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## Peer-Reviewed Original Research

# Common clinical dilemmas in left ventricular assist device therapy: A glimpse into current trends

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## Abstract

### Background

Left ventricular assist device (LVAD) therapy has been thrust into the forefront of surgical treatment for advanced heart failure (HF). Despite advancements in survival and quality of life with these devices, the multi-disciplinary care for these patients remains far from standardized across institutions.



## **Methods**

A survey of current practices in LVAD was carried out at the St. Jude Medical User's meeting representing a variety of caregivers including cardiac surgeons, HF cardiologists, non-HF cardiologists, advanced practice providers and ventricular assist device coordinators, with representation from several continents. Utilizing an audience response system, eleven questions were asked related to the demographics of the audience, left ventricular assist device patient selection and patient management.

## **Results**

A total of 120 audience members representing both transplant and LVAD centers, destination therapy only LVAD centers and non-implanting, shared care centers across a multitude of disciplines responded to the survey. Questions comprised of patient selection (body mass index, pre-existing renal failure, care giver presence and abstinence from substance abuse) and patient management (anticoagulation regimens, first line therapy for hemolysis, implantable cardioverter-defibrillator usage and route of preferred dialysis) issues.

## **Conclusions**

LVAD technology will continue to change and improve with the next generation of pumps on the horizon. Progress cannot be made without pausing to understand the current state of technology, practice patterns and patient determinants of success. This survey underscores the lack of consensus regarding best practice principles and the need for an increased focus on care management for LVAD patients with collaborative, multi-institutional studies.

**Keywords:** Left ventricular assist device, mechanical circulatory support, heart failure

## **Background**

There are an estimated 5.7 million people suffering from HF in the United States with 50% dying within five years of their diagnosis [1]. Although medical therapy and cardiac resynchronization therapy have made significant strides in the last two decades, they are still relatively futile in those with advanced stages of HF [2,3]. Heart transplantation remains the gold standard of therapy for these patients; however, the increase in number of patients with HF combined with the limited donor organ availability have thrust left ventricular assist device (LVAD) therapy into the forefront of treatment. Indeed, there are over 15,000 mechanical circulatory support devices that have been recorded in the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry alone since 2006, with annual LVAD implantations surpassing heart transplantation for the first time in 2014 [4].

Although LVAD therapy has become increasingly more popular with over 150 implanting centers, the multi-disciplinary care for these patients remains far from standardized across institutions. EMERG (Evolving Mechanical Support Research Group) is a collaborative network of 17 physicians from high-volume



LVAD implanting centers, with a combination of cardiologists and cardiac surgeons focused on optimizing and standardizing care for the LVAD patient, and ultimately on conducting investigator-initiated, prospective, randomized, multi-center trials in patients with mechanical circulatory support. We believe as members of EMERG, like HF care providers in every discipline, that we share a common passion for LVAD technology, because of the ever-invigorating fascination of rescuing patients from imminent death. However, it is clear that significant controversies and differences in care practices exist amongst all institutions. As clinicians caring for LVAD recipients, we frequently face clinical dilemmas without available data to provide guidance regarding best practices. To glean insight into key topics where there are clear practice pattern variations across centers, we conducted a survey of the audience at the St. Jude Medical-sponsored User's meeting in 2016. In this manuscript, we summarize those findings with accompanying reviews on each topic.

