HFSA Working Group

Designs for Mechanical Circulatory Support Device Studies

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ABSTRACT

Background: There is increased interest in mechanical circulatory support devices (MCSDs), such as implantable left ventricular assist devices (LVADs), as ''destination'' therapy for patients with advanced heart failure. Because patient availability to evaluate these devices is limited and randomized trials have been slow in enrolling patients, a workshop was convened to consider designs for MCSD development including alternatives to randomized trials.

Methods and Results: A workshop was jointly planned by the Heart Failure Society of America and the US Food and Drug Administration and was convened in March 2006. One of the panels was asked to review different designs for evaluating new MCSDs. Randomized trials have many advantages over studies with no controls or with nonrandomized concurrent or historical controls. These advantages include the elimination of bias in the assignment of treatments and the balancing, on average, of known and unknown baseline covariates that influence response. These advantages of randomization are particularly important for studies in which the treatments may not differ from one another by a large amount (eg, a head-to-head study of an approved LVAD with a new LVAD). However, researchers have found it difficult to recruit patients to randomized studies because the number of clinical sites that can carry out the studies is not large. Also, there is a reluctance to randomize patients when the control device is considered technologically inferior. Thus ways of improving the design of randomized trials were discussed, and the advantages and disadvantages of alternative designs were considered.

Conclusions: The panel concluded that designs should include a randomized component. Randomized designs might be improved by allowing the control device to be chosen before randomization, by first conducting smaller vanguard studies, and by allowing crossovers in trials with optimal medical management controls. With use of data from completed trials, other databases, and registries, alternative designs that include both a randomized component (eg, 2:1 allocation for new device versus control) and a nonrandomized component (eg, concurrent nonrandomized control, historical control, or a comprehensive cohort design) should be evaluated. This will require partnerships among academic, government, and industry scientists. (*J Cardiac Fail 2007;13:63−74*)

Key Words: Devices, Study design, Control groups.

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Mechanical circulatory support devices (MCSDs), such as implantable left ventricular assist devices (LVADs), were initially evaluated and approved to support patients with advanced heart failure while they awaited heart transplantation. Use as a temporizing device to ''bridge'' critically ill patients to cardiac transplant is increasing because of limited heart donor availability. For example, there were only 2125 transplants during 2005,[1] far below the estimated 20,000 to 30,000 patients each year who could benefit from this procedure. Barr et al reported that the percentage of patients awaiting heart transplantation for more than 2 years increased from 23% in 1994 to 49% in 2003.[2] As waiting time increases, the likelihood of clinical deterioration prior to transplant driving desirability of VAD implant, also increases. Figure 1 illustrates the decrease in the number of heart transplants that have occurred annually.[3]

There is also increased interest in MCSDs as ''destination'' therapy (ie, implant without intent to transition to alternative therapy) for patients who are not candidates for transplantation.

Since January 2002, the International Society of Heart Lung Transplantation has been collecting information from centers worldwide known to perform MCSD implantation. As of December 2004, 655 patients had received a MCSD, of whom 542 received an LVAD.[4] Five hundred and thirteen patients received an MCSD as a bridge to cardiac transplantation, and 78 patients received a MCSD for destination therapy, whereas the remaining patients receiving a MCSD as bridge to recovery or for reasons not specified. Therefore, it appears that MCSDs are used primarily as a bridge to transplantation and relatively few patients receive MCSDs as destination therapy. However, after low complication rates and prolonged survival rates with newer MCSDs are demonstrated, the number of patients who receive MCSDs as destination therapy is likely to increase. In the meantime, patient availability to evaluate new devices with potential technologic improvements for destination therapy is limited.

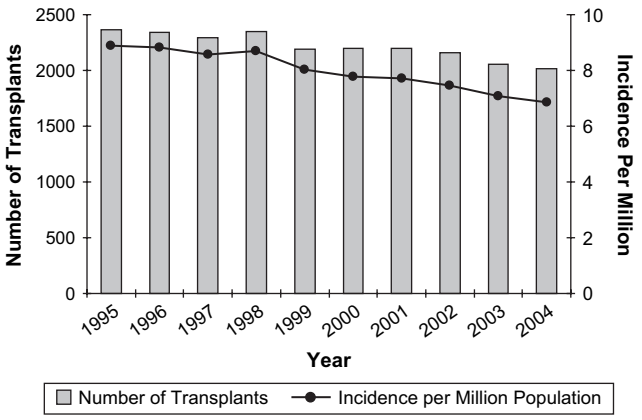

Figure 1. Number of heart transplants and incidence per million population, 1995−2004. Source: 2005 OPTN/SRTR Annual Report, Tables 11.4 and 11.5 (available at http://www.ustransplant.org/anual_reports).

The Heart Failure Society of America convened a workshop with the US Food and Drug Administration (FDA) on March 30−31, 2006, to consider designs for MCSD development, including alternatives to randomized controlled trials. This report summarizes the discussion of that workshop, and is divided into 8 parts: 1) background; 2) randomized trials; 3) no controls; 4) concurrent nonrandomized controls; 5) historical controls; 6) combination of randomized and nonrandomized controls; 7) study design summary; and 8) conclusions.

Background

LVADs as Bridge to Transplant

There are several FDA-approved devices for use as a bridge-to-transplant: Thoratec Corporation's HeartMate I Left Ventricular Assist System (LVAS) Series—implantable pneumatic (IP) and vented electric (VE/XVE); Thoratec ventricular assist device (paracorporeal VAD and implantable VAD); WorldHeart's Novacor LVAS; and Syncardia Systems' CardioWest temporary Total Artificial Heart (TAH-t).

Data from a multicenter study of 34 patients were used to describe the safety and effectiveness of the HeartMate 1000 IP LVAS.[5] Sixty-five percent of patients receiving the device underwent transplantation and 80% of these patients were discharged from the hospital after transplantation. The transplantation rate for 6 concurrent, nonrandomized control patients who met entry criteria but who did not receive the device was 50%; however, all 6 control patients, including the 3 who were transplanted, died within 77 days of meeting the inclusion criteria. A subsequent report described the experience of 75 IP LVAS patients and 33 nonrandomized control patients.[6] Fifty- three (71%) IP LVAS patients survived to transplantation compared with 12 (36%) patients in the control group. The average interval between enrollment and either transplantation or death was 76 days for those in the IP LVAS group (range: <1 to 344 days) and 12 days for the control group (range: 1 to 72 days). A 95% confidence interval (CI) for the percent of IP LVAS patients surviving to transplantation based on the binomial probability model is 61% to 81%.

Data from a study with historical controls conducted at 24 centers have been reported for the VE LVAS device.[7] Twenty-nine percent of VE LVAS-treated patients (82/280) died before receiving a transplant; 188 VE LVAS patients (67%) survived to transplant (95% CI based on binomial probability model: 61.6% to 72.6%); and 10 patients elected to have the device removed before transplantation. By comparison, 67% of patients in the historical control group died (32/48). One-year posttransplant survival was 84% (VE LVAS) versus 63% (controls).

The safety and effectiveness of the CardioWest TAH-t was evaluated in a nonrandomized study that used historical controls.[8] Eighty-one patients received the TAH-t and their survival was compared with 35 control patients who met the same entry criteria. The major outcome variable was