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 nontransplant 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

[1] AAMI, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201-4598, Tel: (703) 525-4890.

[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

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

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

The conference was conducted with assistance from the Staff of the American College of Cardiology. Special thanks to Carolyn Carney Lanham, Grace Ronan, Jayne Jordan, Sabriya Wyatt, Betty Holloway, Angela Mensah, Paula Thompson and Vidya Gopal.

REFERENCES

1. Sun BC. Device Selection. In: Goldstein DJ, Oz MC, editors. Cardiac Assist Devices. Armonk, NY: Futura, 2000:27–36.
2. Pennington DG, Swartz MT, Lohmann DP, McBride LR. Cardiac assist devices. Surg Clin North Am 1998;78:691–704, vii.
3. Curtis JJ. Extracorporeal support: centrifugal pumps. In: Goldstein DJ, Oz MC, editors. Cardiac Assist Devices. Armonk, NY: Futura, 2000:215–50.
4. Jeff GK. Extracorporeal support: the ABIOMED BVS 5000. In: Goldstein DJ, Oz MC, editors. Cardiac Assist Devices. Armonk, NY: Futura, 2000:235–50.
5. McBride LR, Naunheim KS, Fiore AC, Moroney DA, Swartz MT. Clinical experience with 111 thoratec ventricular assist devices. Ann Thorac Surg 1999;67:1233–8.
6. Chen JM, DeRose JJ, Slater JP, et al. Improved survival rates support left ventricular assist device implantation early after myocardial infarction. J Am Coll Cardiol 1999;33:1903–8.
7. Chen JM, Spanier TB, Gonzalez JJ, et al. Improved survival in patients with acute myocarditis using external pulsatile mechanical ventricular assistance. J Heart Lung Transplant 1999;18:351–7.
8. Hetzer R, Muller J, Weng Y, Wallukat G, Spiegelsberger S, Loebe M. Cardiac recovery in dilated cardiomyopathy by unloading with a left ventricular assist device. Ann Thorac Surg 1999;68:742–9.
9. Poirier VL. Worldwide experience with the TCI HeartMate system: issues and future perspective. Thorac Cardiovasc Surg 1999;47 Suppl 2:316–20.
10. El Banayosy A, Deng M, Loisance DY, et al. The European experience of Novacor left ventricular assist (LVAS) therapy as a bridge to transplant: a retrospective multi-centre study. Eur J Cardiothorac Surg 1999;15:835–41.
11. Farrar DJ, Hill JD, Pennington DG, et al. Preoperative and postoperative comparison of patients with univentricular and biventricular support with the thoratec ventricular assist device as a bridge to cardiac transplantation. J Thorac Cardiovasc Surg 1997;113:202–9.
12. Massad MG, Cook DJ, Schmitt SK, et al. Factors influencing HLA sensitization in implantable LVAD recipients. Ann Thorac Surg 1997;64:1120–5.
13. Rose EA, Moskowitz AJ, Packer M, et al. The REMATCH trial: rationale, design, and end points. Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure. Ann Thorac Surg 1999;67:723–30.
14. Torrance GW. Measurement of health state utilities for economic appraisal. J Health Econ 1986;5:1–30.
15. Katz AM. Evolving concepts of heart failure: cooling furnace, malfunctioning pump, enlarging muscle—Part I. J Card Fail 1997; 3:319–34.
16. Katz AM. Evolving concepts of heart failure: cooling furnace, malfunctioning pump, enlarging muscle. Part II: Hypertrophy and dilatation of the failing heart. J Card Fail 1998;4:67–81.
17. Young JB. Chronic heart failure management. In: Topol EJ, editor. Textbook of Cardiovascular Medicine. Philadelphia, PA: Lippincott-Raven, 1998.
18. Uretsky BF, Young JB, Shahidi FE, Yellen LG, Harrison MC, Jolly MK. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. J Am Coll Cardiol 1993;22:955–62.
19. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. N Engl J Med 1993;329:1–7.
20. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997; 336:525–33.
21. Richardson A, Bayliss J, Scriven AJ, Parameshwar J, Poole-Wilson PA, Sutton GC. Double-blind comparison of captopril alone against frusemide plus amiloride in mild heart failure. Lancet 1987;2:709–11.
22. Parker JD, Parker AB, Farrell B, Parker JO. Effects of diuretic therapy on the development of tolerance to nitroglycerin and exercise capacity in patients with chronic stable angina. Circulation 1996;93: 691–6.
23. Silverman WA. Human Experimentation: A Guided Step into the Unknown. Oxford: Oxford University Press, 1985.
24. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans' Administration Cooperative Study. N Engl J Med 1986; 314:1547–52.
25. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril

with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303–10.
26. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–91.
27. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429–35.
28. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival And Ventricular Enlargement trial. The SAVE Investigators. N Engl J Med 1992; 327:669–77.
29. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. N Engl J Med 1991;325:1468–75.
30. Moulopoulos LA, Topaz SR, Kolff WJ. Extracorporeal assistance to the circulation and intraaortic balloon pumping. Transactions Am Soc Artif Internal Organs 1962;8:86.
31. Masters RG. Surgical options for the treatment of heart failure. Boston, MA: Clure Academic Publishers, 1999.
32. Alderman EL, Fisher LD, Litwin P, et al. Results of coronary artery surgery in patients with poor left ventricular function (CASS). Circulation 1983;68:785–95.
33. Murphy ML, Hultgren HN, Detre K, Thomsen J, Takaro T. Treatment of chronic stable angina. A preliminary report of survival data of the randomized Veterans Administration cooperative study. N Engl J Med 1977;297:621–7.
34. Varnauskas E. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. N Engl J Med 1988;319:332–7.
35. Young JB, Kirklin JK. Cardiomyoplasty-Skeletal Muscle Assist Randomized Trial (C-SMART): six month results. Circulation 1999;100:I–514.
36. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med 1999;341: 625–34.
37. Urban P, Stauffer JC, Bleed D, et al. A randomized evaluation of early revascularization to treat shock complicating acute myocardial infarction. The (Swiss) Multicenter Trial of Angioplasty for Shock-(S)MASH. Eur Heart J 1999;20:1030–8.
38. Stevenson LW. When is heart failure a surgical disease? In: Rose EA, Stevenson LW, editors. Management of End Stage Heart Failure. Philadelphia, PA: Lippincott-Raven, 1998.
39. Hosenpud JD, Bennett LE, Keck BM, Fiol B, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: sixteenth official report—1999. J Heart Lung Transplant 1999;18:611–26.
40. United Network of Organ Sharing. 1999 Annual Report of the United States Scientific Registry of Transplant Recipients and Organ Procurement and Transplantation Network. Transplant Data 1989–1998. Washington D.C., Department of Health and Human Services. Health Resources and Services Administration, 1999.
41. United Network of Organ Sharing. 1997 Report OPTN: Waiting List Activity and Donor Procurement. Rockville, MD, UNOS, Richmond, VA, and the Division of Transplantation, Office of Special Programs, Health Resources and Services Administration, United States Department of Health and Human Services, 1997.
42. Willman VL. Expert panel review of the NHLBI Total Artificial Heart Program; http://www.nhlbi.nih.gov/resources/docs/tah-rpt.htm. 1999.
43. Gracin N, Johnson MR, Spokas D, et al. The use of APACHE II scores to select candidates for left ventricular assist device placement. Acute Physiology and Chronic Health Evaluation. J Heart Lung Transplant 1998;17:1017–23.
44. Fedullo AJ, Swinburne AJ, Wahl GW, Bixby KR. APACHE II score and mortality in respiratory failure due to cardiogenic pulmonary edema. Crit Care Med 1988;16:1218–21.
45. Goldhill DR, Sumner A. APACHE II, data accuracy and outcome prediction. Anaesthesia 1998;53:937–43.
46. American Heart Association. 1999 Heart and Stroke Statistical Update. 1999.
47. Holmes DR, Jr., Bates ER, Kleiman NS, et al. Contemporary reperfusion therapy for cardiogenic shock: the GUSTO-I trial experience. The GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol 1995;26:668–74.