## Methods

The St. Jude Medical (LVAD) User's meeting took place in Phoenix, Arizona in May 2016 and included a variety of caregivers including cardiac surgeons, heart failure cardiologists, non-heart failure cardiologists, advanced practice providers and ventricular assist device coordinators, with representation from several continents. The survey concept and questions were conceived independently by members of EMERG, without any industry involvement or influence. The User's meeting was chosen intentionally by the EMERG investigators as the best avenue to conduct a survey that would be a **true cross section** of "best", or at least most common, clinical practices, with substantial minimization of selection and participation bias given most traditional survey studies utilizing e-mail or U.S. mail as media have a shamefully poor response rate of less than 20% introducing irreconcilable skewing of survey results. In contrast, as observed by the EMERG investigators, every institution which implants, or is planning to implant, LVADs, is invited to send representative members to the "User's Meeting" with an attendance of 468 invited guests of which 218 were from an implanting center. As such, the percentage of practicing LVAD implanting institutions included in this survey response should be substantially greater than e-mail based survey based questionnaires. Furthermore, it should be made abundantly clear that there was no contribution to any of the survey questions, or any part of any question, by any employee or functioning employee of St. Jude Medical. Using an audience response system, eleven questions were asked related to the demographics of the audience, left ventricular assist device patient selection and patient management.

## Results

The demographics-related questions in the survey were:

### **Demographics: Which of the below best describes your center?**

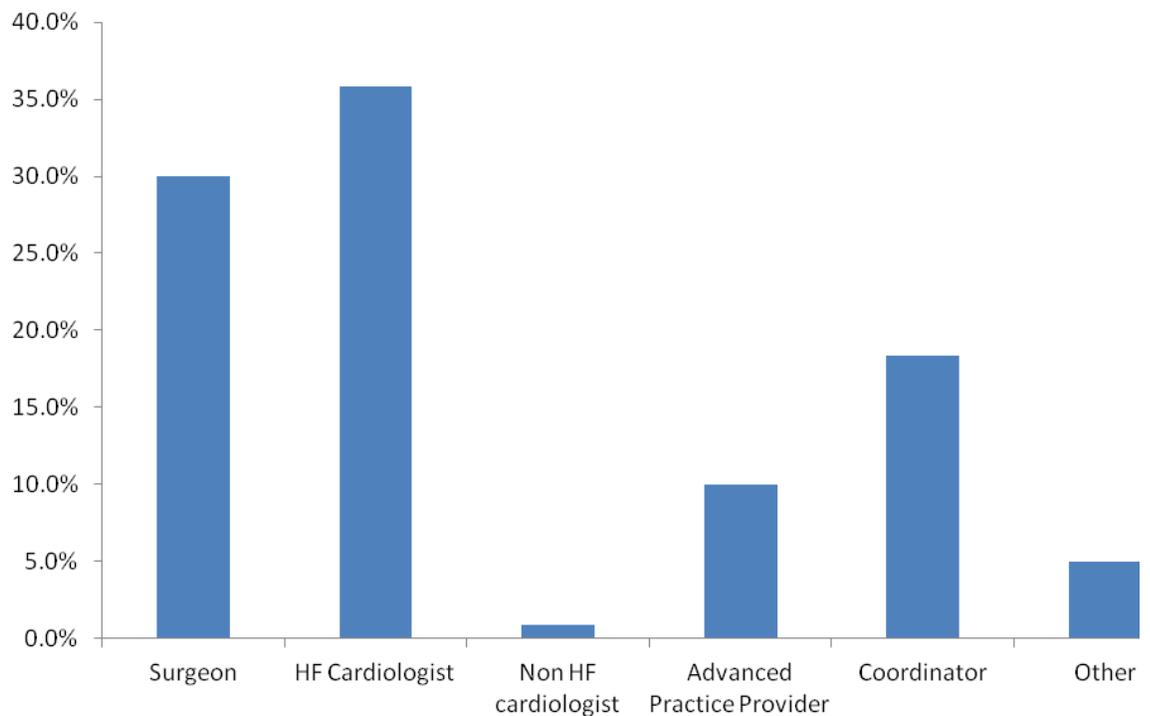
- a. Transplant and LVAD center
- b. DT LVAD center
- c. Non-implanting, shared care site
- d. Neither



**Demographics: Which of the best describes your role?**

- a. Surgeon
- b. HF Cardiologist
- c. Non HF cardiologist
- d. Advanced Practice Provider
- e. Coordinator
- f. Other

There were a total of 120 respondents with 75.9% representing both a transplant and LVAD center, 18.3 % representing a destination therapy (DT) only LVAD center, 5.0 % representing a non-implanting, shared care center and 0.8 % representing none of these. The audience was comprised of multiple disciplines (**Figure 1**).



