specific criteria for determining the ongoing need for intravenous inotropic therapy have not been established, despite numerous reports of chronic and intermittent intravenous inotropic therapy for ambulatory patients with heart failure. The classification of disease severity is ambiguous because patients on inotropic infusions may initially be reclassified to the clinical level of class III symptoms, while deterioration after discontinuation may take over 24 h to become apparent. Definitions of "failed weaning attempts" have been proposed (14), but identification of "symptomatic hypotension" and "worsening renal dysfunction" remains subjective. Despite the lack of uniform criteria for intravenous inotropic support, the prognosis for patients receiving either chronic or intermittent inotropic infusions outside the hospital is remarkably consistent. This may reflect a greater homogeneity of the population than recognized and/or a dominant adverse effect of the infusions themselves. The mortality reported in representative series generally ranges between 30% and 50% by six months.

Among patients listed for transplantation as Status II in the multicenter pre-transplant database, intravenous inotropic infusions were being administered at the time of listing in approximately 10% of the patients, of whom over 90% had died or deteriorated to Status I by the end of one

year (51). In the pilot trial before REMATCH, 80% of the patients were on inotropic infusions at the time of randomization, and 53% of the patients in the medical arm were receiving inotropic infusions after hospital discharge (52). Mortality in the medical treatment arm of the pilot experience for the REMATCH trial was 30% at three months, consistent with the reported experiences on inotropic therapy. There are not yet sufficient data regarding quality of life to compare chronic intravenous inotropic therapy, which requires maintenance of an indwelling catheter and infusions, with LVADs, which require other equipment. Regardless of the difficulties of establishing true dependence on intravenous inotropic therapy, patients in this group would appear to be reasonable candidates for consideration of mechanical support devices, with which intermediate outcomes are expected to be comparable or better.

3. Outpatients with symptomatic heart failure—who is at intermediate risk? It is relatively easy to identify critically ill patients not likely to survive until hospital discharge. For this population, patient-associated factors related to infection, renal failure, hepatic failure and malnutrition may play a greater role than device characteristics in post-operative survival. It is also relatively easy to find patients with good functional capacity and mild symptoms of heart failure who are likely to survive at least two years. This population adds relatively little patient-related risk to a new procedure but does not offer large opportunity for measurable improvement in outcome. Defining a population with intermediate risk and mortality remains a major challenge.

Most of the information regarding outcomes in heart failure derives from multicenter heart failure trials, dominated by mild-to-moderate heart failure and one-year mortality of <20%. Even the trial populations intended to include advanced class IIIb and class IV generally have actual one-year mortality of <30%, suggesting less severe disease. Various biochemical, structural and functional characteristics have been identified singly and in composite scores that predict mortality in these populations but are more uniformly abnormal among patients who would be considered for mechanical support. Among two series of patients with class III and class IV heart failure referred for transplantation—representing a total of almost 1,000 patients—the combined end point of death and urgent transplantation occurred in approximately 50% of the patients by two years (53,54). A multivariate model including continuous variables of heart rate, LVEF, mean blood pressure, presence of intraventricular conduction delay, peak oxygen consumption and serum sodium identified 19% of the population with a one-year survival of 30% to 40% without urgent transplantation (53). The other study indicated that patients referred with class IV symptoms could be divided approximately in half by serum sodium or LV dimension, with a <50% one-year survival for either a serum sodium of <134 mEq/L or an LV diastolic dimension >75 mm (54). From a multicenter study of 967 patients listed as Status II for transplantation, class IV symptoms, higher creatinine, higher pulmonary capillary wedge pressure, diagnosis of ischemic heart disease and inotropic therapy at listing predicted worse outcomes (51). Even among patients awaiting transplantation, however, outcomes were relatively good for patients having a non-urgent status listing, with only 30% dying or deteriorating to an urgent status within the next year—most deaths occurring suddenly. The previous risk predictions will be compromised in future applications by broader use of implantable defibrillators.

Among patients out of the hospital on oral therapy, the major distinctions are made on a clinical basis. Many patients referred with class IV symptoms can regain stability—some immediately, some after a prolonged period of closely monitored adjustment of the medical regimen. From a practical standpoint, many patients exhibit a dynamic state that fluctuates over months, with exacerbations related to dietary indiscretion, seasonal viral infections and other exogenous factors. For ambulatory patients with heart failure, a large component of the decision to receive investigational therapy, either medical or surgical, is the degree to which the current clinical status is unacceptable. Patients able to regain and maintain freedom from congestion during close follow-up have a two-year survival of almost 80% despite an initial admission with class IV symptoms (55). Patient preference for quality of life versus survival shows remarkable variation at every level of disease severity (42). For an individual patient with severe heart failure being evaluated for heart transplantation, certain pre-transplant risk factors may make transplantation a relatively high-risk option (56). Although transplantation may be offered to such a patient despite this increased risk, an alternative mode of therapy may be mechanical assistance. In addition, an individual patient may decline transplantation because of social, psychological or religious reasons. Although transplantation may be indicated by medical standards in such patients, mechanical assistance may also offer improved quality of live and life span. It is not clear whether eligible patients refusing transplantation should be excluded from clinical studies of devices.

4. Uncontrollable ventricular arrhythmias. Approximately half of the deaths from heart failure occur suddenly (57). Unexpected cardiac death is usually due to tachyarrhythmias, but it may result from bradyarrhythmias or electromechanical dissociation in 10% of the general series, more often as the end stages of cardiac disease are reached. The implantable cardioverter-defibrillator is of limited efficacy in the therapy of rapidly recurrent or incessant arrhythmias because of limited battery life, high defibrillation thresholds in the advanced cardiomyopathic ventricle, and the downward spiral of hemodynamic instability. In addition, the quality of life can become unbearable under the shadow of frequent defibrillations without anesthesia.

Therapy with amiodarone or combination of other anti-

JACC Vol. 37, No. 1, 2001
January 2001:340–70

arrhythmic agents may reduce the number of device discharges to a tolerable frequency. Recurrent tachyarrhythmias from an identifiable focus may be amenable to catheter ablation techniques. If symptomatic ventricular tachyarrhythmias are not controllable by all available means they may lead to the need for ventricular assist or the insertion of a total artificial heart (58). Ventricular assist has been used successfully to provide hemodynamic support and allow effective pharmacologic arrhythmia suppression as a bridge to transplantation for refractory arrhythmias (59–62). Although LV support has frequently been adequate for bridging patients with refractory tachyarrhythmias to transplantation, permanent support may be better provided by total support devices.

5. Cardiac allograft dysfunction and/or cardiac allograft vasculopathy. The intermediate-term survival of patients with severe allograft CAD is very poor. Keogh and colleagues reported the mortality of patients with severe CAD in a study of 353 heart transplant recipients from Stanford University with a mean follow-up post transplant of 5.5 years (63). In this study, the mean survival for patients dying from CAD was 15 months from the detection of any coronary disease (range 1 to 74 months). Survival was statistically worse in patients with >70% stenosis in a primary epicardial coronary artery. Survival at two years was 13%. Actuarial survival after the diagnosis of >70% stenosis in three primary epicardial vessels in this population was <50% at one year, half of these patients dying within the first six months. In a recent study from the Cardiac Transplant Research Database, CAD was defined as "severe" if the left main coronary artery or two or more primary vessels had stenoses of >70% or if there were isolated branch vessel stenoses >70% in all three coronary artery systems (64). In 46 patients with severe CAD, actuarial freedom from death due to CAD (n = 17) or re-transplantation for CAD (n = 6) was only approximately 36% by two years after the diagnosis of coronary disease. Although the use of intracoronary stents may alter the natural history of patients who develop more proximal lesions amenable to this mode of therapy (65), the majority of patients who develop CAD will have progressive disease with a similar rate of progression irrespective of when the disease is initially diagnosed (66).

Although re-transplantation is offered to patients with severe disease at some institutions, this practice is discouraged elsewhere in recognition of the limited supply of donor hearts and the lower survival after repeated transplantation (39). Therefore, the population of patients with severe allograft CAD is one that may be considered for studies of biventricular support and the use of the total artificial heart. Current estimates suggest that there may currently be about 2,000 such patients. Table 4 outlines the potential advantages and disadvantages of this population as recipients for long-term destination therapy of mechanical circulatory support devices.

Table 4. Cardiac Allograft Recipients with Severe Allograft CAD: Potential Advantages and Disadvantages of Destination Mechanical Support

A. Advantages
1. Very poor short-term prognosis
2. Followed (usually) by heart failure physicians and surgeons
3. Accustomed to participation in protocols and a structured medical follow-up program
4. Limited options for therapy if not candidate for re-transplantation
5. More qualified to give informed consent after careful consideration
6. Surgical therapy may be scheduled semi-electively
B. Disadvantage of proposed population
1. Immunosuppression (usually relatively low long after transplantation, may be discontinued after total artificial heart other than steroids, which should be weaned)
2. Must be carefully screened for co-morbid medical problems that would affect short- and intermediate-term survival
3. Effect of residual allograft tissue unknown

CAD = coronary artery disease.

