Background. Continued donor organ shortage and improved outcomes with current left ventricular assist device (LVAD) technology have increased the number of patients supported with bridge-to-transplantation (BTT) therapy. Using the United Network of Organ Sharing (UNOS) database, we assessed the impact on survival in patients supported with BTT while on the heart transplant waiting list.

Methods. The UNOS database was queried from January 2005 to June 2012 to identify patients listed for heart transplantation as UNOS status 1A or 1B. Patients implanted with a pulsatile-flow device or an LVAD other than the HeartMate II (HM II; Thoratec Inc, Pleasanton, CA) were excluded. Patients were divided into LVAD and non-LVAD groups based on status at the time of listing. Patients were propensity matched (LVAD–non-LVAD = 1:2) for age, sex, weight, presence of diabetes, creatinine levels, mean pulmonary artery pressure, and UNOS status. Kaplan-Meier curves were analyzed for survival.

Results. A total of 8,688 patients were analyzed, with 1,504 (17%) in the LVAD group. Average age (52.6 ± 11.8 versus 51.3 ± 12.9 years; \( p = 0.0002 \)) and weight (86.6 ± 18.6 versus 80.8 ± 18.2 kg; \( p < 0.0001 \)) at time of listing were higher in the LVAD group. There were more men (79% versus 74%; \( p < 0.0001 \)) and more patients with diabetes (30% versus 27%; \( p = 0.03 \)) in the LVAD group. Of all patients, 6,943 patients (80%) underwent transplantation, 862 (10%) died, and 883 (10%) remained on the waiting list. After propensity matching, survival to transplantation was significantly better in the LVAD group than in the non-LVAD group at both 1 year (91% versus 77%) and 2 years (85% versus 68%).

Conclusions. Patients supported with an HM II LVAD as BTT therapy were older with increased comorbidities; they demonstrated an improved survival while listed for heart transplantation. The use of LVADs as a BTT strategy can potentially improve patient survival while waiting for transplantation and allow better allocation of donor hearts.

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Heart failure remains a significant health problem in the United States, with an estimated prevalence of 6.6 million in the year 2012 [1] and is 1 of the most common causes of death annually [1, 2]. Heart failure progression leads to advanced disease that is refractory to medical management and typically has a 50% mortality within 5 years of diagnosis [1]. Heart transplantation, the gold standard treatment for end-stage heart failure, has a limited clinical impact because of the shortage of suitable donor organs and an increasing number of potentially eligible patients. Because of the continued donor organ shortage, the number of heart transplantations has remained stagnant, with a mortality risk of approximately 10% to 15% annually while patients are on the heart transplant waiting list.

The evolution of mechanical circulatory support from pulsatile-flow left ventricular assist devices (LVADs) to the current continuous-flow (CF) LVADs has resulted in improved survival and quality of life in patients supported with bridge-to-transplantation (BTT) therapy [3]. Contemporary CF devices have better durability and fewer complications than pulsatile-flow devices and thus have become the first choice as an LVAD for BTT when indicated for patients on the waiting list for a donor heart [4]. With these improving outcomes for patients supported with an LVAD as BTT treatment, there are now questions about the best therapy to treat a patient with advanced heart failure so that they can survive with a good quality of life until a donor organ becomes available. Using United Network of Organ Sharing (UNOS) data, we sought to evaluate the impact of current CF LVADs on survival while patients are on the heart transplant waiting list.

Material and Methods

Data and Study Population
The study was conducted after approval by the University of Louisville Institutional Review Board. Thoracic organ...
transplantation data were requested from UNOS (1994–June 2012). The UNOS database was then queried for patients aged 18 years or older who were on the waiting list for heart transplantation between 2005 and 2012. At the time of listing with UNOS, patients who were implanted with an LVAD other than the HeartMate II (HM II) (Thoratec Inc, Pleasanton, CA) for BTT therapy were excluded from the analysis to reduce device-specific bias. Only patients listed as UNOS status 1A and 1B at the time of listing were included. Patients were divided into 2 groups based on their status of LVAD implantation at the time of UNOS listing: HM II LVAD versus no circulatory support (non-LVAD group).