**Figure 1: Demographics of Survey Respondents**

The make-up of the respondents to the survey included a multitude of different backgrounds with heart failure (HF) cardiologists making up the largest number with 35.8% followed by heart failure cardiac surgeons at 30.0 % (n=120).



Questions regarding patient characteristics included:

**Is there a body mass index (BMI - kg/m<sup>2</sup>) above which your center would not offer an LVAD?**

- a. > 40 kg/m<sup>2</sup>
- b. > 45
- c. > 50
- d. No limit

**Does your center implant LVAD in patients with end stage renal failure on chronic hemodialysis (excluding bridge to heart-kidney transplant)?**

- a. yes
- b. no

**If your patient needs dialysis, what is your preferred route of dialysis?**

- a. Tunneled central venous catheter
- b. Arterio-venous (AV) fistula
- c. AV graft
- d. Peritoneal dialysis

The body mass index (BMI in kg/m<sup>2</sup>) above which a program would not offer LVAD implantation was > 40 in 23.8%, > 45 in 15.8%, > 50 in 16.8% and no limit in 43.6% of respondents (n=101) (**Table 1**). In patients with pre-existing end stage renal failure requiring chronic hemodialysis (excluding bridge to heart-kidney transplant candidates), nearly 90% responded that they would not offer LVAD therapy (n=104). In patients requiring post-LVAD dialysis, the preferred route of dialysis was a tunneled central venous catheter in 48.4 %, an arterio-venous (AV) fistula in 33.0 %, peritoneal dialysis in 12.1 % and AV graft in 6.6 % of respondents (**Table 2**) (n=91).

**Table 1: Body Mass Index above which one would not offer LVAD therapy**

Body mass index	Respondents Count (%)
> 40 (BMI) in kg/m <sup>2</sup>	24 (23.8)
> 45 (BMI) in kg/m <sup>2</sup>	16 (15.8)
> 50 (BMI) in kg/m <sup>2</sup>	17 (16.8)
No limit	44 (43.6)



**Table 2: Preferred route of renal replacement therapy in patients requiring dialysis post-LVAD implantation**

Route of Dialysis	Respondents Count (%)
Tunneled central venous catheter	44 (48.4)
Arterio-venous (AV) fistula	30 (33.0)
AV graft	6 (6.6)
Peritoneal dialysis	11 (12.1)

Questions regarding psychosocial support and substance abuse included:

**Does your center mandate that LVAD candidates have 24 hour caregiver support?**

- a. Yes – indefinitely
- b. Yes - for the first 3 months
- c. Yes - for the first 30 days
- d. Yes – but not 24 hours-a-day
- e. No

**For patients implanted as DT (destination therapy) – what is your stance on tobacco and THC (marijuana) use in your program?**

- a. Require abstinence from THC, but not tobacco
- b. Require abstinence from tobacco, but not THC
- c. Require abstinence from BOTH tobacco and THC
- d. Do not require abstinence from either tobacco or THC
- e. Have a don't ask/don't tell policy

As it relates to social requirements for LVAD therapy consideration, 10.7% of survey participants stated that they do not have a 24 hour caregiver support requirement, while the remaining respondents had variable requirements ranging from one month to indefinitely (n=103). In patients implanted as destination therapy, there was an approximately even split between those who required abstinence from both tetrahydrocannabinol (THC - marijuana) and tobacco (smoking) in 42.4 % to those who did not require abstinence from either tobacco or THC in 38.4 % of the audience (**Table 3**) (n=99).