B. Evaluation for Exclusion Criteria

Patients who are acutely ill, including those without prior known cardiovascular disease suffering an acute MI with CS, will often develop some degree of non-cardiac end-organ and systemic dysfunction. Indices of organ dysfunction place the patient into a risk group in which support devices are warranted but in which they also increase the likelihood of post-operative complications. Although current experiences are not large enough for extensive multivariable analysis of risk factors for death and complications after mechanical support, experience with current implantable VADs has revealed some predictors of poor outcome during or post-device implantation (53,67).

In almost every major registry of VAD follow-up (68,69) and a single center review (70), poor renal function or *renal failure* has been a significant predictor of death following LVAD implantation. Although renal insufficiency has customarily been defined by an elevated serum creatinine, oliguria in the face of adequate filling pressures may be more predictive in acute decompensation because the creatinine may not increase quickly, especially in a cachectic patient. In the combined Columbia Presbyterian Hospital and Cleveland Clinic experience, oliguria, defined as urine output <30 cc/h despite maximal medical therapy with diuretics, was the most important predictor of perioperative death, with a risk ratio of 3.9 (67). In this analysis, the second most important predictor was *respiratory failure*, defined as the need for intubation, with a relative risk of 3.0. The presence of a *coagulopathy*, defined as the inability to correct the prothrombin time to <16 s indicated significant liver dysfunction and carried a risk ratio of 2.4. Other preoperative risk factors identified in this study included a central venous pressure ≥16 mm Hg (relative risk 3.1), the LVAD placement as reoperation (relative risk 1.8) and a leukocyte count >15,000/mm^3 (relative risk 1.1).

If the placement of an LV support system alone (without an RV support system) is being considered, the condition of the RV should be assessed. In addition to the possibility of

Table 5. Relative Importance of VAD Characteristics by Potential Patient Population

Patient Population	Chronicity of Underlying Situation	Ease of Insertion	Ease of Removal	Device Longevity	Biventricular Capability	Appropriate for Long-Term Outcome Study	Relative Low Cost
I. CS							
CHF with exacerbation into critical low output state	Chronic	+++	+	+++	++	+++	++
Acute MI	Acute	+++	+++	+	++	+	++
Post-cardiotomy shock	Acute	+++	+++	+	++	+	+++
II. CHF, dependent on intravenous inotropic therapy	Chronic	+	+	+++	+	+++	++
III. CHF, class IV symptoms on oral therapy	Chronic	+	+	+++	+	+++	++
IV. Uncontrolled malignant arrhythmias	Acute/chronic	+++	++	++	+++	+++	++
V. Chronic severe post-transplant graft dysfunction with allograft vasculopathy	Chronic	+	+	+++	+++	+++	++

CHF = chronic heart failure; CS = cardiogenic shock; MI = myocardial infarction; VAD = ventricular assist device; +++ indicates greatest importance.

an elevated pulmonary arterial pressure secondary to HF (71), the reactive pulmonary hypertension associated with cardiopulmonary bypass and thromboxane A_2 release may predispose to significant RV failure early post-isolated LVAD placement. Also, the LVAD may suddenly markedly improve RV filling, leading to worsening RV failure. In one series, although the need for perioperative RV support was low, a low preoperative pulmonary arterial pressure (indicating decreased RV function) and a low RV stroke work index were significant risk factors for RVAD use (72). Others have shown that strong predictors of subsequent RV dysfunction after LVAD implantation were the pre-implant medical condition, presence of end-organ failure, pulmonary edema and coagulation abnormalities (73). Factors to be considered in all patients are prior surgical history, prior radiation therapy, the general medical and nutritional condition of the patient and the patient's social support structure (74).

C. Selection of Devices

Studies of new mechanical support devices should be targeted toward specific populations with high anticipated mortality with conventional therapy but a reasonable chance of surviving device placement and the perioperative period. Two broad categories of potential device recipients can be identified: 1) those with acute, potentially reversible conditions, and 2) those with chronic generally irreversible disease. In the first category, ideally devices should be inexpensive and easily inserted and removed. The second category of patients would benefit from devices with greater longevity, even if the device is more difficult to insert and is more expensive. Patients with intractable malignant arrhythmias and severe transplant vasculopathy will require the capability of biventricular support. Heart transplant candidates requiring mechanical bridging remain an excellent population in which to assess the feasibility of new potential long-term devices. Table 5 outlines the relative importance of various device characteristics as applied to potential recipient populations.

D. End Points for Outcomes

It is clear that appropriate end points to be incorporated into future clinical trial designs for mechanical circulatory support devices will need to vary according to the nature of the patient population to be included in each trial and the particular device being subjected to trial. For instance, simple all-cause mortality at six months might be an appropriate end point in a group of patients selected who had a >50% probability of death within six months, whereas more complex measures of "quality-adjusted survival" would be appropriate in a less sick population. All trials should be designed to incorporate measures of cost, cost-effectiveness and tracking of device malfunction and device failure. Quality of life will become an increasingly important end point to assess and should be compared with valid control groups of patients rather than relying on the patients' own perceptions of their quality of life before and after placement of the device. It should be recognized that quality of life is a subjective and individual assessment and that the currently available tools to measure quality of life are imperfect and have not been well validated in advanced heart failure. It may be necessary to revise and validate tools for this specific patient population.

The following sections outline some generic suggestions for appropriate primary and secondary end points for patient groups of differing severity of illness. Each end point may have time-related "midpoints" to be assessed as well.

1. The end points for critical populations. Survival over the next three to six months is a major challenge for patients who are New York Heart Association (NYHA) functional class IV and compromised enough to depend on ongoing intravenous inotropic support to maintain secondary organ function and overall circulatory sufficiency. When trials of mechanical systems commence in these patient populations,

Table 6. End Points (Assessed at Prespecified Time Intervals)

Primary end point: All-cause mortality
Secondary end points:
A. Quality of life
B. Functional capacity, for example:
Exercise capacity (if applicable)
Hemodynamics
Ability to leave hospital
C. Cost
Device cost—system and replacement parts
In-hospital costs
Out-of-hospital costs (to include medical, caregiver-related and, possibly, travel-related costs)
Cost-effectiveness*
D. Components of morbidity (75), including:
Thromboembolism
Neurologic events
Infection
Bleeding
End-organ dysfunction
Right heart failure
Psychiatric episode
Rehospitalization (if discharged)
Cardiac causes:
Worsening heart failure
MI
Arrhythmia
Non-cardiac reasons
E. Device malfunction (to be specified in detail)
F. Device failure (to be specified in detail)

* Cost-effectiveness—complex analysis based on parameters of quality of life, required care, survival, and cost, see text.
MI = myocardial infarction.

it is suggested that end points of such trials include the components listed in Table 6.

2. Ambulatory heart failure on oral therapy. Patients with NYHA functional class IV symptoms who are candidates for chronic mechanical circulatory support and who are not recurrently hospitalized or dependent on intravenous inotropic agents are generally not "as sick" as patients dependent on intravenous inotropic support. These patients can experience discomfort during any physical activity and may have discomfort while at rest. The hypothesis is that a mechanical circulatory support device will provide such patients with an improved physiologic and functional quality of life and for a duration that extends well beyond the 30-day post-implant period. As discussed above, the probability of survival at a specific time is not well established.

The primary end point for clinical studies of devices intended for use in these patients would be all-cause mortality at a specified duration, such as six months, one or two years, although mortality due specifically to cardiac events should also be captured. End points of quality of life may assume more importance for these patients, for whom a sustained improvement in quality of life may be considered a significant benefit even if survival is equivalent (76). Quality of life is a multidimensional construct measuring outcomes in the following domains: emotional state, general health perception, pain, social function and physical functioning. There is considerable debate about appropriate measurements for quality of life, but experience in assessing these aspects is rapidly being gained (77,78).

These domains can be analyzed and integrated in the context of patient preferences for health-related quality of life versus length of life. These measurements seek to capture the overall value or preference that a patient holds for a particular health outcome. Both the time trade-off instrument and the standard gamble questionnaire have been used to determine the relative value placed by an individual patient on the degree of perceived health versus remaining survival time or risk of death while pursuing better health (42,76,79). They may have greater relevance to decision-making than abstract scores. Preference ratings can serve as the quality adjustment factors for calculating quality adjusted survival, measured in quality adjusted life years (QALY). Such measures are expressed as numeric values on a uniform scale (0 to 1). They are particularly useful for summarizing overall changes in health-related quality of life because they are expressed as a single score.

Morbidity parameters as listed in Table 6 should be secondary end points, but they will assume increasing significance and may become primary end points in trials of less sick patients for whom, if survival is equivalent and is associated with significantly less morbidity, significant benefit may be considered to have been demonstrated. The frequency of each event and the time to each event should be captured for reporting in the application for approval for marketing by the FDA. In addition, device (system) malfunctions and device (system) failures are adverse events that should be captured for purposes of facilitating design improvements. The location where each morbidity event occurs and where each device malfunction and device failure occurs should be documented to establish device (system) safety in its intended user environment (in-hospital vs. out-of-hospital).

