Does Renal Dysfunction and Method of Bridging Support Influence Heart Transplant Graft Survival?

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Background. Renal insufficiency is common in status 1B patients supported with inotropes or a continuous flow left ventricular device (CF-LVAD) as a bridge to heart transplantation. We evaluated the association of renal function and inotrope versus CF-LVAD support on posttransplant graft survival in status 1B patients.

Methods. The Scientific Registry for Transplant Recipients database was analyzed for posttransplant survival in status 1B patients bridged with inotropes or CF-LVAD who underwent transplantation between 2003 and 2012. Pretransplant renal function was measured by estimating glomerular filtration rate (GFR) and was stratified as less than 45 mL·min⁻¹·1.73m⁻², 45 to 59, and 60 or greater. Univariate Kaplan-Meier and multivariate Cox regression models were used to evaluate the main effects of GFR strata and inotropes versus CF-LVAD, and the interaction effect of GFR strata by CF-LVAD, and the interaction effect of GFR strata by estimating glomerular filtration rate (GFR) and was stratified as less than 45 mL·min⁻¹·1.73m⁻², 45 to 59, and 60 or greater. Univariate Kaplan-Meier and multivariate Cox regression models were used to evaluate the main effects of GFR strata and inotropes versus CF-LVAD, and the interaction effect of GFR strata by CF-LVAD, on graft survival.

Results. This study included 4,158 status 1B patients (74% male, aged 53 ± 12 years). Of those, 659 patients had a CF-LVAD (HeartMate-II [Thoratec, Pleasanton, CA], n = 638; HVAD [HeartWare, Framingham, MA], n = 21), and 3,530 were receiving inotropes (31 CF-LVAD patients were also receiving inotropes). Kaplan-Meier analyses demonstrated reduced graft survival (p = 0.022) in patients with pretransplant GFR less than 45 versus GFR 45 to 59 (p = 0.062) and versus GFR 60 or greater (p = 0.007), and no effect of inotrope versus CF-LVAD support on graft survival (p = 0.402). Multivariate analysis demonstrated that, after adjusting for the main effects of GFR stratum, CF-LVAD, and inotropes, status 1B patients bridged with a CF-LVAD and GFR in the lowest stratum had reduced graft survival (interaction effect p = 0.040).

Conclusions. Pretransplant renal insufficiency was associated with reduced posttransplant graft survival in status 1B patients. This risk is increased for patients bridged with a CF-LVAD (versus inotropes) who have GFR in the lowest stratum.


Heart transplantation (HT) is the treatment of choice for patients with end-stage heart failure who have refractory symptoms despite maximal medical therapy [1]. The number of donor hearts has remained unchanged over decades despite increasing demand and longer transplant waiting times [1]. Patients listed as status 1B for HT have two treatment options until a suitable donor organ becomes available: chronic inotropic infusion therapy or implantation of a long-term continuous flow left ventricular assist device (CF-LVAD) [2, 3]. The decision to pursue inotrope versus LVAD therapy for a bridge to transplantation (BTT) strategy is complex, based on patient comorbidities, estimations of wait time to HT, and reversibility of end-organ dysfunction, specifically renal dysfunction [4, 5].

Renal dysfunction has been identified as a major risk factor for worse outcomes in patients with end-stage heart failure and in patients supported with inotrope and CF-LVAD therapies [2, 6–10]. Preoperative renal dysfunction, as estimated by the glomerular filtration rate (GFR), has also been associated with decreased survival after HT [1, 11, 12]. Further defining the relationship between renal dysfunction and optimal patient selection for advanced heart failure therapies is critical. Although survival outcomes for patients bridged to HT with a long-term CF-LVAD are comparable to those of patients bridged without devices [13], the relationship between renal dysfunction, method of bridging support, and posttransplant graft survival is unclear. We sought to test whether renal dysfunction and method of bridging support (inotrope versus CF-LVAD) is associated with posttransplant graft survival in a contemporary cohort of status 1B HT recipients.

Dr Maltais discloses a financial relationship with HeartWare HVAD.
Patients and Methods

This study was a retrospective analysis of the Scientific Registry of Transplant Recipients (SRTR) database. The SRTR data system includes data on donor, wait-listed candidates, and transplant recipients in the United States submitted by members of the Organ Procurement and Transplantation Network. This research has been approved by the Vanderbilt University Institutional Review Board.