**Table 3: Social requirements for LVAD consideration**

Social Requirement Question	Respondents Count (%)
<b>1. Does your center mandate that LVAD candidates have 24 hour caregiver support?</b>	
Yes – indefinitely	15 (14.6)
Yes – for the first 3 months	24 (23.3)
Yes – for the first 30 days	28 (27.2)
Yes – but not 24 hours-a-day	25 (24.3)
No	11 (10.7)
<b>2. For patients implanted as destination therapy – what is your stance on tobacco and THC (marijuana) use in your program?</b>	
Require abstinence from THC, but not tobacco	11 (11.1)
Require abstinence from tobacco, but not THC	2 (2.0)
Require abstinence from BOTH tobacco and THC	42 (42.4)
Do not require abstinence from either	38 (38.4)
Have a don't ask / don't tell policy	6 (6.1)

Questions regarding anticoagulation centered around:

**What laboratory test does your program use to monitor the intensity of intravenous heparin in patients with LVAD?**

- a. aPTT (activated partial thromboplastin time)
- b. Anti-factor Xa
- c. ACT (activated clotting time)
- d. Do not use heparin

**In the asymptomatic, outpatient setting, your program's approach for patients with a sub-therapeutic INR (international normalization ratio) is:**

- a. Admit for heparin gtt bridge if INR < 2.0
- b. Admit for heparin if INR < 1.8
- c. Admit for heparin gtt bridge if INR < 1.5
- d. Use enoxaparin subcutaneous as outpatient bridge
- e. Observation as outpatient with increased Coumadin dosing



Most respondents reported using intravenous unfractionated heparin therapy post-LVAD implantation (96.0 %), with 67.3 % reported utilizing activated partial thromboplastin time (aPTT) to monitor the effectiveness of their anticoagulation strategy (n=101). Once patients were successfully transitioned to outpatient anticoagulation, there were clear differences in the management of patients with a sub-therapeutic INR (international normalization ratio). In an asymptomatic, outpatient setting, 52.2 % of respondents stated they use enoxaparin as a bridging strategy for patients, while 27.2 % would admit for intravenous heparin bridging for varying degrees of sub-therapeutic INR. The remainder of respondents (20.7 %) increased the intensity of outpatient Coumadin therapy without bridging therapy (**Table 4**) (n=92).

**Table 4: Anticoagulation monitoring and outpatient strategy**

Anticoagulation Related Question	Respondents Count (%)
<b>1. What laboratory test does your program use to monitor intensity of intravenous heparin therapy in patients with LVAD?</b>	
aPTT (activated partial thromboplastin time)	68 (67.3)
Anti-Factor Xa	24 (23.8)
ACT (activated clotting time)	5 (5.0)
Do not use heparin	4 (4.0)
<b>2. In the asymptomatic, outpatient setting, your program's approach for patients with a sub-therapeutic INR (International normalization ratio) is?</b>	
Admit for heparin gtt bridge if INR < 2.0	3 (3.3)
Admit for heparin if INR < 1.8	8 (8.7)
Admit for heparin gtt bridge if INR < 1.5	14 (15.2)
Use enoxaparin subcutaneous as outpatient bridge	48 (52.2)
Observation as outpatient with increased Coumadin	19 (20.7)