Because the relationship between cost and benefit is a significant issue in the evaluation of these devices, all cost information associated with this therapy should be collected for comparison with costs incurred by patients who do not receive a device. This includes costs associated with hospitalizations, caregivers in and out of the home, travel and medications. Cost-effectiveness is an analytical technique that looks at the rate paid to obtain a measure of health. This is often expressed in dollars per life year saved. When quality of life is taken into consideration, this is expressed as dollar cost per QALY saved. This form of analysis provides the optimal means to allocate health care resources to maximize the health benefits achieved.

Some might argue that certain therapies that are shown to have a defined benefit would prove to be too expensive for society to bear. On the other hand, we recognize that in some cases society has been willing to expend significant resources for a limited benefit to the population as a whole. It is conceivable that, although the actual cost may be extremely expensive for mechanical circulatory support, this

therapy may significantly improve quality of life and return large numbers of individuals to a productive role in society and thus ultimately be considered cost-effective. Analysis of cost-effectiveness during the current stage of device development may not adequately reflect the eventual value or beneficial impact of mechanical circulatory support therapies, but such assessment can be expected to become more favorable as experience with devices, quality of devices and scope of their use expand in the future.

IV. ESTABLISHING EFFICACY FOR DEVICES: ETHICAL AND PRACTICAL CHALLENGES

A. Therapies for Life-threatening Illness

The life-saving potential, procedural risks and costs associated with mechanical circulatory support for patients with end-stage heart failure mandate the thoughtful development of a basis of evidence for efficacy, safety and cost-effectiveness. The Medical Device Amendments of the Food, Drug, and Cosmetic Act require that new devices be "safe and effective" before they can be marketed and that this evidence be provided through "well-controlled scientific studies" or through "valid scientific evidence" (80). Mechanical assist devices fall into the highest of three risk categories defined by the Amendments; class III being life supporting or sustaining and having substantial importance in preventing impairment of health or having a potential to incur risk of injury or illness. For these devices, the sponsor must conduct clinical trials before the FDA grants marketing approval through a so-called PMA decision. Incremental changes to already marketed devices may be approved through a supplemental PMA. Selection of the research design for evaluating a specific mechanical circulatory support device must reflect: 1) the nature of the medical device innovation, 2) the severity of illness of the patients, and 3) the timing within the regulatory approval process (i.e., pre- and post-marketing observations).

The devices under imminent consideration are designed for patients with advanced stages of heart disease. Duration of observation is more limited when severity of illness is higher, as in current populations with acute or chronic refractory class IV heart failure. Knowledge of the grim natural history at this stage increases allowance for consideration of therapies available outside of the device investigational protocol. In other areas of life-threatening illnesses, such as cancer and AIDS, limitations in life expectancy have led to attempts to look at alternative research designs for approving new regimens of care, which would minimize the ethical conflicts of offering only one "active" treatment arm (81). Under these conditions, efforts have also focused on trying to shorten the pre-marketing clinical trial and FDA review processes, lessening the level of evidence necessary for safety and efficacy PMA, while shifting more emphasis to rigorous post-marketing studies.

B. Differences Between Development of Drugs and Devices

By comparison to pharmaceutical innovation, device innovation is more incremental and iterative in nature, as has been the case for LVADs. Both before and after approval for clinical indications, these devices have undergone continuous modification of drivelines, electronic controllers, alarms, connectors, vents, conduits and power supply systems. In the initial stage, this process merits a determination of the initial feasibility without a control arm for devices not previously tested in humans. For drugs, this has often been a dose-ranging study with non-mortality end points such as hemodynamics or exercise capacity. Further benefits of the initial testing phase for any therapy include the defining of promising study end points and the estimation of the sample size required to show a clinically significant benefit. Perhaps even more so for devices than for drugs, premature entry into a clinical trial phase invites the risk of failure or, at least, the need for redesign and retesting.

The relationship between cause and effect is generally more transparent for devices than for drug therapies. Both good and bad results of device implantation are often evident within hours or days, compared with longer and more modest effects over years during the recent drug trials in mild-to-moderate heart failure. It is less likely that the benefit or harm of devices can be masked or mimicked by the natural history of heart failure. The attribution of outcomes may thus be somewhat less prone to bias for devices than for drugs.

The transparent effects of devices also inform both patient and physician with regard to treatment arm in a randomized trial. Even if it were acceptable to perform sham surgery, the physical characteristics of the device would challenge provision of a placebo. This is a major difference between trials of devices and trials of drugs, in which patients on a placebo often assume that they are receiving active and "best" therapy. In addition, treatment is in general difficult or impossible to withdraw for recipients of support devices, by contrast with the trivial nature of withdrawal from a drug study. The cost of developing, manufacturing and ensuring quality of devices is vastly higher for devices than for drugs. Many innovative devices are developed in small companies without previous product revenue to support clinical trials. The total cost per patient is more than an order of magnitude higher than for drugs. The higher costs are balanced in part by the higher expected magnitude of benefit, such that calculated sample sizes are proportionately lower than for drug trials. The expertise and experience required for successful device implantation restrict the eligible sites in trials of devices. These restrictions also limit the generalizability of results after approval, when use extends to centers with less expertise.

The sum of evidence guiding therapy for drugs is dominated by evidence from the large trials completed prior to drug approval. Once approved, it is difficult to identify use

JACC Vol. 37, No. 1, 2001
January 2001:340–70

and attribute effects of any particular drug because of the variability of prescription and adherence in complex regimens of other medications. For this reason, post-marketing surveillance provides limited information regarding drugs for heart failure except for non-cardiovascular side effects. By contrast, the very complexity and undisguised impact of devices render their use and outcomes easier to track, as long as appropriate registries are maintained. The cumulative body of evidence guiding the ultimate use of devices may in the final analysis be weighted more heavily by information gained after initial approval.

C. The Potential for "Breakthrough" Devices

It is possible that initial studies in the future could identify a therapy with such obvious impact that it would be considered a "breakthrough" for a population with otherwise high early mortality. In this case it would be neither necessary nor ethical to perform a prospective trial with a control group in this population. Freedman acknowledges: "In the rare case when the first evidence of a novel therapy's superiority would be entirely convincing to the clinical community, equipoise is already disturbed" (82). As was pointed out by Norman Shumway, the pioneer of cardiac transplantation, no randomized trial of cardiac transplantation has even been conducted, and it is likely that none will ever be. In retrospect, cardiac transplantation was thus a breakthrough. Early mortality was high, but transplantation was considered to represent a major advance over the presumed imminent mortality of the initial recipients. Current mechanical support devices as bridge to transplantation were in fact recognized as effective for this purpose and accepted with only contemporary cohort data. In part, because of the differences described in the preceding text, such a breakthrough in the near future appears more likely for a device for heart failure than for a drug.

Most new therapies do not achieve breakthrough status during preliminary testing but fall somewhere along the spectrum before approval (Fig. 1). Short of an unequivocal breakthrough, there may be some therapies that are not yet approved but are nonetheless considered by experienced clinicians to be sufficiently effective that an RCT is not acceptable. When this is recognized, clinical equipoise is absent, and a randomized clinical trial cannot ethically be performed. The best way to bridge this gap and expedite regulatory approval of effective therapies has not yet been determined for any of the life-threatening diseases.

It is important to recognize that no new technology is likely to represent a breakthrough for every population considered. Even for a device promising 80% six-month survival for patients with end-stage heart failure, the design of trials would remain relevant when extending the technology to those populations with lesser severity of illness in whom the benefit of the device could not be assumed.

D. Ethical Considerations Governing Trials of Mechanical Circulatory Support

1. Requirement for clinical equipoise. The ethical basis of randomized clinical trials in general has been debated (83,84). On one hand, a physician has a responsibility to an individual patient to provide the best care possible, and a randomized treatment would not allow the clinician to provide the perceived best care. On the other hand, it has been argued that without robust, clinical evidence from well-designed trials, physicians cannot decide what is best care, and indeed, physicians' perceptions of optimal treatment have at times been shown to be wrong (84). When the question is one that is appropriately addressed by a randomized clinical trial, a fundamental task for investigators is to understand the ethical and scientific principles.