Statistical Analysis and Propensity Matching

After applying the inclusion/exclusion criteria, the data set was analyzed to identify differences in various clinical factors—eg, age, sex, weight, UNOS status—between the HM II group and the non-LVAD group. Actuarial patient survival while on the heart transplant waiting list was used as the primary end point for the study. Days spent on the waiting list from the time of UNOS listing until the time of removal from the waiting list (because of transplantation, death, or censor at time of analysis) was used as the survival time. All patients who underwent transplantation were censored at the time of transplantation. Kaplan-Meier curves were computed to analyze the differences in survival between HM II and non-LVAD groups. All statistical analyses were performed using SAS statistical software (SAS Inc, Cary, NC).

To minimize differences between the HM II group and the non-LVAD group, propensity matching was performed. Logistic regression analysis—including age, sex, weight, presence of diabetes, creatinine levels, mean pulmonary pressure, and UNOS status at listing—was used to compute propensity scores to match the HM II group with the non-LVAD group in a ratio of 1:2.

Results

From 2005 to 2012, there were a total of 8,688 patients who met the criteria, with 1,504 (17%) supported with an HM II LVAD as BTT treatment. The average age (52.6 ± 11.8 years; \( p = 0.0002 \)) and weight (86.6 ± 18.6 versus 80.8 ± 18.2 kg \( p < 0.0001 \)) at the time of listing were higher in the HM II group than in the non-LVAD group. In addition, there were more men (79% versus 74%; \( p < 0.0001 \)) and more patients with diabetes (30% versus 27%; \( p = 0.03 \)) in the HM II group than in those without device support (Table 1). The non-LVAD group had a higher mean pulmonary artery pressure (32.6 ± 9.8 versus 29.2 ± 11 mm Hg; \( p < 0.0001 \)). Overall survival at 1 year between the HM II group and the non-LVAD group in the unmatched cohort was 91% and 77% (\( p < 0.05 \)), respectively (Fig 1).

Analyzing yearly trends showed that HM II use for BTT therapy increased from 2% in 2005 to 30% in 2011 (Fig 2). The annual mortality rate for our study population on the heart transplant waiting list decreased in recent years from 15% in 2005 to 4.7% in 2012 (Fig 3). Patients in the HM II group spent more time on the waiting list than did the non-LVAD group (211.5 ± 255.4 versus 130.9 ± 217.2 days; \( p < 0.0001 \)) in the unmatched cohort. Of all patients, 6,943 (80%) underwent transplantation, 862 (10%) died, and 883 (10%) remained on the waiting list. The rate of heart transplantation in the HM II group and the non-LVAD group was 74% (\( n = 1,111 \)) and 81% (\( n = 5,832 \)), respectively. Blood type O was the most common blood type in both groups and had a marginally higher patient proportion in the HM II group (45%) than in the non-LVAD group (41%). Survival on the transplant waiting list was better in the HM II group than in the non-LVAD group irrespective of blood type.

After performing propensity matching, there were 1,495 patients in the HM II group and 2,990 patients in the non-LVAD group. Propensity matching for clinical factors was well matched between both groups as demonstrated in Table 1. The survival between the HM II group and the non-LVAD group was still superior at 1 year (91% versus 79%; \( p < 0.05 \)) after propensity matching (Fig 4). The HM II group also still had a longer waiting time than non-LVAD patients in the propensity-matched cohort (211.2 ± 255 versus 139.1 ± 226.2 days; \( p < 0.0001 \)).

