EDITORIAL COMMENT
Heart Transplantation: The Increasing Challenges of Evidence-Based Decision-Making*

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The benefit of heart transplantation has never been tested in a randomized clinical trial because heart transplantation has always been considered a breakthrough therapy according to criteria of evidence-based medicine, namely following early clinical results from Stanford University (1). Although heart transplantation has become the accepted gold standard for the treatment of carefully selected patients (2) with stage D heart failure (3), patient selection criteria for and outcomes after heart transplantation have to constantly be reevaluated in the context of contemporary organ-saving therapies for advanced heart failure. The Comparative Outcomes & Clinical Profiles in Transplantation study in Germany suggested that those patients who, according to the use of a validated heart failure survival score (HFSS), would have the highest risk of dying from their heart failure would derive the greatest survival benefit during the first year after heart transplantation (4). Similar results were obtained in the U.S. (5). Based on these results, the hypothesis has been raised that stable outpatients on the United Network for Organ Sharing (UNOS) status 2 heart transplantation waiting list may not derive a clear benefit from transplantation. Although this hypothesis could theoretically be tested in a randomized clinical trial (6), this study would be difficult to design and conduct (7). Alternatively, observational data gathered by a sophisticated database mechanism may provide clues, albeit with less strength.

To provide this type of information, these observational data require stratification of heart failure risk at the time of listing and transplantation. To be translated into clinical practice, these risk scores have to be incorporated into the daily decision-making algorithm of experienced heart failure/transplant centers. Currently, there are two scores available, the HFSS (8), which is based on the peak oxygen consumption measurement that was introduced by Mancini et al. (9) into heart failure risk stratification, and the German Transplantation Society Score (10).

In this context, the two studies in this issue of the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

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The group from Vanderbilt University (11) addresses the changing role of a validated heart failure risk score, indicating that in the more recent contemporary era it loses some of its predictive potential. This is a very interesting clinical study investigating the relationship between pretransplant survival, peak exercise oxygen consumption, and the HFSS in two different eras and comparing the survival outcomes of these two cohorts to the respective survival outcomes after heart transplantation. The authors hypothesize that outcomes with conventional heart failure therapy have improved over time and that, therefore, the risk prediction by VO2 and HFSS, as well as the survival benefit from cardiac transplantation, is less clear in the more recent era. The design chosen to examine this hypothesis was a retrospective analysis at Vanderbilt University of 320 patients who were listed for cardiac transplantation and followed medically between 1993 and 1997, 187 patients who were listed for cardiac transplantation and followed medically between 1999 and 2001, and 184 patients who were undergoing heart transplantation between 1993 and 2001. The authors found that in the medically treated group, survival in the past era was 78% at one year and 67% at two years as compared with 88% and 79% in the current era, respectively. One-year post transplantation survival was 88%. The authors conclude that patients with a low-risk HFSS and VO2 between 10 and 14 ml/kg/min should no longer be listed for cardiac transplantation because the one-year post-transplantation survival rate was similar.

The group from Harvard University (12) addresses—in a complementary way in discussing the above outlined problem—the integration of risk predictors in a practical clinical algorithm and its impact on outcomes. This is a very interesting clinical study investigating the impact of delayed listing for cardiac transplantation on survival. The authors hypothesize that because outcomes with conventional heart failure therapy have improved over time, delayed versus immediate listing for heart transplantation in stable patients would not reduce overall survival because the survival benefit from cardiac transplantation in stable patients is less clear in the more recent era. The design chosen to examine this hypothesis was a retrospective analysis at Harvard Medical School of transplant committee decisions classifying patients after initial evaluation with respect to cardiac transplantation listing into “eligible,” “potentially eligible,” “ineligible,” and “deferred” and their survival outcomes before and after heart transplantation. Within the group considered “eligible,” the subgroups listed “early” (within 10 days after the committee decision) and “not early” were compared. The authors found that of a total of 214 patients evaluated for transplant, 44% were deemed eligible, 25% potentially eligible, 19% ineligible, and 12% were deferred. Of the eligible patients, 37% of patients were listed within 10 days, and a total of 71% were listed at any time. Three-year survival rates in eligible patients were similar in eligible patients not listed early and in patients listed early.
Ineligible and potentially eligible patients had higher three-year mortality rates than eligible patients with or without transplantation. The authors conclude that using currently accepted guidelines, many patients referred for transplant evaluation and considered eligible who were not listed initially did well long term and therefore may not require early listing and that patients with relative contraindications had worse outcomes with or without transplantation.