The ethical conduct for clinical trials of a new therapy rests on a fundamental tenet: the therapy has the promise of some benefit, but its efficacy to achieve this benefit is unknown and the new therapy always carries some risk. Clinical trial ethics demand genuine uncertainty over whether the treatment arm is superior or inferior to the control arm. Equipoise, the principle of uncertainty regarding the merits of two or more treatments (82), is required of the investigators to conduct ethical research. If an investigator believes that one treatment has been proven to be superior to another, then the ethical basis for the RCT is lost and the investigator may not ethically randomize his or her patient to the inferior treatment. However, investigators generally have some bias about which treatment is "best," which has led to considerable debate about what is truly required for an investigator to maintain equipoise. "Theoretical equipoise" has been described as an odd and ethically irrelevant state that could exist only when the clinical data supporting two treatments is essentially equal. Theoretical equipoise is fragile; it is easily disturbed by new data, and it may be inappropriately sensitive to the investigator's perceptions of trial outcomes. A more insightful understanding of equipoise, Freedman proposes, is that of "clinical equipoise," in which genuine debate and uncertainty exist in the clinical community regarding a new treatment or intervention. Evidence must be present to support both sides, and for new treatments with little or no preliminary data, opinion must exist both for and against such a new treatment. Clinical equipoise accommodates even decided treatment preferences by individual clinician investigators during the conduct of a clinical trial if widely spread debate exists between clinicians, and clinical equipoise remains until convincing evidence has been formally presented, reviewed and widely accepted by the medical community at large (82). The clinical equipoise paradigm has been extended recently by the suggestion that the physician investigator, as part of the subject recruitment, divulge his or her treatment preference (85). It is possible that this may cause greater numbers of patients to take the "best medical advice" from their physicians, with the result that fewer patients

may enroll in trials, particularly of therapies available elsewhere. However, this potential conflict may be mitigated by a careful and complete presentation of the scientific merit for the trial, including evidence both for and against the investigational treatment, which forms the ethical basis for the study design and conduct.

It is not ethical to do a trial that is unlikely to provide adequate information. The research protocol must be properly designed to test the new approach. Because of the potential for harm, the question being addressed must be one that is medically important. There needs to be proper matching of the active and control interventions to the patient group being studied. The trial must also be feasible, with adequate resources available to properly conduct and complete the trial. The trial must be able to measure the end points chosen and generate useful data. Finally, it must actively monitor for known and unknown adverse effects, and it must be approved by an institutional review board whose major mandate is to protect the rights and safeguard the welfare of human research subjects. The approved protocol must be thoroughly presented to a subject and accompanied by a written consent form. In the most commonly used design, the subject then decides whether or not to participate in the clinical trial and, if he or she agrees to participate, provides voluntary consent and is randomized.

2. Ethical issues in patient selection for mechanical circulatory support. Which aspects of RCTs for circulatory support devices merit special ethical consideration? Because these devices are currently designed to intervene for life-threatening heart failure, one ethical challenge is the question of whether any imminently terminally ill patients should be entered into RCTs. It has been suggested in the oncology literature that such recruitment for otherwise unavailable therapy may have aspects of coercion (83). Several points, however, emerge in support of enrollment. First, some patients seek clinical trial participation. They may receive purpose and device satisfaction from participation in a research protocol prior to death. They may provide themselves with more comprehensive care. Their participation may ensure that they will not be abandoned, and their interaction with clinical trial staff may yield greater comfort. Second, and more specific to trials of end-stage heart failure, defining the "imminently terminally ill" condition for patients is extremely difficult if not impossible, as described in the preceding text. For clinical trials of surgically implanted devices, it may be unwise to recruit and randomize a truly moribund patient, because the higher operative risks may obviate any clinical benefit and may jeopardize the clinical trial end points. If the recruitment of such a patient flirts with medical futility, it may also be ethically questionable because it may jeopardize meaningful end points contributed by other subjects. As the severity of both natural illness and operative risk shift down, as described above, the more appropriate operative candidates for device therapy also have a greater likelihood that enhanced medical therapy, perhaps including outpatient inotropic therapy, may provide months of survival with some reasonable quality of life outside of the hospital (86). The difficulty in making accurate predictions of life expectancy for presumed end-stage heart failure, in combination with the unknown risk/benefit outcome with mechanical circulatory support, provide the most persuasive foundation for clinical equipoise regarding randomized clinical trials of current circulatory support devices.

Allocation of mechanical circulatory support also raises a question of whether it is ethical to restrict a novel but unproven technology to a certain group of people. Left ventricular assist devices have been approved by the FDA only for use as bridging devices for heart transplant recipients. The current randomized clinical LVAD trial restricts the study population to those with advanced heart failure who require but do not qualify for cardiac transplantation (13). The ethics of this issue have been extensively reviewed (87). Clinical trials demand that subjects be selected so that some benefit from an LVAD intervention can be demonstrated, thereby benefiting the trial and other patients in the trial. Left ventricular assist device therapy has been seen as inferior to cardiac transplantation; therefore, potential cardiac transplant patients may reasonably be excluded from a destination therapy trial because investigators are not ethically mandated to offer an inferior treatment (87).

3. Ethical issues surrounding randomization. When an appropriate candidate has been identified, randomization in a trial of mechanical circulatory support poses unique challenges if subjects may be randomized to receive a device or conventional therapy consisting primarily of drug treatment. Such fundamentally different treatment approaches—one surgical and the other medical—have been associated with substantial subject and investigator treatment bias and ambivalence about random treatment assignments. This bias is of special significance for a fatal disease, as previously noted for cancer patients (81). Patients may passionately favor the new device technology, or they may shrink from a mechanical approach that requires a life-threatening operative intervention. Such fears are magnified by the nature of device surgery, which makes "treatment withdrawal" difficult, unlikely and inadvisable, by contrast with pharmaceutical trials. Technical considerations that prevent blinding of either investigator or patient to treatment selection remove an otherwise powerful antidote to investigator and subject bias. Such concerns have created considerable difficulty in recruiting patients for the first randomized LVAD clinical trial. Finally, for physician investigators, attaining and maintaining clinical equipoise throughout a randomized clinical trial between dramatically different treatment options may be inherently problematic.

A major conflict arises for clinician investigators who then perceive an obligation to provide device treatment, if in light of the new and extensive information provided as part of the consent process, the patient has concluded that the device therapy may be life-saving and is clearly in his or her interest for survival. The investigator must rightfully acknowledge that the dilemma of a patient's requesting one

JACC Vol. 37, No. 1, 2001
January 2001:340–70

arm of a randomized trial would be less likely to arise if comprehensive information had not been provided during recruitment efforts. Increasingly, however, patients arrive with a preconceived notion of their imminent mortality and a favorable impression of the device therapy that has been disseminated through the media prior to patient recruitment. Anecdotal reports indicate that this situation has occurred—and understandably so, considering the nature of the designated population, which suffers the chronic low cardiac output syndrome and faces death over days, weeks or months. The patient with far-advanced disease may perceive that a successful device implant, although not guaranteed, may provide some reasonable chance to survive with improved quality of life. Does the scientific community, as investigators, linger at equipoise longer than they would as these patients?

What is an appropriate response from the investigator to a potential study subject who requests the device therapy arm rather than randomization? One generic response might be that the presentation by the investigator may not have been appropriately balanced. Although this generic comment is highly relevant to most clinical trial protocols, certain patients and circumstances may make this outcome unavoidable for mechanical cardiac assist device trials. It may in fact not be possible to adequately transmit information from which patients could provide a truly informed consent to a complex trial with outcomes that are outside any of their known experiences. Should a patient be permitted to choose the device therapy arm?

Similar issues have been raised in drug development for AIDS (83). Alternative trial designs to include patient preferences (88) have been proposed. Such trials might conceivably lessen conflicts with patient preferences and perhaps enhance recruitment, with greater generalizability of outcomes (89), as described in the following text. It has been argued that most patients in clinical trials are likely to have preferences anyway, which may influence outcomes (90). However, such trials may increase cost and compromise scientific integrity of the data (88). Ethically, it does not appear mandatory that a patient be offered the perceived superior "treatment arm" preference as long as clinical equipoise is present.

4. Ethical issues after randomization. For patients who do proceed with trial participation to randomization, anecdotal reports of patients randomized to the control arm without device suggest some may be despondent and feel that they have been "sentenced to death." Such responses give rise to two concerns. First, it is possible that a patient's preference for the treatment not received may influence his or her own quality and length of life and bias the outcome of a device trial, which preferentially enrolls patients who prefer active treatment. That patient preferences may have an important impact on the outcomes of randomized clinical trials has been postulated, but little data exist in this area (91). Depression has been well-documented to lead to worse outcomes with chronic illness. Expert clinicians know well that a significant loss and the consequent despondency can precipitate decompensation in an otherwise stable HF patient; it is conceivable that such an emotional blow as to miss a randomization to a perceived life-saving device might be life-threatening in itself. If patient despair occurs in significant numbers, the resultant drop out or loss-to-follow-up and patient defection to receive investigational therapies elsewhere could prevent meaningful comparison of the treatment arms. Such experiences challenge the otherwise persuasive Freedman position of "clinical equipoise." There may be both ethical and practical rationale for considering some controlled circumstances in which devices could be provided for "compassionate use" during the course of a trial (see "Design of Clinical Trials for Mechanical Circulatory Support" below).