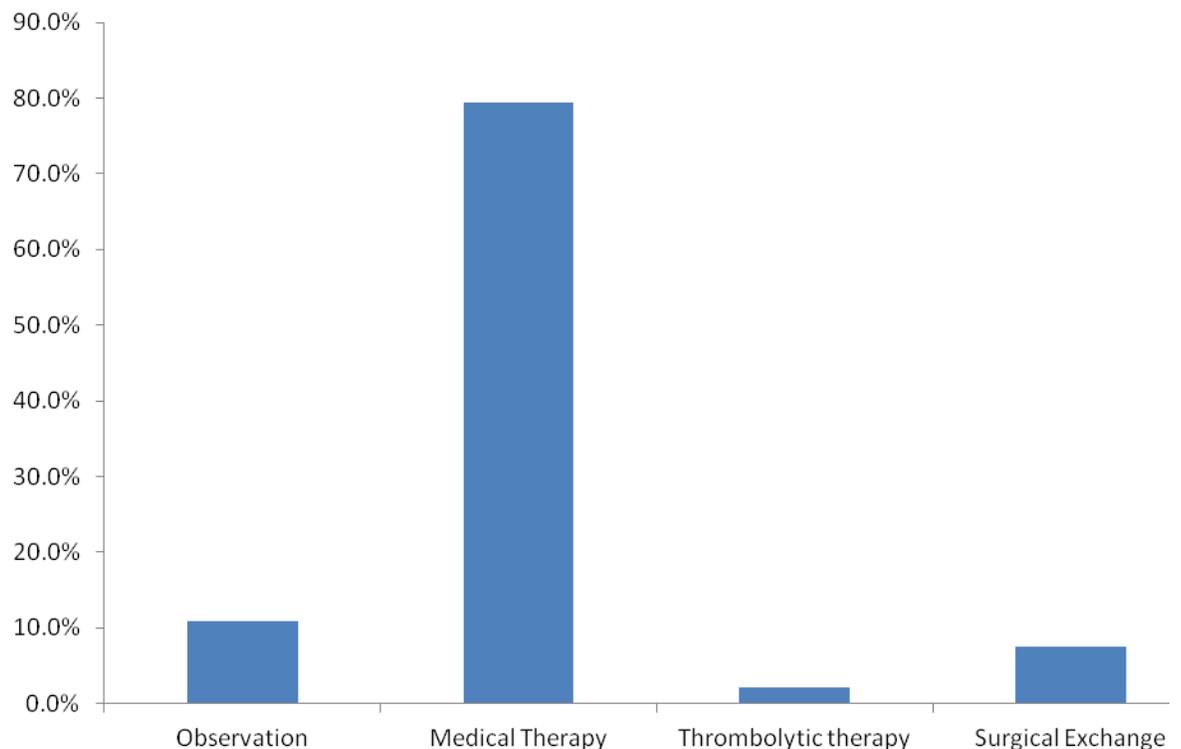


Question regarding pump thrombosis management included:

**In the setting of hemolysis (lactate dehydrogenase (LDH) > 3 x upper limit of normal) with the HeartMate II LVAD, what is your first line management?**

- a. Observation
- b. Trial of medical therapy (intensification of anticoagulant/antithrombotic therapy – excluding lytics)
- a. Thrombolytic therapy
- b. Direct surgical LVAD exchange

In patients with evidence of hemolysis, defined as a lactate dehydrogenase (LDH) greater than three times the upper limit of normal) with a HeartMate II (St. Jude Medical, Pleasanton, CA) LVAD, first line management was intensification of anticoagulation and/or anti-thrombotic (excluding lytic) therapy in 79.4 % of respondents, with other choices being observation (10.9 %), thrombolytic therapy (2.2 %) and direct surgical LVAD exchange (7.6 %) (**Figure 2**) (n=92).



**Figure 2: First line management in the setting of hemolysis defined as an elevated lactate dehydrogenase level with the HeartMate II.**



The most common first line therapy for setting of hemolysis defined as lactate dehydrogenase (LDH) greater than three times upper limit of normal with the HeartMate II was intensification of anticoagulation and/or anti-thrombotic (defined as medical therapy excluding lytic) therapy in 79.4 % of respondents with other choices being observation (10.9 %), thrombolytic therapy (2.2 %) and direct surgical LVAD exchange (7.6 %) (n=92).