48. Hochman JS, Boland J, Sleeper LA, et al. Current spectrum of cardiogenic shock and effect of early revascularization on mortality. Results of an International Registry. SHOCK Registry Investigators. Circulation 1995;91:873–81.
49. Hasdai D, Holmes DR, Jr., Califf RM, et al. Cardiogenic shock complicating acute myocardial infarction: predictors of death. GUSTO Investigators. Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries. Am Heart J 1999;138:21–31.
50. Lewis EF, Johnson PA, Johnson W, et al. Heart failure patients express strong polarity of preference for either quality of life or survival. Circulation 1998;98:I–86.
51. Kubo SH, Stevenson LW, Miller LW, et al. Outcomes in non-urgent patients awaiting transplantation. J Heart Lung Transplant 2001. In Press.
52. Moskowitz AJ, Shapiro PA, Sollano JA, et al. Left ventricular assist devices as long-term therapy for severe heart failure. Pilot study results demonstrate feasibility of randomized trial. Circulation 1999; 100 Suppl 1:I–514.
53. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation 1997;95:2660–7.
54. Lucas C, Johnson W, Hamilton MA, et al. Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure. Am Heart J 2001. In Press.
55. Black N, Brazier J, Fitzpatrick R, Reeves B. Health Services Research Methods: A Guide to Better Practice. London: BMJ Books, 1998.
56. Bourge RC, Naftel DC, Costanzo-Nordin MR, et al. Pretransplantation risk factors for death after heart transplantation: a multiinstitutional study. The Transplant Cardiologists Research Database Group. J Heart Lung Transplant 1993;12:549–62.
57. Naccarelli GV, Wolbrette DL, Dell'Orfano JT, Patel HM, Luck JC. A decade of clinical trial developments in postmyocardial infarction, congestive heart failure, and sustained ventricular tachyarrhythmia patients: from CAST to AVID and beyond. Cardiac Arrhythmic Suppression Trial. Antiarrhythmic Versus Implantable Defibrillators. J Cardiovasc Electrophysiol 1998;9:864–91.
58. Pennington DG, Reedy JE, Swartz MT, et al. Univentricular versus biventricular assist device support. J Heart Lung Transplant 1991;10: 258–63.
59. Farrar DJ, Hill JD, Gray LA, Jr., Galbraith TA, Chow E, Hershon JJ. Successful biventricular circulatory support as a bridge to cardiac transplantation during prolonged ventricular fibrillation and asystole. Circulation 1989;80:III147–III151.
60. Holman WL, Roye GD, Bourge RC, McGiffin DC, Iyer SS, Kirklin JK. Circulatory support for myocardial infarction with ventricular arrhythmias. Ann Thorac Surg 1995;59:1230–1.
61. Geannopoulos CJ, Wilber DJ, Olshansky B. Control of refractory ventricular tachycardia with biventricular assist devices. Pacing Clin Electrophysiol 1991;14:1432–4.
62. Kulick DM, Bolman RM, III, Salerno CT, Bank AJ, Park SJ. Management of recurrent ventricular tachycardia with ventricular assist device placement. Ann Thorac Surg 1998;66:571–3.
63. Keogh AM, Valantine HA, Hunt SA, et al. Impact of proximal or midvessel discrete coronary artery stenoses on survival after heart transplantation. J Heart Lung Transplant 1992;11:892–901.
64. Costanzo MR, Naftel DC, Pritzker MR, et al. Heart transplant coronary artery disease detected by coronary angiography: a multiinstitutional study of preoperative donor and recipient risk factors. Cardiac Transplant Research Database. J Heart Lung Transplant 1998;17:744–53.
65. Wong PM, Piamsomboon C, Mathur A, et al. Efficacy of coronary stenting in the management of cardiac allograft vasculopathy. Am J Cardiol 1998;82:239–41.
66. McGiffin DC, Savunen T, Kirklin JK, et al. Cardiac transplant coronary artery disease. A multivariable analysis of pretransplantation risk factors for disease development and morbid events. J Thorac Cardiovasc Surg 1995;109:1081–8.