All patients included were status 1B at the time of transplantation to capture an ambulatory population receiving intravenous inotropic or contemporary CF-LVAD support. Patients who were status 1A (for any reason) at the time of HT were not included in this analysis because they represent a more severely ill and heterogeneous population with labile GFRs who may be at greater risk for posttransplant mortality compared with a status 1B population. Patients with pulsatile or temporary ventricular assist devices, right ventricular assist devices, and total artificial heart devices were also excluded from this analysis because of similar considerations.

Data Management and Statistical Methods

Estimated GFR was determined on the basis of demographic (age, sex, race) and laboratory (serum creatinine) data using the Modification of Diet in Renal Disease (MDRD) equation [14]:

\[
\text{GFR (mL·min}^{-1}·1.73\text{m}^2) = 175 \times (\text{Scr} - 1.154 \times (\text{Age}) - 0.203 \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}) \text{ normalized to a body surface area of 1.73 m}^2.
\]

This equation has been validated in an advanced heart failure population [15]. Because the time between listing and transplantation varied, GFR was estimated using serum creatinine values recorded as being the most proximal to posttransplant mortality compared with a status 1B population. Patients with pulsatile or temporary ventricular assist devices, right ventricular assist devices, and total artificial heart devices were also excluded from this analysis because of similar considerations.

Summary data are expressed as frequencies, proportions, or means ± SD. Glomerular filtration rate data were stratified as 60 or greater, 45 to 59, and less than 45. This approach was taken because the GFR formula stipulates that values of 60 or greater be treated as a class (ie, values are not fully continuous above 60 mL·min}^{-1}·1.73\text{m}^2) [14]. Continuous values less than 60 were then stratified at their median. The association between diabetes and GFR strata was examined using the \( \chi^2 \) test with column-wise tests of proportional differences.

The effects of CF-LVAD, inotropes, and GFR stratum on graft survival were tested using the Kaplan-Meier method with the log rank test. Graft failure was defined as death or retransplantation. Multivariate Cox proportional hazards regression analysis, using a model that was determined a priori without stepwise variable selection, tested the effects on graft survival of GFR stratum and whether pretransplant support was provided by CF-LVAD or inotropes or both. A CF-LVAD by GFR stratum interaction term was included to evaluate whether the effect of CF-LVAD versus inotrope support on graft survival differed on the basis of GFR stratum.

Results

Patient Characteristics

Summary patient characteristics are presented in Table 1. Included were 4,158 adult HT recipients listed as status 1B at the time of transplantation between 2003 and 2012. Average patient age was 53 ± 12 years (range, 18 to 77), and 3,061 patients (74%) were male. Follow-up time averaged 38 ± 30 months (range, less than 1 to 111). At the time of HT, 3,530 patients were supported with inotropes, 659 patients were supported with CF-LVAD (HeartMate-II [Thoratec, Pleasanton, CA], 638; HVAD [HeartWare, Framingham, MA], 21), and 31 patients were supported with both CF-LVAD and inotropes. Initial listing status data indicated that most patients’ status remained stable (at 1B) or increased (eg, from status 2 to 1B) before transplantation. The single most frequent cardiomyopathy etiology undergoing HT was dilated nonischemic type (48%). Overall, 26% of patients had diabetes and diabetes was associated with the poorest renal function (GFR less than 45% of normal).

| Table 1. Patient Characteristics |
|-------------------------------|---|
| Variables | n = 4,158 |
| Age, years | 53 ± 12 |
| Male | 3,061 (74) |
| Primary diagnosis | 1,548 (37) |
| Ischemic dilated cardiomyopathy | 1,321 (32) |
| Nonischemic dilated cardiomyopathy | 1,990 (48) |
| Other | 620 (15) |
| Diabetes mellitus | 1,081 (26) |
| Inotrope support | 3,530 (85) |
| CF-LVAD support | 659 (16) |
| HeartMate-II | 638 (97) |
| HeartWare | 21 (3) |
| eGFR, mL·min}^{-1}·1.73\text{m}^2 | 952 (23) |
| < 45 | 1,070 (26) |
| 45–59 | 2,136 (51) |
| ≥ 60 | 1,070 (26) |
| Initial listing status | 317 (7) |
| 1A | 2,399 (58) |
| 2 | 1,321 (32) |
| Other | 121 (3) |

| Includes “restrictive, congenital, valvular, or unspecified” cardiomyopathy. |
| Thirty-one recipients had inotrope plus continuous flow left ventricular assist device (CF-LVAD) support. |
| Percent of CF-LVAD. |
| Estimated using serum creatinine data most proximal to transplantation. |
| Initial listing status as recorded in database; all recipients were status 1B at the time of transplant. |
| Includes “old status 1” or “temporarily inactive.” |

Values are mean ± SD or n (%).