5. Future ethical issues for equipoise. To date, the Freedman concept of clinical equipoise has been appropriate and attainable for an RCT for mechanical circulatory support, granted that reasonable and serious debate has existed about which treatment may be superior and comprehensive longitudinal clinical data have not been available in non-transplant patients. With the anticipated rapid progress of mechanical circulatory support development and additional clinical trials, considerable effort will be required to maintain clinical equipoise. Although clinical equipoise provides a powerful basis for assessing the ethical conduct of proposed controlled clinical trials, the mechanisms by which clinical equipoise moves ahead to reach a new ethical basis is poorly defined for specific issues, perhaps particularly so for rapidly evolving device innovations. Our current society receives broad but shallow information, with immediate reports of clinical trial results and patient testimonials on the front pages of national newspapers. Both professionals and the public are challenged to discern knowledge from information and to know what is right for now; that is, to decide the basis for clinical equipoise. As we assess new generations of mechanical support devices, how will our present ethical basis be challenged, and for what reason and by whom will our ethical basis be shifted? Will it be led by governmental agencies, industry, investors, clinical investigators and patients reading news reports, or by other groups? Perhaps an objective, expert multidisciplinary group would be helpful in identifying and resolving the ethical dimensions of clinical trials of assist devices.

E. Design of Clinical Trials for Mechanical Circulatory Support

Over time, a wide variety of methods (clinical trials, quasi-experimental techniques, decision analysis, economic analysis and meta-analysis) have evolved to assess outcomes of new therapies. Those that involve primary data collection can be differentiated by whether or not reliable techniques were used at the data acquisition stage to control for variables that can limit the identification of cause and effect relationships between the intervention and outcome of benefit or harm.

1. Randomized clinical trials. The prospective randomized clinical trial is the consummate clinical experiment designed to minimize ambiguity in the interpretation of study results by striving for equality between comparison groups at the time of their assembly. It is widely regarded as the most powerful and sensitive tool for comparing therapeutic interventions (85). As discussed above, this experience has derived largely from trials of drugs for mild-to-moderate HF. Despite the theoretical strengths of the method, and its pivotal importance in trials of pharmaceutical agents in HF, there are daunting challenges in applying randomized clinical trials to the evaluation of potentially life-saving devices for end-stage heart failure. Many of these challenges arise from the differences between drugs and devices as detailed above, particularly with regard to the ethical issues arising from the inability to blind the patient or physician to the treatment arm. The unique nature of these challenges was discussed in detail in the preceding section. It should be emphasized, however, that knowledge of the treatment assignment has immediate practical implications also because the patient's preferences for a device or for no device may compromise both enrollment in, and adherence to, the treatment assignment. In one of the original trials of therapy for AIDS, blood tests were positive for the investigational therapy in 9% of the patients in the placebo arm, indicating off-protocol drug acquisition (92).

Interpretation of outcomes is also influenced by knowledge of the treatment arm. Sham operations are very controversial (91,92) and would not be compatible with the palpable and audible function of current mechanical devices. Expectations by patients and physicians may influence the recognition of complications, the intensity of other therapies and perhaps even survival. Important study end points also include the subjective assessment of symptoms and quality of life. Even exercise performance, ostensibly more objective, is influenced by the expectations of patients and physicians.

Measuring survival in trials that compare devices to medical therapies presents methodological concerns different from those presented when comparing similar therapies. When device therapy involves a high up-front operative risk, with a subsequently reduced mortality compared with controls, the survival curves are likely to cross. Analyzing the differences between such curves depends on the analytical method chosen and the time frame of the analysis. Most analyses such as the log-rank and Wilcoxon methods average risk over the follow-up period. Extending or reducing the follow-up time then has the potential to reverse the order of relative efficacy, because more or less weight will be given to the respective mortality in the perioperative period. Moreover, crossing survival curves imply lack of a consistent proportional relationship in the relative mortality of the two treatments. This violates the basic assumption in using proportional hazard methods, which have been the standard for survival analysis procedures.

Special needs in cancer and AIDS research have affected a number of advances in clinical trial methodology by employing statistical methods that permit not only more rapid and sensitive evaluation of toxicity but also adjustments in design based on the interim outcome experience within a trial (81). Further successful community-based strategies, particularly in the testing of anti-AIDS interventions, have overcome problems with patient recruitment, treatment and development of appropriate informed consent. Understanding of the special challenges involved in evaluating mechanical support will be necessary in the development of novel trial designs that lower obstacles while preserving the advantages offered by the randomized clinical trial.

Financial impediments have affected the conduct of VAD clinical trials profoundly. The issue of funding is central because device companies are often innovative organizations with limited cash reserves and few sources of income. Shrinking budgets for academic centers limit their resources in the face of the increased time required to prepare documents for institutional review boards, screen patients and provide detailed data for studies with limited enrollment. Moreover, the unreimbursed costs of the surgical procedure and recovery are substantial. Cutbacks in health care reimbursement prevent hospitals from continuing to support such visible programs internally as "loss leaders." These disincentives to patient enrollment ultimately increase the overall duration and cost of the study.

The decision by the executive branch of the federal government to begin reimbursing the routine treatment costs of Medicare patients enrolled in clinical trials is an important step in the right direction. Beyond payment for routine costs, the concept of conditional coverage is increasingly advocated, in which insurers (such as Health Care Financing Administration [HCFA]) support the costs of patient treatment associated with both arms of a well-designed clinical trial, while the sponsors (e.g., National Institutes of Health or Industry) cover the costs of conducting the research. There is strong support from this conference for such conditional coverage.

2. The REMATCH trial. Despite the above limitations, an RCT to determine the impact of a mechanical circulatory support device on outcomes with end-stage heart failure is nearing completion. The ongoing REMATCH trial compares the ThermoCardio System implantable LVAD as "destination therapy" with optimal medical therapy in patients who are not candidates for transplantation (13), using the criteria defined above. Initiation and enrollment into this study have been delayed for both centers and patients by many of the issues described. Sufficient patients have been randomized, however, to reach meaningful conclusions. If a survival benefit is proven for this device in this population, future control groups for destination therapy may be receiving this device or receiving continued medical therapy if they have established contraindications to its placement. Even if no statistically significant benefit is demonstrated in the mechanical device-supported patients, the information

JACC Vol. 37, No. 1, 2001
January 2001:340–70

obtained from both standard therapy and the assist device arms will influence device testing and population selection for future clinical device trials.

3. Modifications of the randomized controlled trial for mechanical circulatory support devices

a. OPTION OF LATER "COMPASSIONATE" USE OF DEVICE. It should be re-emphasized that the gold standard methodology for deriving firm information regarding the impact of the treatment on outcomes remains the randomized, double-blinded, placebo-controlled trial, with hard, well-defined primary end points of major clinical importance (23). It should also be recognized, however, that surgical interventions in patients with advanced illness may not appropriately lend themselves to all aspects of this methodologic gold standard, such as blinding to treatment. In designing trials for such interventions, one should begin by seeking to implement the ideal design and to deviate from the ideal only as is practically necessary. It is essential to take into account the impact of trial design modifications on the resulting data before drawing conclusions regarding the treatment effect.

Future design of a trial in which a circulatory device is compared with medical therapy might include a later offer of "compassionate cross-over" for interested patients. This would technically not be a "cross-over" trial because patients with HF would not routinely have the option to cross back from device to medical therapy and the patients receiving a device after randomization to the control arm would not be analyzed with the original device cohort. Provision of the device could be offered after a predetermined time period during which early survival and intermediate-term functional data would be obtained. Alternatively or additionally, the demonstration of certain pre-established criteria of disease progression could be considered as a surrogate end point, after which the device would be offered compassionately, recognizing that the operative risk might be higher at this time than at the time of randomization. The option of receiving a device in the future would offer hope to patients disappointed by initial assignment to no device. In addition to reducing some of the ethical concerns, this provision might actually render a more valid comparison of the two arms, by realigning the incentives for both physicians and patients to persevere through the control period without the device. It would hopefully decrease the risk of losing patients to follow-up as they seek this therapy in a less supervised setting elsewhere. For many of the reasons discussed above, these increased options would be expected to enhance enrollment and adherence to follow-up. This potential increase in enrollment needs to be balanced with the increase in sample size required to determine clinically significant differences.

b. POTENTIAL INFLUENCE OF INITIAL PATIENT PREFERENCE. The ability of a patient to select a particular modality of therapy in a clinical trial may not only significantly enhance enrollment but also potentially influence the outcomes after treatment (88–90). This argues for examining the preferences of patients as a factor that might influence the end point of the trial. One way of accomplishing this is to measure patient preferences for treatment assignment immediately before randomization and, if they are related to the primary end point, to use the results to adjust the primary comparison. A partially randomized design would give patients the option to either become part of a traditional randomized trial or take the therapy of their choosing. In a trial of two interventions, this results in four arms. The comparison of the two randomized arms offers the information of a standard RCT. Absolute confirmation regarding device outcome and complications is available for the patients choosing the device therapy, although there is no parallel control group. Comparisons between the randomized and nonrandomized arms, which must be treated as observational study, would give some indication of the effect of patient preferences on outcome.