67. Oz MC, Goldstein DJ, Pepino P, et al. Screening scale predicts patients successfully receiving long-term implantable left ventricular assist devices. Circulation 1995;92:II169–II173.
68. Thoratec VAD Voluntary Registry. Pleasanton, CA, Thoratec Laboratories Corporation, 2000.
69. Thermocardiosystem HeartMate Registry. Wooster, MA, Thermocardiosystems, 2000.
70. Sun BC, Catanese KA, Spanier TB, et al. 100 long-term implantable left ventricular assist devices: the Columbia Presbyterian interim experience. Ann Thorac Surg 1999;68:688–94.
71. Bourge RC, Kirklin JK, Naftel DC, White C, Mason DA, Epstein AE. Analysis and predictors of pulmonary vascular resistance after cardiac transplantation. J Thorac Cardiovasc Surg 1991;101:432–44.
72. Fukamachi K, McCarthy PM, Smedira NG, Vargo RL, Starling RC, Young JB. Preoperative risk factors for right ventricular failure after implantable left ventricular assist device insertion. Ann Thorac Surg 1999;68:2181–4.
73. Kormos RL, Gasior TA, Kawai A, et al. Transplant candidate's clinical status rather than right ventricular function defines need for univentricular versus biventricular support. J Thorac Cardiovasc Surg 1996;111:773–82.
74. Oz MC, Rose EA, Levin HR. Selection criteria for placement of left ventricular assist devices. Am Heart J 1995;129:173–7.
75. Bethesda Conference: conference for the design of clinical trials to study circulatory support devices for chronic heart failure. Ann Thorac Surg 1998;66:1452–65.
76. Moskowitz AJ, Weinberg AD, Oz MC, Williams DL. Quality of life with an implanted left ventricular assist device. Ann Thorac Surg 1997;64:1764–9.
77. Stevenson LW, Couper G, Natterson B, et al. Target heart failure populations for newer therapies. Circulation 1995;92:II174–II181.
78. Byock IR, Merriman MP. Measuring quality of life for patients with terminal illness: the Missoula-VITAS quality of life index. Palliat Med 1998;12:231–44.
79. Levenson JW, McCarthy EP, Lynn J, Davis RB, Phillips RS. The last six months of life for patients with congestive heart failure. J Am Geriatr Soc 2000;48:S101–9.
80. Food, Drug, and Cosmetic Act. 501–21. 2000.
81. Grage TJ, Zelen M. The controlled randomized clinical trial in the evaluation of cancer treatment—the dilemma and alternative trial design. UICC Tech Rep Ser 1982;70:20–46.
82. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987;317:141–5.
83. Hellman S, Hellman DS. Of mice but not men. Problems of the randomized clinical trial. N Engl J Med 1991;324:1585–9.
84. Passamani E. Clinical trials—are they ethical? N Engl J Med 1991;324:1589–92.
85. Marquis D. How to resolve an ethical dilemma concerning randomized clinical trials. N Engl J Med 1999;341:691–3.
86. Crispell K, Nauman D, Walker T, et al. Outpatient continuous inotropic therapy with end stage heart failure: palliative or life-prolonging? J Card Fail 1998;4:39.
87. Parker LS, Arnold RM, Meisel A, Siminoff LA, Roth LH. Ethical factors in the allocation of experimental medical therapies: the chronic left ventricular assist system. Clin Res 1990;38:537–44.
88. Torgerson DJ, Sibbald B. Understanding controlled trials. What is a patient preference trial? BMJ 1998;316:360.
89. Lambert MF, Wood J. Incorporating patient preferences into randomized trials. J Clin Epidemiol 2000;53:163–6.
90. Brewin CR, Bradley C. Patient preferences and randomised clinical trials. BMJ 1989;299:313–5.
91. McPherson K, Britton AR, Wennberg JE. Are randomized controlled trials controlled? Patient preferences and unblind trials. J R Soc Med 1997;90:652–6.
92. Volberding PA, Lagakos SW, Koch MA, et al. Zidovudine in asymptomatic human immunodeficiency virus infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. The AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. N Engl J Med 1990;322:941–9.
93. Kern MJ, Cohen M, Talley JD, et al. Early ambulation after 5 French diagnostic cardiac catheterization: results of a multicenter trial. J Am Coll Cardiol 1990;15:1475–83.
94. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. N Engl J Med 2000;342:1878–86.
95. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000;342:1887–92.
96. Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? [editorial comment]. N Engl J Med 2000;342:1907–9.
97. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1997;134:44–54.
98. Cuffe MS, Califf RM, Adams KF, et al. Rationale and design of the OPTIME CHF trial: outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure. Am Heart J 2000;139:15–22.
99. Finkelstein MO, Levin B, Robbins H. Clinical and prophylactic trials with assured new treatment for those at greater risk: I. A design proposal. Am J Public Health 1996;86:691–5.
100. Pantalos GM, Altieri F, Berson A, et al. Long-term mechanical circulatory support system reliability recommendation: American Society for Artificial Internal Organs and The Society of Thoracic Surgeons: long-term mechanical circulatory support system reliability recommendation. Ann Thorac Surg 1998;66:1852–9.
101. Butler K, Thomas D, Antaki J, et al. Development of the Nimbus/Pittsburgh axial flow left ventricular assist system. Artif Organs 1997;21:602–10.
102. Marlinski E, Jacobs G, Deirmengian C, Jarvik R. Durability testing of components for the Jarvik 2000 completely implantable axial flow left ventricular assist device. ASAIO J 1998;44:M741–4.
103. Kaplon RJ, Oz MC, Kwiatkowski PA, et al. Miniature axial flow pump for ventricular assistance in children and small adults. J Thorac Cardiovasc Surg 1996;111:13–8.
104. Wieselthaler GM, Schima H, Hiesmayr M, et al. First clinical experience with the DeBakey VAD continuous-axial-flow pump for bridge to transplantation. Circulation 2000;101:356–9.
105. Clark RE, Walters RA, Hughson S, Davis SA, Sr., Magovern GJ. Left ventricular support with the implantable AB-180 centrifugal pump in sheep with acute myocardial infarction. ASAIO J 1998;44:804–11.
106. Griffin WP, Savage EB, Clark RE, et al. AB-180 circulatory support system: summary of development and phase I clinical trial. ASAIO J 1998;44:M719–24.
107. Farrar DJ, Buck KE, Coulter JH, Kupa EJ. Portable pneumatic biventricular driver for the Thoratec ventricular assist device. ASAIO J 1997;43:M631–4.
108. Farrar DJ, K-rfer R, El Banayosy A, Posival H, Loisance DY, Tixier D. First clinical use of the Thoratec TLC-II portable VAD driver in ambulatory and patient discharge settings. ASAIO J 1998;44:35A.
109. Weiss WJ, Rosenberg G, Snyder AJ, et al. A completely implanted left ventricular assist device. Chronic in vivo testing. ASAIO J 1993;39:M427–32.
110. Kung RT, Yu LS, Ochs B, Parnis S, Frazier OH. An atrial hydraulic shunt in a total artificial heart. A balance mechanism for the bronchial shunt. ASAIO J 1993;39:M213–7.
111. Weiss WJ, Rosenberg G, Snyder AJ, et al. Steady state hemodynamic and energetic characterization of the Penn State/3M Health Care Total Artificial Heart. ASAIO J 1999;45:189–93.