Comment

Heart failure remains 1 of the most significant health problems in the United States, with high morbidity,
mortality, and resource use. Progression of heart failure leads to advanced disease that is refractory to medical management and was noted as a direct cause of death in 56,000 patients and an associated cause of death in about 280,000 patients in 2009 [2]. According to a national hospital discharge survey, heart failure was the first-listed diagnosis on 30% of all hospital admissions and an additional diagnosis in 35% of all admissions in the United States [5]. Analysis of Centers for Medicare and Medicaid Services data for deceased patients with heart failure suggests that mean expenditure of medically managed patients in the last 2 years of life is about $156,169, and 50% of this is spent within the last 6 months of their life [6].

UNOS data document that the number of heart transplantations in the United States has been essentially stagnant in the past decade because of a limited supply of suitable donor organs. The limited supply of donor organs and increased waiting times has led to the emergence of BTT therapies using mechanical circulatory support. Initial use of pulsatile-flow LVADs and total artificial hearts showed improved survival in patients with advanced heart failure treated with BTT [7, 8]. More recent studies have shown continued improvement in survival and quality of life in patients implanted with CF LVADs compared with first-generation pulsatile devices [9, 10]. The HM II was the first CF LVAD to receive US Food and Drug Administration approval for commercial use as BTT therapy for patients with advanced heart failure waiting for a heart transplant. Subsequently, CF devices are now predominantly used for BTT [4]. Recent registry data demonstrate that the use of the HM II as BTT has increased since 2008, and in 2011 about 30% of patients at time of listing were implanted with an HM II. Our findings also indicate that annual mortality of status 1A and 1B patients on the UNOS waiting list has decreased in recent years, which correlates with an increase in HM II use.

Although multicenter clinical trials and postmarket approval studies have demonstrated improvements in survival and quality of life in patients treated with LVADs [7, 9–11], there are still concerns regarding the overall use of LVADs and their impact on survival of patients on the waiting list. Our findings suggest that support with an HM II LVAD compared with no mechanical circulatory support significantly improved survival at 1 year for patients still waiting on the heart transplant list. The patients with HM II devices have a longer waiting time until a suitable donor organ is identified but have similar rates of transplantation within 1 year of being listed. This difference in waiting time might reflect regional
differences in access to donors and possibly the ability to be more selective because the patient is more stable. Although not addressed in this study, the quality of life for a patient with an LVAD who is listed as status 1B is potentially better compared with that in a patient supported with continuous intravenous inotropic agents. The UNOS database did not have information on device complications (or 30-day grace period) that might have led to status 1A at time of transplantation in the HM II group, but based on Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) reporting, freedom from major events at 1 year is 30% [4]. In the HM II group, 69% of patients were status 1A at time of transplantation compared with 54% patients in the non-LVAD group, but we could not conclude that status 1A in the HM II group (device complication or 30-day grace period) was strategically used to gain advantage over the non-LVAD group, because the HM II group had a lower rate of transplantation (74% versus 81%) and a longer time on the waiting list (211 versus 131 days).

Identifying a suitable donor organ is an important component to survival after transplantation. Several recent studies have demonstrated equivalent and potentially better survival after transplantation in patients supported with an HM II LVAD compared with patients with no mechanical circulatory support [11, 12]. With the increasing burden of patients with advanced heart failure and longer waiting times, organ allocation has become more challenging. Russo and colleagues [13] have shown worse outcomes after transplantation in high-risk patients undergoing transplantation with marginal donor organs. The use of CF LVADs could potentially allow more patients the luxury of time and improve their chance of receiving suitable donor organs.

Limitations
This study is limited because of its retrospective nature. Information on patients who received an LVAD after being on the transplantation list was incomplete, so they were included in the non-LVAD group (considered as an intention-to-treat group at the time of listing). If these patients were separated from the non-LVAD group, there could be an even greater potential survival benefit from HM II LVAD support as BTT treatment. Data on INTERMACS profiles at the time of listing was not available in the UNOS database, but differences between the HM II and non-LVAD groups were alleviated with the use of propensity matching.