GFR = estimated glomerular filtration rate.
than 45) ($\chi^2 < 0.001$). Specifically, the proportion of patients with diabetes was significantly higher ($p < 0.05$) within GFR less than 45 (33% with diabetes) in comparison to both GFR 45 to 59 (26% with diabetes) and GFR 60 or greater (23% with diabetes), which did not differ from each other.

**Univariate Models of Graft Survival After Heart Transplantation**

Kaplan-Meier analysis of the effect of CF-LVAD versus inotrope support alone demonstrated the duration of graft survival was not statistically different between groups (CF-LVAD, mean 66 months, SE 1.906, 95% confidence interval [CI]: 62 to 70; inotropes alone, mean 84 months, SE 0.862, 95% CI: 82 to 86; $p = 0.402$). Similarly, because very few patients were supported by both CF-LVAD and inotropes, the complementary analysis of the effect of inotrope support (yes or no), which includes those supported by CF-LAD and inotropes in the inotropes−yes condition, showed no difference in graft survival (no inotropes, mean 66 months, 95% CI: 62 to 69; inotropes, mean 84 months, 95% CI: 82 to 86; $p = 0.402$). In both models, while log rank $p$ values were 0.40 or greater, 95% confidence intervals for the mean did not overlap. Kaplan-Meier analysis demonstrated a statistically significant overall effect of GFR stratum on graft survival ($p = 0.022$) with pairwise log rank tests showing (1) GFR less than 45 versus 45 to 59 ($p = 0.062$); (2) GFR less than 45 versus 60 or greater ($p = 0.007$); and (3) GFR 45 to 59 versus 60 or greater ($p = 0.554$; Fig 1). The collective findings of these univariate analyses support including a GFR stratum by CF-LVAD interaction term in the multivariate model.

**Multivariate Models of Graft Survival After Heart Transplantation**

The multivariate Cox proportional hazards regression model (model $p = 0.008$) included three main effects: (1) inotropes (versus none); (2) no CF-LVAD (versus CF-LVAD); and (3) GFR stratum, plus a GFR-stratum by CF-LVAD interaction term, summarized in Table 2. After adjusting for the main effects of CF-LVAD ($p = 0.375$), inotropes ($p = 0.666$) and GFR ($p = 0.040$), where GFR 45 to 59 and 60 or greater were associated with

<table>
<thead>
<tr>
<th>Variables</th>
<th>$B$</th>
<th>$p$ Value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inotropes (reference, no inotropes)</td>
<td>-0.201</td>
<td>0.666</td>
<td>0.818</td>
<td>0.329–2.035</td>
</tr>
<tr>
<td>No CF-LVAD (reference, CF-LVAD)</td>
<td>-0.416</td>
<td>0.375</td>
<td>0.660</td>
<td>0.264–1.652</td>
</tr>
<tr>
<td>GFR strata (reference, &lt; 45)</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–59</td>
<td>-0.631</td>
<td>0.037</td>
<td>0.532</td>
<td>0.295–0.962</td>
</tr>
<tr>
<td>$\geq 60$</td>
<td>-0.848</td>
<td>0.001</td>
<td>0.428</td>
<td>0.260–0.705</td>
</tr>
<tr>
<td>GFR by CF-LVAD interaction effect</td>
<td>0.040</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45–59 by CF-LVAD/no device</td>
<td>0.494</td>
<td>0.119</td>
<td>1.639</td>
<td>0.880–3.054</td>
</tr>
<tr>
<td>$\geq 60$ by CF-LVAD/no device</td>
<td>0.680</td>
<td>0.011</td>
<td>1.974</td>
<td>1.166–3.341</td>
</tr>
</tbody>
</table>

CF-LVAD = continuous flow left ventricular assist device; CI = confidence interval; GFR = glomerular filtration rate; HR = hazard ratio.
significantly reduced overall likelihood of graft failure compared with GFR less than 45 (both contrasts \( p < 0.05 \)), the relationship between CF-LVAD support (versus no device) and the risk of graft failure was not consistent across all GFR strata (GFR stratum by CF-LVAD interaction \( p = 0.040 \)). This interaction effect is illustrated in Figure 2, which uses a Kaplan-Meier approach to demonstrate that persons with GFR less than 45 who were supported by CF-LVAD had significantly worse graft survival compared with each of the five other GFR stratum by CF-LVAD conditions (all log rank \( p < 0.05 \)). Additionally, pairwise tests indicated that graft survival did not differ significantly among the five alternate conditions (GFR 60 or greater and GFR 45 to 59 with or without CF-LVAD, and GFR less than 45 without CF-LVAD; all log rank \( p > 0.05 \)).