Journal of the American College of Cardiology
© 2001 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 37, No. 1, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(00)01099-8

コンセンサス会議報告

機械的心臓補助 2000:
現在の適用法と将来の試験デザイン

2000 年 6 月 15～16 日
メリーランド州ベセズダにて

Lynne Warner Stevenson, MD, FACC, Conference Co-Chair
Robert L. Kormos, MD, Conference Co-Chair

運営委員会委員

ROBERT C. BOURGE, MD, FACC
ANNETINE GELIJNS, PHD
BARTLEY P. GRIFFITH, MD
RAY E. HERSHBERGER, MD, FACC
SHARON HUNT, MD, FACC
JAMES KIRKLIN, MD, FACC
LESLIE W. MILLER, MD, FACC
WALTER E. PAE, JR., MD, FACC
GEORGE PANTALOS, PHD
D. GLENN PENNINGTON, MD, FACC
ERIC A. ROSE, MD, FACC
JOHN T. WATSON, PHD
JAMES T. WILLERSON, MD, FACC
JAMES B. YOUNG, MD, FACC

文書作成グループ参加者

MARK L. BARR, MD
MARIA ROSA COSTANZO, MD, FACC
PATRICE DESVIGNE-NICKENS, MD
ARTHUR MICHAEL FELDMAN, MD, PHD, FACC
O. HOWARD (BUD) FRAZIER, MD, FACC
LAWRENCE FRIEDMAN, MD
J. DONALD HILL, MD, FACC
MARVIN A. KONSTAM, MD, FACC
PATRICK McGUANE McCARTHY, MD
ROBERT E. MICHLER, MD, FACC
MEHMET C. OZ, MD, FACC
BRUCE R. ROSENGARD, MD
WOLF SAPIRSTEIN, MD
RHONA SHANKER
CRAIG R. SMITH. MD
RANDALL C. STARLING, MD, MPH, FACC
DAVID O. TAYLOR, MD, FACC
ALISON WICHMAN, MD

招待業界代表者

DALLAS W. ANDERSON
KEN CHARHUT
LAURA DAMME, RN, MPH
MICHAEL R. DEVRIES
LORENZO DICARLO, MD. FACC
DAVID J. FARRAR, PHD
LEONARD A. R. GOLDING, MD, FACC
STEVEN A. KOLENIK
TIM KRAUSKOPF
DOUGLAS McNAIR, MD, PHD
TOFY MUSSIVAND, PHD
CHISATO NOJIRI, MD, PHD
GERGE P. NOON, MD
STEVEN J. PHILLIPS, MD, FACC
PEER M. PORTNER, PHD, FACC
ERIC SCHORSCH
JOSEPH J. SCHWOEBEL, MBA
WINSTON UMEMURA
ROBERT L. WHALEN, PHD
HELENE ZINTAK, PA

後援団体

本会議の実施にあたり、以下の組織から財政的その他の支援を受けた：アメリカ心臓病学会、アメリカ心臓病協会、国際心肺移植学会、アメリカ移植学会、アメリカ心不全学会、アメリカ胸部外科学会、胸部外科学会、アメリカ移植外科学会*。また、次の機関の職員が参加者に含まれる：食品医薬品局、国立衛生研究所、アメリカ人工臓器学会。