Question regarding the use of defibrillator policy on LVAD patients included:

**Which of the following best describes your center's policy regarding the use of ICDs (implantable cardioverter-defibrillator) in LVAD patients?**

- a. All patients must have an active ICD prior to discharge
- b. All BTT (bridge-to-transplant) patients must be discharged with an active ICD
- c. All DT (destination therapy) patient must be discharged with an active ICD
- d. All patients are discharged with an inactivated ICD (if one was present prior to LVAD implantation)
- e. Patients can choose whether or not to be discharged home with either an active or inactivated ICD

Policies reported for implantable cardioverter-defibrillators (ICDs) in patients after LVAD therapy were also variable. A requirement for all patients to have an active ICD prior to discharge was reported by 31.0 % of respondents, active ICD only in BTT (bridge-to-transplant) patients by 11.3 %, ICD only in DT patients by 9.9 %, and inactivation regardless of intent of therapy by 7.0 %. The majority (40.9%) responded that all patients can choose whether or not to be discharged home with either an active or inactivated ICD (**Table 5**) (n=71). Details of the questions did not allow for capture of data regarding patient history of ventricular arrhythmias.

**Table 5: Center policy regarding the use of implantable cardioverter-defibrillator (ICD) in LVAD patients**

Policy on ICD	Respondents Count (%)
All patients must have an active ICD prior to discharge	22 (31)
All BTT (bridge-to-transplant) patients must be discharged with an active ICD	9 (11.3)
All DT (destination therapy) patients must be discharged with an active ICD	8 (9.9)
All patients must be discharged with an inactive ICD (if one was present prior to LVAD implantation)	5 (7.0)
Patients can choose whether or not to be discharged home with either and active or inactivated ICD	29 (40.9)



## **Discussion**

Although there is a significant amount of literature on the impact of variables such as the INTERMACS profile, patient age and center volume with regards to outcomes, there is a paucity of data on other factors that may influence a successful LVAD implant. The field of surgical therapy for heart failure, in particular mechanical circulatory support, is an ever changing landscape with new devices, new techniques and new management paradigms. As a result, no definitive evidence exists in the selection and management of these patients.

The influence that body mass index (BMI in kg/m<sup>2</sup>) plays on surgical outcomes remains unclear [5,6]. Although there are theoretical considerations for driveline infections, pump migration, pump thrombosis or post-implant right ventricular failure, there is no consistency in our current understanding or the available literature. The results of the survey confirm the lack of consensus that a specific BMI should preclude consideration for LVAD therapy.

Perhaps the most nebulous criteria for patient selection is in the arena of psychosocial risk factors. While professional guidelines suggest that all candidates for MCS be screened for psychosocial function before device placement, there are no standardized or validated methods to assess psychosocial function. There are no universal behavioral? contraindications for LVAD placement, particularly when the intended strategy is DT, and thus there remain large inconsistencies among institutional practices. Typically, these evaluations are “extrapolated” from the heart transplant literature. The viewpoint of how much support is needed to care for these devices is also a critical one. Without data to support adverse events in the absence of a 24-hour caregiver, it would be disappointing for an isolated criterion to prevent the application of this technology in patients who would otherwise benefit from it. It is encouraging that the shift seen in our survey has increasing flexibility with regard to a caregiver plan.

Unlike the clarity of data with the heart transplant literature, studies aiming to stratify risk according to social support in LVAD candidates have been less than impressive. [7]. Standardized instruments used for assessing transplant candidates, like the Psychosocial Assessment of Candidates for Transplantation (PACT) or the Stanford Integrated Psychosocial Assessment for Transplant (SIPAT) have not been studied in VAD patients. In one retrospective study testing the utility of the transplant evaluation rating scale (TERS) in VAD recipients, none of the objective endpoints showed significant difference based on psychosocial risk profile. [8]. While more research is needed, it is encouraging to see the survey respondents seemingly less “prescriptive” with regard to social support for LVAD therapy.