Comment
Main Findings of the Study
This study evaluated the effect of renal dysfunction in patients bridged with inotrope versus CF-LVAD support on posttransplant graft survival. Specifically, we evaluated (1) the overall impact of pretransplant renal dysfunction on graft survival, and (2) whether inotrope versus CF-LVAD support was differentially associated with posttransplant graft survival as a function of the degree of renal impairment. Overall, advanced renal dysfunction (GFR less than 45), measured most proximal to transplantation, was common and associated with reduced posttransplant graft survival. Furthermore, we found decreased posttransplant graft survival in status 1B patients who were bridged to transplantation with a CF-LVAD (versus inotropes only) and who had renal dysfunction within the lowest GFR stratum (\( p = 0.040 \)). These findings have important clinical implications, as trends in the Interagency Registry for Mechanically Assisted Circulatory Support indicate CF-LVADs are commonly utilized for bridge to decision or BTT indications [2]. Our results highlight the need to carefully assess the probability of renal functional improvement before the decision to proceed with HT.

Dynamic Nature of Renal Function After LVAD Implantation
The etiology of renal dysfunction in patients with advanced heart failure supported with CF-LVAD is multifactorial. Renal dysfunction stems from comorbidities causing intrinsic renal disease and superimposed acute and chronic hemodynamic changes related to renal hypoperfusion and venous congestion [17]. Cardiorenal syndrome conceptually describes these acute and chronic bidirectional interactions between the heart and kidney and is important in determining a therapeutic approach and probability of renal improvement [18]. Hasin and colleagues [10] assessed GFR after CF-LVAD implantation and found dramatic early improvements in renal function; however, there were less robust improvements after 6 months of CF-LVAD support. These findings suggest a dynamic, reversible component to renal dysfunction likely related to altered renal hemodynamics.
Brisco and associates [9] demonstrated early improvements in GFR after device implantation; however, the GFR improvement was transient, and by 1 year, was only 6.7% above preimplant values. Interestingly, reduced survival after LVAD implantation was associated with any longitudinal change in GFR (increased or decreased). That suggests a more complex relationship than previously reported, and raises concern over the chronic effects of continuous flow physiology on renal structure and function [19]. Although periodic assessment of renal function is recommended during CF-LVAD support [20], we chose to assess the GFR closest to transplantation to avoid potential confounding effects from fluctuations in GFR after device implantation and during CF-LVAD support, and variability in the duration that patients were supported with inotropes or CF-LVAD before transplantation. The effects of continuous flow physiology on adverse renal outcomes and better etiology based (intrinsic versus cardiorenal syndrome) risk prediction models are needed to improve the timing of transplantation versus ongoing mechanical circulatory support.

**Inotropes in Heart Failure: When to Proceed With LVAD Implant?**

The relationship between renal dysfunction and increased risk of morbidity and mortality has made GFR a major prognostic marker among patients with end-stage heart failure [7, 8]. Dries and coworkers [7] found that even moderately impaired renal function was independently associated with mortality and progression of heart failure, suggesting that renal function may be more than just a marker of heart failure severity and may be a primary determinant of heart failure compensation. However, the relationship between renal dysfunction and adverse outcomes in patients supported with inotropes or CF-LVAD as a BTT strategy is more complex. Literature supporting the use of chronic inotropes as a therapy to improve renal and other end-organ dysfunction, as for BTT, is scarce and largely anecdotal [3, 21]. Pal and coworkers [5] assessed status 1B patients supported with chronic inotrope infusion or pulsatile LVAD before HT and found that patients who received LVADs represented a subgroup of patients who had “failed” inotrope therapy owing to worsening hemodynamics or progressive renal dysfunction. Despite this observation, pretransplant renal function and posttransplant survival was similar between groups, suggesting that CF-LVADs can effectively restore hemodynamics and end-organ perfusion [5].