目次

本報告において推奨している内容は本会議参加者によるものであり、必ずしもアメリカ心臓病学会の公的立場を反映したものではない。本文書の全文は Journal of the American College of Cardiology に、要旨は Circulation、Journal of Heart and Lung Transplantation、Journal of Thoracic and Cardiovascular Surgery に掲載予定である。本文書はアメリカ心臓病学会のワールドワイドウェブサイト（www.acc.org）で参照可能である。本文書の別刷は、一部 5 ドルで入手可能。電話による問合せは 800-253-4636（米国のみ）、書面による問合せはアメリカ心臓病学会資料センター（Resource Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20814）まで。

影響評価

冠動脈疾患と高血圧による死亡率は低下しつつあるにもかかわらず、心不全による罹患と死亡の健康保険負担は増大傾向にある。軽～中等度の心不全においては、効果的な薬理学的治療による転帰（アウトカム）が向上しているが、重度心不全に対する新しい治療法や機械的循環補助の効果は未だ具現していない。植込み型デバイスは、心臓移植までのつなぎとして安全かつ有効であることが示されているが、心筋の回復や長期的補助に対する機械的補助の役割を確立するためにはさらなる研究が必要である。今回の会議は、現在の機械的補助の適用状況の評価、また、上記で言及した健康保険問題に影響を与える調査のための将来の試験デザインの評価を目的として開催された。

参加者はデバイスと薬物に重要な相違があるからこそ、革新性と柔軟性を特徴とした新奇な試験デザインが必要になる、という結論に達した。複数のインターベンションを明瞭に比較するための最も強力なツールはやはりランダム化臨床試験であるが、そのバリエーションには、対照から試験治療への時限移行、患者のリスクや好みに応じた割り付け、および道義的にデバイスを使用するための任意クロスオーバー基準などが考えられる。
新しい治療から最も大きな利益が得られると考えられる高リスク集団のための重度心不全の全国的転帰データベースがあれば、おそらく大きな影響がもたらされ、それによってデバイスの設計と試験を促すことができる。また、産業界と協力してデバイス装着後の転帰に関するレジストリを設定することは、「突破口となる」デバイス療法の特定と、この新しいテクノロジーの改良と容認の促進に役立つであろう。本会議で示されたとおり、科学者、技術者、産業界、臨床検査担当医師ならびに規制および支払い当局が今後の提携において継続的に協調していくことが、機械的循環補助の進歩を加速させることになる。

はじめに

機械的循環補助デバイスは、過去 5 年間において進化を続け、初期の研究段階から、移植までをつなぐ標準的治療法となった。一部においては、当初の適応を遙かに超えて拡大している。機械的循環補助の最初のランダム化対照試験として、鬱血性心不全の治療にお

ける機械的補助のランダム化評価（Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure；REMATCH）試験が1998年に開始され、患者集団とデバイスそのものについて得られた経験に基づき、定期的にそのプロトコルに修正が加えられている。1999年、国立心肺血液研究所（NHLBI）の専門家調査委員会は完全人工心臓プログラムの進展を継続的に支持していくことを推奨した。現行の左心（LV）デバイスには着実に改良が加え続けられており、多くの新しいタイプの補助デバイスが現在臨床試験中、または臨床試験間近である。将来の臨床試験のデザインと資金調達については、倫理的および実際的問題が浮上している。回復、移植までのつなぎ、および永久的使用という適応の区別が曖昧になりつつあり、最適な適用法という課題はますます複雑化している。

1995年にPaeが中心となって開催した機械的循環補助のための試験デザインに関する最初の会議と同様、研究者、政府機関および産業界の目標は依然として、「科学的に堅実で臨床的に有意義であり、有限期間内に妥当な費用で達成可能な」臨床試験の確立である。重度心不全集団を扱う経験数の急速な増加、現行デバイスの臨床適用の拡大、および将来に向けての新しい補助テクノロジーの有望性を受け、NHLBI、食品医薬品局（FDA）、末期心不全に関するアメリカ心臓病学会委員会および国際心肺移植学会の運営グループは、2000年以降の将来に備え機械的循環補助の試験デザインに関わる問題に対応するために、専門家団体と産業界の広範囲にわたって陳述を求めた。