Critically reflecting on both studies, the main methodological problem in the Butler et al. (11) in comparing outcomes between the two medically treated groups as well as between the medically treated groups and the heart transplant group is the assumption that each of the groups has a similar clinical and heart failure risk profile. This assumption is necessary to allow for the conclusion that differences in survival outcomes are due to differences in the effectiveness of the interventions (medical heart failure therapy in two eras, and heart transplantation, respectively). Is this assumption valid in the Butler et al. (11) study? The HFSS score distribution between the medically treated patients of the past era and the present era was not the same. There was a lower fraction of high- and medium-risk patients and a higher fraction of low-risk patients in the current era. Thus, differences in survival could be potentially, at least partially, due to differences in baseline characteristics. The clinical profile, Vo2, and HFSS risk score of patients undergoing heart transplantation was not described and statistically compared with either or both pretransplant groups.

On a similar notion in the Lewis et al. paper (12), the main methodological problem in this retrospective observational study in testing the effect of early versus delayed transplant listing on outcomes between the different groups that were “eligible” and listed as “early” or “not early” is the assumption that the groups have a comparable clinical profile regarding their risk of death from heart failure without transplantation and that, indeed, the intervention “early versus delayed intention to treat by cardiac transplantation” is being tested. This assumption is necessary to allow for the conclusion that differences in survival outcomes are due to differences in the timing of the intervention (early vs. delayed listing for heart transplantation, respectively). However, if this assumption is violated and the clinical profile and associated risk of dying from heart failure without transplantation is different between the two groups, then differences in outcome may have to be attributed to these differences as opposed to the timing of transplant listing. Indeed, the patients listed early had a lower peak oxygen consumption (11.4 vs. 13.3 ml/kg/min, p = 0.02). A similar methodological problem in this retrospective observational study exists with the opposite assumption that the clinical profile and thus the risk of dying from heart failure without transplantation between the groups considered “eligible,” “potentially eligible,” “ineligible,” and “deferred” is different. This assumption is necessary to allow for the conclusion that differences in survival outcomes are due to differences in the clinical profile at the time of the initial evaluation. However, it is conceivable that by making a committee decision the subsequent management would not continue to be the same for the different groups and, thus, have an impact on outcomes themselves. Indeed, not all ineligible patients who were not listed for transplantation were followed by the Heart Failure/Transplant group at Harvard University.

The second methodological challenge in this kind of analysis is the form of transition from the pretransplant group into the post-transplant group over the time course of the respective study periods. For example, if a UNOS rule favors elective transplantation as UNOS status 2 patients and thereby leads to continuous removal of a large fraction of stable patients from the waiting list, there may be a time-dependent increase in the severity of heart failure in the remaining waiting list population, increasing their risk of dying. At the same time, this would lead to a favorable post-transplantation outcome because of the high fraction of stable patients being transplanted. If, however, the UNOS rule would favor the transplantation of critically ill and/or unstable patients, the opposite trend would ensue. Thus, this transition requires methods for time-dependent modeling of risks in the respective groups.

Bearing these limitations in mind, one would agree with the conclusion of the Butler et al. (11) and Lewis et al. (12) studies that patients at low (not high or intermediate) risk of dying from heart failure may not require immediate listing and possibly should not undergo transplantation in the current era. This discussion has been open for some years (4,6).

In summary, with contemporary therapy, less benefit of heart transplantation in stable patients is seen. Although heart transplantation may not be in a crisis altogether (13), heart failure risk scores and heart transplantation survival and quality of life benefit need to be continuously reevaluated in the context of constantly changing competing therapies for advanced heart failure that not only include advances in medical, defibrillator and pacemaker therapy but also chronic mechanical circulatory support device therapy (14–16). The major continuous challenge is to integrate this information into our daily encounter with and management algorithms for our advanced heart failure patients (17).

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