4. Comparison of non-randomized cohorts. Alternative designs may be considered when the RCT is not considered appropriate, such as for established devices that incorporate limited improvements. It is also conceivable that cohort studies may be found acceptable when initial evidence of efficacy has persuaded the clinical community away from equipoise but has not yet led to formal device approval (Fig. 1). Cohort studies have employed both historical and prospective controls. With RCTs at the top of the hierarchy of research design, there are various levels of descending rigor for observational reports, all of which are susceptible to considerable bias. Controlling for selection bias can be improved by: 1) restriction of inclusion criteria to define relatively homogeneous cohorts with some loss of generalizability; 2) matching, such that each patient in one cohort is paired with one or more patients with a similar baseline profile for a limited number of key prognostic factors, which need to be better defined for advanced HF; 3) stratifying—comparing rates within subgroups with clinical characteristics that put them at the same risk of the outcome event, which can be done only for a few characteristics before statistical power is lost; and/or 4) adjusting for difference in clinical characteristics between the cohorts, using regression techniques. Unfortunately, none of these can control completely for the factors that led to the provision of a therapy to one patient and not to another, if the therapy was potentially available for both. An interesting example is the comparison of patients who received implantable LVADs as bridges to cardiac transplantation and those in the same centers who did not, for reasons attributed to device availability. This indicated a major benefit from devices used as bridges to transplantation, for which they were subsequently approved. However, generalization of the results to non-transplant candidates predicted a substantial benefit that was not borne out in the randomized pilot trial (52). Meta-analyses of observational trials have in some cases predicted the results of well-designed randomized trials (93,94) but in other cases have been contradicted and

supplanted by such trials (95). It has been suggested that "when recruitment of patients for an RCT is exceptionally difficult, threatening to make the sample of patients unrepresentative, neither reliance on RCTs nor reliance on observational studies is wholly satisfactory" (95,96).

a. HISTORICAL CONTROLS. There is a paucity of large "clinically rich" datasets in patients with class III and class IV heart failure. There is also little data on the components of medical therapy for truly class IV CHF patients. The Flolan International Randomized Survival Trial (FIRST) (97), examining the use of the vasodilator epoprostenol, and the recent Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME CHF) trial (98), examining the use of milrinone during HF hospitalization, demonstrated high mortality regardless of medical treatment. The Pre-Transplant Research Database (51) demonstrated high mortality in patients hospitalized or on intravenous inotropic agents, with mortality of only 13% for other patients awaiting transplantation (a younger population with fewer co-morbidities than patients currently considered for implantable devices). When concluded, the REMATCH trial will provide unique information on approximately 70 such patients receiving optimal medical therapy, and for a brief period, it will represent the most current data available. Historical controls provide useful information that requires interpretation in the context of the original reasons for data collection. Medical therapy is in a dynamic state, so reference to databases previously obtained may provide general guidance but is unlikely to sufficiently validate a new therapy unless it is in the breakthrough realm.

b. PROSPECTIVE CONTROLS. Some of the problems of historical controls can be addressed by assembling the control cohort prospectively, along with the "experimental" cohort group. Once patients have qualified for participation in the study, their assignment to a particular cohort will depend on the goals of the study. Patient assignment, however, must be made in light of the need to establish cohorts that are equally constituted with respect to the risk for the primary measure of outcome. Despite the use of restriction, matching and stratification, cohorts are rarely evenly matched, and comparisons between the cohorts require analytical adjustment to account for differences in baseline patient characteristics.

i. Timed graduation from control cohort to active therapy. One approach is to enroll patients formally for a fixed time period before the device is implanted. This provides a brief period during which early mortality for the population can be determined. There is reason to suspect, however, that the patients dying during this interval were at initially higher risk than those surviving the observation interval preceding implantation. Alternatively, the period of delay may lead to clinical deterioration that increases the operative risk to a higher level than it was at the time of enrollment. Several factors thus render the initial cohort different from the group later undergoing device implantation.

ii. Patient preference cohort studies. A patient preference study (a prospective cohort study allowing patients to choose which therapy they want) may be of considerable appeal to patients (see preceding text). Those patients selecting their preferred treatment rather than randomization would constitute the preference cohorts. Depending on the planned comparisons, patients might also be given the option to cross over to the newer therapy after specific early end points if their opinions change and the change is technically feasible. This type of trial might greatly enhance recruitment because eligible patients with end-stage HF who fear a device may be more willing to allow themselves to be followed in the medical treatment arm. Such patients are currently not likely to be enrolled in any device trials. Similarly, many patients who would be reluctant to enroll in a trial because they might have only a 50% chance of being assigned to a device would now enroll. The fundamental drawback to this design is the possibility that self-selection of a particular therapy is, in some way, associated with the primary measure of outcome, making the groups unequal at baseline. This has not been determined.

iii. Risk-based allocation cohort studies. One approach that is being investigated for breast cancer therapy is to allocate therapy in clinical trials based on risk assessment, such that those patients deemed at greater risk of dying from the underlying disease would receive the experimental therapy and those at less risk would receive standard therapy (99). The treatment effect is measured by comparing the observed results of the experimental group with a projection of the effect of standard treatment on the experimental group, based on a mathematical model. The model would be derived from observations made on the control group. Although this type of trial design is only now being examined, it may provide a novel method for studying the use of VADs in patients with complex heart failure. For investigating therapies of advanced HF, this trial design would be hindered by the limitations of our ability to identify risk profiles and predict outcomes in advanced HF.

F. The Vital Importance of Registries

1. Outcomes database for advanced heart failure. The growing national burden of advanced heart failure argues for the establishment of an ongoing registry at a number of institutions that would include information regarding therapies and outcomes. The large heart failure databases that have generated new mechanistic hypotheses have been of mild-to-moderate heart failure rather than the more severe heart failure responsible for most of the morbidity and mortality associated with this diagnosis. The complexity of this condition, with multiple etiologies, co-morbidities, therapies and modes of death, poses greater challenges to risk profiling and modelling than those encountered with specific cancers or AIDS. Despite the prevalence of advanced HF, however, there have been no national resources devoted to collaborative efforts to assemble such data.

JACC Vol. 37, No. 1, 2001
January 2001:340–70

There are several scientific and societal reasons for a greater commitment to this population. A registry of advanced heart failure would accelerate progress in developing mechanical circulatory support and other new therapies. Greater confidence in our ability to identify high-risk populations would accelerate the recognition of devices in the breakthrough realm. Indications for specific populations could be more readily defined. By virtue of its larger size, a registry offers a better opportunity for matching characteristics of an experimental group with a cohort of controls selected from the dataset. Moreover, a registry would support the development of a regression model that can be used to adjust for differences in assembled cohorts, multivariate regression modeling being the major technique employed for diminishing bias in cohort comparisons. The design of RCTs would be streamlined by better selection of target populations and prediction of event rates.

2. Registries for implantable devices. There is now broad consensus that there should be a mandatory registry for all implantable mechanical circulatory support devices. The impact and implications of device approval and acceptance are much greater than for those of any pharmacologic component of the medical regimen. The number of devices and patients that form the basis of approval is of necessity relatively small, and extensive further experience is required to optimize the clinical utility of new devices. The current consensus is that further development of implanted circulatory devices without plans for such a registry is unethical.

The same factors of technical complexity—cost outlays for the device and consoles, requirements for site expertise and the transparent impact of devices—that hinder large randomized trials prior to device approval may in fact facilitate ongoing surveillance after device release. In recent years, there has been increased attention to the potential of post-marketing studies to accelerate the process of approval. By contrast with pharmaceutical therapies, which are easier to study before approval and harder to supervise afterward, mechanical circulatory support devices may be supported by a weight of evidence distributed differently between pre- and post-approval experiences.

Past experience with all manufacturers has, however, demonstrated the numerous limitations of a voluntary registry, including a lack of uniform criteria for device insertion, variable surgical experience, incomplete data submission at all time points, cost issues and proprietary/marketing issues. There is nonetheless strong precedence for maintaining registries for implanted valves and pacing devices. Device manufacturers as well as health care providers must report information indicating that a device may have caused or contributed to a death or serious injury. In the case of high-risk devices, companies must keep records of patients with implanted devices. It should be possible to require specific baseline data collection on patients with mechanical assist devices after device approval if that stipulation is formally linked to the initial approval of the device.

In addition to patient survival data, regulatory agencies are likely to require post-approval clinical studies to expand on specific components of the safety profile for devices, such as infections or thromboembolic events and documented device failures and replacement. It is not known to what extent a mandatory registry can require specific detailed data, but a registry would provide a useful common denominator as a template. While post-marketing studies have generally used observational methods, the concomitant development of improved registries both for devices and advanced HF should allow more sophisticated modeling to determine relative outcomes of devices versus medical strategies. If there are numerous post-marketing studies that address the same issue, meta-analyses can be used to statistically combine the results of these individual studies to a degree justified by the similarity of devices. This form of analysis can help to resolve uncertainty when studies disagree as well as to answer questions that were not posed at the start of the individual studies. Moreover, it can improve estimates of the magnitude of therapeutic benefits and risks. Compared with trials of drugs and drug classes, meta-analysis has perhaps been underutilized for the analysis of the effects of mechanical assist devices.