この分野に大きな関心を持つ専門家団体が、本会議を共催し、草案文書の検討と作成に参加する代表者を選ぶという依頼を受けた。文書作成グループは、メリーランド州ベセズダのハートハウスでの会議において、全ての参加者が討論の上、文書に改訂を加える際の結論の基礎となるものを定めた。この会議には、産業界からの代表者も招かれていた。発表された文書は、運営委員会が承認した参加者のコンセンサス（総意）を示したものであり、参加者が代表する特定の団体による公式な受諾を意味するものではない。今後の新たな発展により、本文書の細目はやがては時代遅れになるであろう。しかし、ここに定められた基礎となる検討材料が、近い将来において、試験デザインや臨床的意志決定の目安として役立てば幸いである。

要旨

心不全用デバイスの現状

機械的循環補助デバイスは、心臓切開後のショックおよび心臓移植までのつなぎでの使用、という適応が、現在は主流である。米国では、年間およそ6,000例の患者に心臓手術後に補助デバイスが適用され、病院内生存率は20～40％である。移植候補者の5～15％では補助後に生来の心機能が持続的に改善することもあり、回復頻度が比較的高いのは劇症心筋炎患者である。国内では、心臓移植へのつなぎ処置を受ける患者が年間300～400例であり、デバイス植込みから移植までの全体的退院率は50～70％である。

デバイス適応症に関する現在の我々の概念には、いくつかの限界があることを認識しておかなければならない。第一に、両室補助と単室補助のどちらが必要かを判定することは困難である。第二に、完全人工心臓と心室補助装置（VAD）を比較した最終的有用性は未だ確立されていない。第三に、機械的補助の対象となる期間は移動標的である。デバイスの使用時間とタイプは、心筋回復までの時間、ドナー臓器の利用可能性、外来治療の可能性、および新しいテクノロジーにまつわる有害事象の予測不能性などの外部要因によって異なる。そのため、現在利用されているデバイスの範囲内であっても、新出適応症を考えると利用ガイドラインは柔軟なものにしておかなければならない。

重度心不全における薬物と外科デバイスの発達

初期には、数々の心不全治療のための基礎となるものが観察所見から得られたが、その多くが後に放棄されることとなった。心不全における薬理学的治療試験に対して系統的アプローチが採られるようになったのは、ここ20年のことに過ぎない。アンジオテンシン変換酵素阻害薬やベータアドレナリン受容体拮抗薬による現在の内科的治療を裏付けるエビデンスの基礎は、数百から数千例の軽度～中等度心不全の患者における二重盲検ランダム化対照試験から得られたものである。複数の対照試験において、ジゴキシンを除く経口強心薬は、堅実な理論的根拠を持つにもかかわらず死亡率を上昇させることが示されている。二重盲検ランダム化対照試験の枠組みは、新しい薬理学的治療を評価するためのゴールドスタンダードとして出現した。これは、プラセボ治療ではおそらく許容されないと思われる緊急治療、すなわち肺水腫を緩和するための利尿薬治療や心原性ショック（CS）に対する静脈内強心薬治療などには適用されていない。

心不全には多くの外科的なアプローチが導入されてきた。冠動脈外科試験は左室駆出率（LVEF）が低下している患者に有益であることが実証されたが、症候性心不全の患者は対象とされていなかった。登録完了までに5年を要した急性CSに対する血管再生術の試験では、75歳未満の患者に有益であることが実証された。血管再生術、弁膜手術、その他のリ

モデリング術は現在、比較的重度の慢性心不全（HG）患者の一部に採用されている。比較プラセボ治療が実施不能であること、侵襲性手技に関する患者の強い優先傾向、および術式の初期段階ほどリスクが高くなること（リスクの前倒し）などにより、これらの新しいアプローチの評価は複雑なものとなっている。

薬物とデバイスの根本的相違点. 薬物による心不全治療が、施術やデバイスの利用へと進歩するに伴い、有効性評価には根本的な相違点が生じている。薬物の開発とは異なり、デバイスの進歩は追加的であり、経験に基づいて改良される。デバイスの影響は目に見えて分かりやすい。デバイスの場合、最も明白なリスクが、新薬のそれに先行して明らかになるということが、理由の一部である。心不全が発生した際の自然な経過によって、デバイスの効果が覆い隠されたり、デバイスの働きに似た作用が発生したりすることないと考えられる。実際的に考慮すべきは、患者 1 例あたりの 1 つの試験におけるコストに関連している。既製品による大きな利益を得ていない企業に、金銭的な抑制がかかる。しかし、臨床的に有意な利益はデバイスが新薬の開発を上回るため、推定サンプルサイズは数千単位ではなく数百単位で済む。最適な転帰を達成するためには経験や技能が必要である。しかし、それによって試験への施設参加が制限され、結果の一般化可能性に抑制がかかってしまう。薬物とデバイスの決定的な相異と言えるのは、治療に対して患者や医師を盲検化することができないことである。これにより、臨床試験に対する倫理的および実際的結果に制限がかかってしまう。