Overall, our study did not find an association between method of support (inotrope versus CF-LVAD) on posttransplant graft survival; however, we found that when pretransplant renal function was analyzed, a GFR less than 45 was associated with overall reduced transplant survival. This finding suggests that the pretransplant GFR may be used to gauge the response to a given bridging therapy (inotrope versus CF-LVAD) and may be more important in determining the effects of renal dysfunction on posttransplant outcomes than GFR obtained at the time of transplant listing [16, 22]. Acute versus chronic changes in GFR were not specifically studied in this analysis; however, acute GFR fluctuations likely reflect dynamic changes in the underlying illness, which should prompt aggressive attempts at improving renal function compared to chronic GFR changes that may be less likely to improve. We were unable to determine using these SRTR data whether patients initially supported with inotropes were subsequently implanted with a CF-LVAD owing to failure of inotropes or whether other factors leading to a perceived long transplant wait list time (ABO blood group, sensitization, and geographical region) influenced the decision to pursue mechanical circulatory support. Emerging data suggest that waiting until inotropes fail and then moving to (emergent) CF-LVAD support leads to worse posttransplant survival; however, renal function was not assessed in this analysis [23]. Studies assessing the optimal timing and transition from inotropes to CF-LVAD support are needed; furthermore, serial assessments of GFR warrant further exploration as a marker that links efficacy of pretransplant support to posttransplant survival outcomes.

**Renal Dysfunction and Posttransplant Outcomes: The Times Are A-Changin’**

Renal dysfunction (GFR less than 60) measured before HT has been associated with increased posttransplant need for dialysis and reduced survival among patients for whom CF-LVAD was not used as a BTT strategy [11, 12, 24]. These data are concerning, given our findings that 49% of patients had a pretransplant GFR less than 60, and 23% had a pretransplant GFR less than 45. Arnaoutakis and colleagues [25] showed that a pretransplant GFR less than 60 was associated with increased risk of posttransplant mortality for patients supported with a CF-LVAD. Singh and coworkers [16] found that renal outcomes after HT were most dependent on the level of renal function achieved during LVAD support compared with before LVAD implantation.

Determining how to optimally manage patients originally implanted with a CF-LVAD for BTT indications who have renal dysfunction (or when renal function fails to improve) is challenging when posttransplant outcomes on dialysis are poor and donor organ availability is limited [22, 26]. Russo and colleagues [27] analyzed the United Network for Organ Sharing database and found a survival benefit in patients with a GFR less than 33 who underwent simultaneous heart and kidney transplantation (HKT) rather than isolated HT. Karamlou and associates [28] found the prevalence of HKT is increasing out of proportion to isolated HT. Interestingly, when GFR was assessed, isolated HT recipients in the lowest GFR strata (less than 37) had inferior posttransplant survival when compared with HKT recipients in the same pretransplant GFR strata [28].

Our analysis complements these reports and highlights previously unknown findings of inferior posttransplant survival in a CF-LVAD cohort with pretransplant GFR within the lowest strata (less than 45). Further investigation to determine clinically meaningful GFR cutpoints are needed to delineate which patients would be best served by HKT or by destination therapy CF-LVAD alone [29].
Based on this analysis, we advocate (1) increased provider awareness that pretransplant renal dysfunction is clinically meaningful; (2) efforts to improve renal dysfunction by increasing renal perfusion (by hemodynamic, CF-LVAD, and medication optimization) should be attempted; and (3) assessment for transplant suitability should be individualized on a case by case basis. If the GFR remains less than 45 despite attempts at improving renal dysfunction, proceeding with isolated HT may carry increased risk of worse survival and should be balanced by consideration of HKT in collaboration with transplant nephrologists versus continuation of LVAD support as destination therapy. If isolated HT in the setting of significant renal dysfunction is chosen, aggressive comorbidity management (diabetes and hypertension) delaying or minimizing calcineurin inhibitor use through induction therapy and innovative combinations of immuno-suppressive therapy (and steroid minimization) should be considered [30].

Study Limitations

This study did not specifically examine patient or donor characteristics or United Network for Organ Sharing status changes during the waitlist period, all of which may contribute to posttransplant graft survival. Additionally, specific LVAD variables such as LVAD-related complications, duration of LVAD, and inotrope support, and LVAD-related operative characteristics may be associated with posttransplant graft survival; however, these data were not reliably available or well populated in the SRTR database. This analysis was meant to be an evaluation of posttransplant outcomes in a large cohort of status 1B HT recipients and not a center- or patient-specific study. The HVAD is underrepresented in this study compared with the HeartMate-II device, and therefore, our results may be generalizable to class (continuous flow), but not to device type.