It is unclear how the responsibility of supporting such registries should be allocated between industry and governmental agencies. The greater challenge is presented by the larger and more diffuse population with advanced HF, for whom there is no industry incentive to support systematic recording of outcomes. There are currently a number of proposals in the process of submission to direct and maintain a registry of implantable devices.

V. FUTURE DEVICES ENTERING CLINICAL DEVELOPMENT

A. Existing Minimum Standards for Pre-Clinical Device Evaluation

There is presently no standard for the pre-clinical evaluation of devices used in mechanical circulatory support systems. The FDA Office of Device Evaluation still provides useful information and interaction for blood pump developers, but officially, there is no existing standard for the pre-clinical evaluation of these devices. Consequently, it is recommended that circulatory support system developers schedule a pre-investigational device exemption (IDE) submission meeting with the FDA to educate the reviewers in advance on the specifics of their system and to receive feedback from the FDA on the appropriate criteria for the review of their system. Two guidelines for pre-clinical device evaluation do exist. First, the Preliminary Draft Guidance for Ventricular Assist Devices and Total Artificial Hearts issued by the FDA in December 1987 is the original document. Although it is useful in presenting criteria for device evaluation, it is considered obsolete. It also needs to be recognized that the document was issued early in the clinical experience of using VADs and total artificial hearts for bridging to transplan-

tation. The full extent of the circumstances in which these devices would be used (i.e., in and out of the hospital and for durations of months to over a year) could not be fully anticipated by that document. Hence, the periodic revision of the criteria for evaluation became both necessary and appropriate for the evaluation process and a source of frustration for device developers and investigators.

The second guideline comes from a joint paper developed by an ASAIO and the STS interdisciplinary working group (including participants from academia, industry, the NIH and the FDA). This working group jointly published a reliability recommendation for long-term blood pump systems in 1998 (100). This recommendation has been used to guide the reliability evaluations for blood pump systems that are currently under development or that have recently entered clinical trials. It needs to be emphasized, however, that this recommendation is limited to reliability concerns for long-term devices, so there is still a need for a more comprehensive standard with specific criteria for pre-clinical in vitro and in vivo testing and evaluation of devices.

As long-term clinical experience has been gained with circulatory support systems in bridge-to-transplant, bridge-to-recovery and alternative-to-transplant settings, it has become clear that the performance goals for these systems needs to be revised from values stated in or related to the FDA Preliminary Draft Guidance. Controversy has existed over the required duration of pre-clinical animal implantation tests and reliability mission life duration. Concern has been expressed over the recommended duration of pre-clinical reliability mission life duration (some consider the recommended minimum of one year to be too short for a long-term system) and the duration of the animal implantation trials (some consider the recommended 90 days to be too long), but there is insufficient evidence to address these concerns at this time. It also needs to be recognized that although the longer use of these circulatory support systems is the primary motivation for updating minimum criteria for pre-clinical device evaluation, the pre-clinical criteria for devices intended for short-term use (i.e., post-cardiotomy CS and transient right heart failure after LV assist implantation) and bridge-to-recovery also need to be examined and accommodated in a new standard. The revision of these guidelines becomes even more crucial as the definitions for short- and long-term devices become less clear based on clinical applicability. Previously, patients undergoing post-cardiotomy support were felt to require periods of support not extending beyond 10 days to 2 weeks. There are now anecdotal reports showing that recovery has, in fact, been seen with periods of support extending several weeks to several months. In addition, there is the distinct possibility that the patient may become device-dependent, changing what was originally anticipated to be a short-term support period to an extended period as either destination therapy or a bridge to cardiac transplantation. Another perspective to consider is that devices need to be specifically designed to meet the needs of the identified patient population.

The FDA Preliminary Draft Guidance Document and the ASAIO/STS Reliability Recommendation are still considered to be useful documents by several blood pump development groups. However, the need for a current and comprehensive standard for pre-clinical evaluation of devices remains. To begin to address this need, the Association for the Advancement of Medical Instrumentation (AAMI)[1] is presently leading the interdisciplinary development (including participation by the FDA[2] of a Technical Information Report (TIR). The AAMI TIR is in the final development stages. It is expected to be available from the AAMI by the end of the summer of 2000. It must be recognized that due to the uniqueness of each blood pump system, this document provides a comprehensive review of blood pump system issues to be evaluated and considered for inclusion in a FDA IDE submission, but it does not provide a checklist of specific performance requirements. However, the AAMI document does provide several references to guidelines and standards on specific topics related to blood pump systems. Ultimately, the comprehensive design, implementation and documentation of a blood pump system development program with validated in vitro and in vivo testing using sound scientific protocols for data collection and analysis will lead to a successful FDA device review.

Finally, some criteria need to be developed to clearly identify system standards for devices that can be used in different situations for variable clinical indications as the definitions of bridge-to-transplantation, bridge-to-recovery and destination therapy become less distinct. It is not uncommon for example, for a device to be implanted for a post-cardiotomy indication, and then removed much later (three to six months) than intended, because the recovery process may be longer than anticipated. In addition, at some point if the patient cannot be weaned, he or she can be converted to a transplant candidate. On the other hand, if adverse events occur that preclude transplantation, the device may have to perform in the mode of destination therapy. Thus, reliability requirements, which may have been sufficient for post-cardiotomy use, are now ill-defined for permanent use.

The development of a comprehensive standard for the pre-clinical evaluation of blood pump systems, though needed, is not presently being planned. The effort to create such a standard would require a rigorous interdisciplinary effort over a period of three to five years. Until such a standard is developed, it is incumbent upon the members of the blood pump development community and the FDA Device Evaluation staff to share the lessons they have learned to advance the understanding of the pre-clinical blood pump evaluation process. It is also incumbent upon the FDA Device Evaluation staff to continue their difficult

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[2] U.S. FDA, Center for Devices and Radiological Health, Office of Device Evaluation, Division of Cardiovascular and Respiratory Devices, 9200 Corporate Boulevard, Rockville, MD 20878, Tel: (301) 443-8262.

JACC Vol. 37, No. 1, 2001
January 2001:340–70

job of fairly and expeditiously submitting reviews, while being cognizant of the need to revise their criteria as the clinical experience with circulatory support systems grows. Because of the uniqueness of each blood pump system and its intended use, the development of a fixed true standard may be an unachievable goal. A more farsighted approach may be a continuing, interdisciplinary revision of a guidance document for blood pumping systems.

B. Devices Currently in Clinical Development

The first section of this conference document reviewed the devices currently available in the U.S. for intermediate or long-term support. This section reviews the mechanical circulatory support systems that are likely to enter clinical trials as chronic support devices in the U.S. within the next five years. Such devices fall into four major categories: 1) continuous flow LVADs (including axial flow and centrifugal flow pumps), 2) pulsatile LVADs, 3) the total artificial heart and 4) devices without blood contact.

In general, these new devices first undergo extensive ex-vivo reliability testing followed by chronic animal implantations. The third phase is human trials, which generally begin with a single site and then expand to five to twenty centers, testing the device initially as either a bridge to transplantation or as a chronic implant. Clinical trials are then performed to obtain PMA.

1. Continuous flow left ventricular assist devices. Continuous flow, or rotary devices, are currently of two basic types: axial flow pumps and centrifugal flow pumps. They have several potential advantages over current pulsatile pumps: 1) they are smaller devices and therefore can be used in smaller patients (less than the 1.5 m^2 body surface area (BSA) required for most pulsatile devices); 2) they are relatively simple, have fewer moving parts than pulsatile pumps and thus may be less prone to mechanical failures, although this is unproven; 3) because of the continuous flow characteristics, they do not require a compliance chamber in the system; 4) they have lower energy requirements; and 5) the small size of the device and the pocket may decrease the risk of infection, although this is also unproven. These devices also have potential disadvantages that remain to be quantified: 1) current axial flow pumps use bearings lubricated by blood, and this area of relative stasis is a potential source of in-situ thrombus or thromboemboli; 2) chronic anti-coagulation is necessary; 3) some degree of hemolysis is common, the long-term effects of which are unknown; 4) the long-term effects of non-pulsatile (or essentially non-pulsatile) flow are unknown; and 5) feedback control mechanisms for pump speed are complex and unproven.

a. AXIAL FLOW PUMPS. Three axial flow pumps are likely to undergo "first generation" chronic device trials in the U.S., with several trials underway in Europe. They include the Nimbus/TCI IVAS, the Jarvik 2000 IVAS and the DeBakey/MicroMed IVAS. The axial flow motor is small and contains rotary blades that spin at 10,000 to 20,000 rpm and can pump approximately five to six l/min. Because of the continuous flow properties of the axial flow pumps, there are no valves in the system.