Conclusions
In summary, the use of contemporary CF LVADs in patients awaiting heart transplantation appears to improve survival compared with a matched cohort treated with standard medical therapy. This finding warrants additional investigation because it has implications for future donor heart allocation and avoiding the need to occasionally use marginal donors.

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REFERENCES
list our patients before VAD? I know a number of institutions probably have been doing that at least with some of their patients, during this period of time you were reviewing this.

DR TRIVEDI: That’s a good question. First of all, with the UNOS database we do not know exactly when after listing the patients get LVAD, so when we performed the analysis, about 5 to 7% of patients, depending on the year, were excluded from the analysis because they got their device after they were listed.

DR AHMAD: And then my second question, is not getting an LVAD at time of listing, if the patient was not an LVAD candidate, a marker for risk? Did you see a difference in the survival just as a surrogate for higher risk patients? For example, the surgeons don’t want to consider putting an LVAD in because they either had multiple sternotomies or they are a little bit older, they are obese, something of this sort, that they would want to avoid mechanical support?

DR TRIVEDI: Since it’s a retrospective study, we cannot say that for sure (if not implanting an LVAD in certain high-risk patients is risk factor itself), but when you look at the prospective trials done on these devices, they show that putting LVAD in the high-risk patient also is associated with improved survival when you compare to the equally high-risk patients, because these are prospective trials and randomized and in well-matched groups.

DR AHMAD: I understand. I just point out potentially another error artifact in the data that might confound it.

DR TRIVEDI: Thank you.

DR SIMON MALTAIS (Nashville, TN): I really enjoyed that talk. It was very informative. Two questions. I guess it’s all on bias and semantics, but do you think including everybody on the transplant list regardless of status really makes a difference on survival on the list, whether the patient with potentially status 2 is not as sick as a status 1B, which most of the HeartMate II are?

My second question is in regards to etiology. Did you have a sense of that? So I guess the indications for listing also could affect your outcomes and time on the list.

DR TRIVEDI: For the first question, being a retrospective study, that’s a limitation. So for the whole cohort of patients, we matched them to equalize their differences between several factors so that we have a propensity-matched cohort. Most patients with HeartMate II are in UNOS status 1A or 1B, so they could not be propensity matched with status 2 patients who do not have device, so we only included status 1A and 1B patients from both HeartMate II group and non-LVAD group and excluded all status 2 patients to reduce the selection bias.

And to the second question: most patients had a diagnosis of idiopathic cardiomyopathy, but we did not have information that specifically indicated reasons for not being able to implant LVAD in certain patients based on etiology.

DR MALTAIS: So you think by your propensity matching you probably alleviate some of those differences?

DR TRIVEDI: Yes.

DR R. DUANE DAVIS (Durham, NC): I guess one suggestion I’d have is trying to work and merge this data with the INTERMACS data, because there is some of that in INTERMACS, particularly if they go to another device or even other components that may be able to give you some of those answers.

The other analysis to consider is to examine the impact of center location, which may address the geographic or center bias about when they do VAD versus medical management. If you are in an OPO that you don’t have a lot of competition, you may choose just to kind of ride it out and get them transplanted because you have access to organs.

DR SLAUGHTER: It’s a very important point, because there clearly are regional differences, particularly on the coast, because they have much greater access to organs, and so it is much easier to get an organ for someone on inotropes either hospitalized or at home. So if that information would be available, plus the etiology of their heart failure, it would add significant value as to when would be the appropriate time and should patients essentially be getting them electively, as they deteriorate for some groups.

DR DAVIS: The comment you made, and I’ll ask you, is that 1 of the take-home messages that you might come away from this, and I will ask you if you can say yes or no, is that if you had somebody deteriorating that going on inotropes is probably not appropriate. You should go towards a ventricular assist device as your safety net and fairly quick. Do you concur with that or would you think that ongoing inotrope as your bailout point is appropriate?

DR TRIVEDI: I think in most of the patients the device strategy is more appropriate and increases the patients’ survival and the chances of patients to receive a suitable donor organ.