In summary, pretransplant renal dysfunction is common and associated with reduced graft survival in status 1B patients undergoing HT. Patients bridged with a CF-LVAD (versus inotropes only) and who had renal dysfunction in the lowest GFR stratum had reduced posttransplant graft survival compared with patients supported with inotropes only. As increasing numbers of patients are bridged to transplantation with CF-LVADs, this study underscores the importance of determining the probability of renal functional improvement before the decision to proceed with transplantation.

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References


DISCUSSION

DR ROBERT KORMOS (Pittsburgh, PA): This is a very interesting paper because it raises some important questions. And one of the things I wanted to ask you is, how big was the low glomerular filtration rate (GFR) group plus left ventricular assist device (LVAD) group, how many patients were in that category, do you recall?

DR MALTAIS: Yes. Approximately, we had—if I can go back to the slide—it’s approximately 30% of patients who have a continuous flow LVAD, a third of these patients have a lower GFR. And lower GFR here being defined as less than 45. So it’s a more significant number of patients than we think it is.

DR KORMOS: And how many of those also included the inotrope plus the continuous flow VAD group and were there some on frank dialysis? Did you have any VAD patients who were in that group on dialysis?

DR MALTAIS: Before transplant, no, none of these patients were on dialysis prior. So this is an analysis of GFR only. And 31 recipients were on both inotropes and LVAD support.

DR KORMOS: For right heart failure?

DR MALTAIS: One can assume that, yes.

DR ADEL TASH (Riyadh, Saudi Arabia): Thank you for the interesting paper and presentation here. You didn’t mention what is the percentage of patients with a high GFR who have diabetes? Because, you know, the diabetic nephropathy, what is the etiology of the renal impairment in these patients? Is it just a prerenal azotemia because of heart failure or is it because of a right ventricle failure or because of an inherent or a coexisting diabetic enteropathy?

DR MALTAIS: Unfortunately, we didn’t detail this in this presentation or in the paper and we may probably do that. This really wanted to be a paper looking at whatever the cause of lower GFR is before transplant. It could be prerenal, it could be hypertension, it could be diabetes. And we assume that everybody who is listed has had optimization of GFR before transplant. And so we look at this as more of an overall kind of message, less of a specific group, but it would be very interesting to substratify groups and say patients who have diabetes, for example, and a low GFR have an increased risk of problems afterward as well.

DR TASH: Because, you know, you would expect, if the patient does not have diabetes with no diabetic nephropathy, you would expect that GFR to improve on the LVAD or on the inotropes.

DR MALTAIS: And that’s a very good question and we can get this information pretty easily.

DR SAGAR DAMLE (Lincoln, NE): Two quick questions. First, is there any way to determine how long the patients were on support before getting transplant, in the sense of how many of these patients were transplanted sort of urgently for VAD problems which may predispose to renal issues. And the second one is, if you go into a transplant knowing you have a higher creatinine, did that alter the posttransplant immunosuppression strategy? Is it the immunosuppression that’s leading to this graft dysfunction or is it the renal dysfunction?

DR MALTAIS: Also a very good question and I kind of feel like I’m going back to the same answer. So the problem with Scientific Registry of Transplant Recipients, and we’ve published data with this before, is you don’t have the time on LVAD support. And so you know in patients—it’s censored for transplantation—so you know whether they had or not an LVAD at time of transplant. And so, of course, based on other published reports that creatinine usually gets better and eventually stabilizes and starts to worsen, one can assume that the time on support would also influence the degree of renal dysfunction over time.

Unfortunately, also, we have those data in regard to immunosuppressive medication after transplant. And again, we really wanted to make this a paper not based on center-specific characteristics but an overall look at the field and say people who have optimized or lower creatinine undergoing heart transplant on a VAD do worse than people who have a lower creatinine on inotropes after transplant. And so again, all these little details will need to be discussed, but this is more of an overall paper. By choosing people on a 1B status, we assume that most of these people have been done “electively.” Because if people are in the hospital on inotropes waiting for a heart or have problems for infection or gastrointestinal bleeding, most of these people nowadays will have a—although things can change over time—a 1A status and so for that reason I think in this study we’ve tried to normalize for this as well.