薬物治療の指針となるエビデンスの骨子は、主として薬物承認前に完了している大規模試験からのエビデンスによるものである。一度承認されると、処方、用法遵守および他剤との併用が多様となるため、特定の薬物の使用を確認したり、また、効果が特定の薬物に起因すると証明したりすることが困難となる。このような理由から、市販後調査では心不全に対する薬物に関して限られた情報しか得られない（循環器系以外の副作用に関する情報は除く）。それに対して、デバイスは正にその複雑さとその影響の明白さゆえ、適切なレジストリが維持されている限り、その使用や転帰を追跡することが比較的容易である。したがって、デバイスの最終的な使用の指針となる一連の累積エビデンスは、最初の承認以後に得られた情報から、より多く得られることになる。

機械的循環補助の標的集団とエンドポイント

機械的循環補助の標的集団は、予測可能な心不全の自然経過によって見極めることが可能である。CS 患者は病院内死亡率が 50%超であるが、患者側に原因がある手術合併症のリスクも高い。安静時に症状が出ない外来患者は標準的な経口治療によって 2 年以上生存することが多い。リスクの層別化には多様なアプローチがあるが、中間リスク集団を特定することは未だに困難である。外来で静脈内強心薬治療を受けている患者の 6 カ月死亡率は

現在 50%程度である。しかし、治療に対する客観的な適応や制限を設定しないことで、それほど重症ではない集団を侵害するおそれがある。もう 1 つの標的集団は、三枝冠動脈病変（CAD）があって駆出率が低下しており、1 年生存率が 50%未満の心臓移植患者であるが、移植後集団における機械的デバイスでは、以前の手術や免疫抑制により合併症が生じる場合がある。試験の標的集団は、そのデバイスによる治療で、症状の改善がある程度確実であると思われる最良の自然経過が認められる患者を含むよう、広く定義する必要がある。これは、重度心不全の多施設共同レジストリにすることで、大いに実施が容易となる。成功しているデバイスの承認後の継続的再評価は、リスクを下方修正できることが認められた傾向を反映すべきである。またその場合、高リスク集団で効果が証明された手技は、術後合併症のリスクは低いが得られる効果も低い可能性がある患者へと一般化される。

臨床試験のエンドポイントは、選択した集団における疾患重篤度に応じて選択される。疾患が最も重度の患者では、早期生存率が基本的エンドポイントとなる。内科的治療にランダム化した患者に対し、最終的にはデバイス植込みが可能な試験にするためには、早期生存率と機能的エンドポイントを併用するのが最も適切である。死亡リスクが切迫するにつれ、患者に選択を委ねた上で決定する、機能的能力、クォリティ・オブ・ライフおよび生存率の測定がますます重要になる。どのようなレベルにおいても、有効性の測定を費用効果の測定で補足することが必要になる。しかし、奏功するデバイスの費用効果は、承認後に経験が豊富になりコストが低下するに従って向上する可能性が高いことを強調しておかなければならない。

「突破口となる」デバイスを含む治療の範疇

将来的には、生存率に明らかな影響を与える治療法が最初の試験で特定できるようになるだろう（図 1）。これ以外では早期死亡率の増加が見込まれる集団にとって、この治療法は「突破口」となり得る。これまでのことを考えると、心臓移植は突破口と見なされ、対照試験を行わずとも広く受け入れられてきた。予備的試験が行われている期間に、新しい治療法が「突破口」の範疇に入れられることはほとんどない。承認に至る前の段階で、別の範疇に収まることになる。「突破口」範疇とは別に、承認は未だ受けていないが非常に有効な治療法であるということが経験豊富な臨床医に認められ、したがって、対照試験を待つのは非倫理的である、と考えられる治療法が存在する場合もある。このギャップを埋めるための、規制当局による承認を早めるための最良の方法は、生命を脅かす疾患のいずれにおいても未だ存在しない。本会議は、承認手続きに焦点をあてているのではない。有効性に関して合理的疑いがあるデバイスの試験をデザインすることである。たとえ末期疾患に対して「突破口」の範疇内とみなされるデバイスであっても、そのデバイスの効果を推定することが難しいと考えられる比較的「軽度」の疾患である集団に利用を拡大するためには、やはり試験のデザインが重要となる。