The Nimbus IVAS (HeartMate II) is a small (7 cm length) axial flow pump that connects to the LV apex for inflow and the ascending aorta for outflow (101). Under normal operation, the inlet pressure to the axial flow pump will be cyclical, varying with the systolic-diastolic phases of the LV, creating some degree of pulsatility. An electromagnetic motor (pump rotor) turns the turbine. A low-pulse mode produced by variable motor speed will also be available. Two cup-socket ruby bearings support the pump rotor. The outer boundary of the bearing's adjacent static and moving surfaces is washed directly by blood flow. The pump's speed can be controlled manually and by a proposed auto-mode that relies on an algorithm based on pump speed, inherent native cardiac pulsatility and current. A first version of this device is powered through a percutaneous small-diameter electrical cable connected to the system's external electrical controller. A fully implantable system is under development.

The Jarvik 2000 Heart is a similar, compact (5.5 cm length, 85 gm weight) axial flow pump that receives inflow from the LV apex and outflow through a Dacron graft anastomosed to the descending thoracic aorta (102). The rotor constitutes the only moving part of the device and is supported at each end by tiny blood-immersed ceramic bearings (103). The currently existing device is tethered to an external electrical power source through a percutaneous wire, but a subsequent totally implantable version will contain a microprocessor-based controller that can sense and change pump speed according to different phases of the cardiac cycle and receive power via a transcutaneous energy transfer system coil.

The MicroMed DeBakey Axial Flow Pump is an electromagnetically actuated, implantable titanium axial flow pump that connects to the LV apex and ascending aorta. The pump is designed to produce flows of 5 l/min against 100 mm Hg pressure with a rotor speed of 10,000 rpm (104). The currently existing design of this pump includes a fixed rpm rate that can be adjusted through an external device. During periods of patient mobilizations, power can be supplied by two 12-volt DC batteries for several hours.

b. CENTRIFUGAL FLOW PUMPS. Centrifugal flow devices are somewhat larger than axial flow pumps and provide non-pulsatile flow, but the rotational speeds are much slower (about 2,000–4,000 vs. 10,000–20,000 rpm). The same general advantages and disadvantages apply to centrifugal flow pumps as to axial flow pumps.

The AB-180 Circulatory Support System is a small, durable implantable centrifugal pump that receives inflow from the left atrium and empties into the ascending aorta (105,106). The rotor is powered by electromagnetic coupling. A solution of distilled water and heparin provides a high local concentration of anticoagulant within the pump.

An occluder device prevents retrograde flow from the aorta to the left atrium in the event of pump failure. Although it is potentially useful for long-term support, the AB-180 CSS will first be tested as a support device for post-cardiotomy shock.

The HeartMate III LVAD is a centrifugal pump powered by magnetic levitation, a process that combines the functions of levitation and rotation in a single magnetic structure. The small pump rotor does not contain bearings and is completely encased in titanium.

The CorAide™ centrifugal blood pump is an implantable LVAD with a suspended rotor that is noncontacting. The pump produces 8 liters/min flow at 6.5 W.

2. Pulsatile flow devices. Excluding the Novocor and TCI HeartMate (discussed under "Current State of Devices"), pulsatile LVADs likely to enter long-term clinical trials within the next five years are the Thoratec Intracorporeal Ventricular Assist Device (IVAD), the Novacor II, the Worldheart HeartSaver VAD and the Arrow Lionheart VAD. Each of these chronic LVADs requires chronic anti-coagulation with coumadin.

The Thoratec IVAD is designed as a small lightweight device for left or biventricular support (107,108). This IVAD maintains the same blood flow path, valves and polyurethane blood pump sac as the paracorporeal Thoratec device. The major advantage of this IVAD is its relatively small size (339 gm) and simplicity in a pulsatile system that can be implanted in patients ranging in weight from 40 to ≥100 kg. Only the small blood pump is implanted in a pre-peritoneal position with a small (9 mm) percutaneous pneumatic drive line for each VAD connected to a more complex control unit externally, where it can be serviced and replaced. The pump is controlled with a small briefcase-sized, battery powered pneumatic control unit.

The Novacor II miniaturized pulsatile pump is an extension of the current Novacor technology that substantially reduces pump size. The single pump is replaced by two small sac-type pumps, each driven by a central pusher plate mechanism, supporting the LV output through multiple pump cycles. The pusher plate is driven by direct electromagnetic actuation, resulting in a simple bearingless system.

The Worldheart HeartSaver VAD was designed as a totally implantable chronic VAD and has several major attributes: 1) the device is totally implantable and requires no percutaneous connections; 2) it is designed for implantation in the left hemothorax adjacent to the natural heart and can be anchored to the rib cage; 3) the device is remotely monitored and controlled; 4) an internally implanted and rechargeable battery allows the patient to partake in a variety of activities, unencumbered by any external components; and 5) the device can be implanted without cardiopulmonary bypass. The blood contact surface of the sac is fabricated from polyurethane and the valves are porcine tissue valves. An electromagnetic coupling device transfers power across the intact skin and tissue. Wireless monitoring and control of the device is provided by a transcutaneous infrared biotelemetry system.

The Arrow LionHeart VAD is another totally implantable LVAD system with tilting disc valves in which transcutaneous energy is transferred to implanted batteries (109). The energy converter is based on a roller screw mechanism, which in turn causes linear motion at a circular pusher plate that compresses the polyurethane blood sac during systole. In diastole the motor reverses to withdraw the pusher plate. An intrathoracic compliance chamber maintains near-thoracic pressures in the energy converter airspace. External electronics consist of the energy transmission source, a power pack, a battery charger and portable power supplies.

3. Total artificial hearts. Two total artificial heart systems are expected to enter clinical trials in the U.S. within the next five years. They include the Abiomed Total Artificial Heart and the Penn State Total Artificial Heart. Both pumps require chronic anticoagulation with warfarin ± anti-platelet agents.

The Abiomed Total Artificial Heart (AbioCor) is a completely implantable system that can generate cardiac output in excess of 10 liters/m. Powered by transcutaneous energy via coils, an internal battery is included for 20 to 40 min of tether-free time. All blood-contacting surfaces, including the two blood pumps and four tri-leaflet valves, are fabricated from seamless polyurethane (angioflex). Blood flow is maintained by a high-efficiency miniature centrifugal pump, which operates unidirectionally, while a cylindrical rotary valve alternates the direction of the hydraulic fluid flow between the left and right pumping chambers. Left/right balance is achieved by adjusting the right prosthetic ventricle stroke volume via a hydraulic shunt mechanism that incorporates a balancing chamber attached to the left prosthetic ventricle inflow port (110).

The Penn State/3M Total Artificial Heart is a totally implantable device based on a rotor screw mechanism that produces 8 liters/min with a stroke of 64 ml (111). Circular pusher plates are attached to the two ends of the rotor screw shaft, and a brushless DC electric motor rotates the screw 6.3 revolutions to provide a full pusher plate stroke with 1.9 cm linear motion. One pump empties while the other fills, and the motor then reverses to eject the opposite pump. A seamless polyurethane blood sac fits within each titanium pump case, and Bjork-Shiley convexo-concave or Delrin monostrut valves (2.5 mm inlet, 27 outlet) provide unidirectional flow. Left/right balance is achieved by the use of estimated end-diastolic volume from motor speed and voltage. A compliance chamber is coupled to the housing to accommodate volume changes caused by gas diffusion from the blood and changes in atmospheric pressure. Energy is passed through a transcutaneous system to an implanted controller box and Nilco rechargeable battery (45 min tether-free). There is a subcutaneous port for access to the compliance chamber.

4. Devices without blood contact. Currently existing devices without blood contact are designed for short-term

support. However, the development of similar devices for chronic therapy appears likely. The Abiomed Heart Booster combines an LV volume constraining device with a contractile component. Control of LV dilatation is effected by a conical "jacket" that fits over the apex of the heart. The contractile component is based on a change in the shape of multiple thin-walled tubes from a circular cross-section to a highly elliptical or flat cross-section, and vice versa. Rapid hydraulic inflation of the tubes (toward a circular shape) results in a smaller enclosed volume, and rapid deflation of the tubes (toward highly elliptical shape) results in a larger enclosed volume. When negative pressure is applied to the tubes during diastole, the tubes collapse completely in such a way that the pericardial wrap becomes a thin structure that is relatively pliable and does not impede diastolic filling. The device wraps around the apex of the heart and, like other volume constraining devices, does not require cardiopulmonary bypass for implantation. A smooth outer surface is used to prevent tissue ingrowth around the outer surfaces of the device and reduce diastolic dysfunction.

C. Conclusions

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

Responsible progress in this field requires the establishment and maintenance of a mandatory registry that includes all implantable devices, both before and after approval. The combined effort of the various stakeholders is required to address issues of funding, data format and management, compliance and access, while balancing proprietary concerns. A major achievement of this conference is the recognition that the field will advance further and more rapidly if the various groups involved in developing and testing new devices can collaborate effectively in the future.

STAFF

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