Patients are often denied therapy to transplantation because of either THC or tobacco addiction. There are many centers that extend these criteria for LVAD therapy while others use it as a social stress test to determine transplant eligibility after LVAD implantation. Smoking is an addiction and a proven risk factor for increased mortality and morbidity [9]. Previously described perioperative



complications and decreased survival in heart transplant recipients in addition to the need for patients to show their “participation in the healing process” have denied surgical therapy for patients suffering from advanced heart failure who continue to smoke. Most centers require at least three months of abstinence from smoking to be considered for heart transplantation [10-12]. As seen from our survey, nearly half of the centers require the same for VADs as destination therapy. Given the extent of the surgery and the consequences of the perioperative complications, it is imperative to educate patients on the importance of abstinence.

Pre-implant renal dysfunction (RD) remains a strong predictor of post-LVAD mortality, particularly in those patients who are on dialysis at the time of surgery where the mortality rate exceeds 30% at 3 months post implant [13,14]. It is not surprising that 90% of reporting centers do not offer LVADs to chronic dialysis patients ineligible for heart-kidney transplantation. However it is often patients with the most severe pre-implant RD who have the potential to experience marked improvements in renal function with mechanical support, assuming the RD present is HF-induced [15,16]. Unfortunately, there is currently no definitive testing to either differentiate HF-induced RD from other irreversible etiologies or to predict post-LVAD reversibility of RD. The management of renal failure in this population is further complicated by the lack of consensus on the best mode of renal replacement therapy. The most commonly utilized modality is tunneled catheters; however, there is significant risk of bacteremia and potential subsequent pump infection with continued use [17]. Unfortunately, the continuous-flow environment may impair a less infectious option, specifically the arteriovenous (AV) fistula, from maturing [18]. Still, AV fistulas and grafts have been used successfully in the LVAD population while peritoneal dialysis (PD) is only utilized at a small percentage of LVAD centers [19]. The theoretical advantage for PD is the reduction of systemic bacteremia, less hemodynamic variability, ability for daily ultrafiltration, and importantly, the in-home use.

Although ICDs have proven morbidity and mortality benefit in heart failure patients with reduced ejection fraction, we are lacking universal recommendations for ICD implantation in patients receiving a CF-LVAD or those already implanted with a CF-LVAD who do not have a pre-existing ICD. In the pulsatile flow era, a retrospective analysis has shown improved survival in LVAD patients who have ICDs as well as improved survival to cardiac transplantation [20], however, this has not been demonstrated with contemporary CF-LVADs. A retrospective single center study of 23 consecutive patients implanted with a HeartMate II LVAD demonstrated that sustained ventricular tachycardia or fibrillation occurred in 52% of the patients, with the majority of arrhythmias occurring within the first month of LVAD implantation [21]. A prospective single center study of 94 patients showed that an absence of pre-operative ventricular arrhythmia conferred a low risk of post-operative ventricular arrhythmia [22]. In their analysis, none of the patients discharged from the hospital following CF-LVAD implant without an ICD died during median follow up of 12.7±12.3 months [22].

Financial interests in reducing the burden of rehospitalization in the heart failure population in addition to optimizing care that can be provided in the outpatient



setting has led to differing approaches in LVAD patients with a sub-therapeutic INR. In the absence of published data to guide decision-making, the decision of whether and how to “bridge” patients with sub-therapeutic anticoagulation is center- and even clinician-specific. At the very least, our survey provides confidence that there is no “standard” approach, and that a center- or patient-specific approach is defensible.

Intravenous unfractionated heparin remains the most commonly used parenteral anticoagulant for patients requiring anticoagulation. Activated partial thromboplastin time (aPTT) has been the standard method at most centers, regardless of the indication for anticoagulation although Anti-factor Xa (anti-FXa) has been suggested as an alternative method to ascertain whether a particular dose of heparin is therapeutic [23]. The choice of assay to monitor anticoagulation is often institution-specific and there is insufficient data to declare either the “gold standard.” Recent publications have highlighted a high level of discordance between aPTT and anti-FXa in the CF-VAD population, suggesting careful interpretation of available information [24,25]. Although a prospective randomized trial on this question is unlikely to be performed, perhaps a comparison of the rates of thrombosis and hemorrhage between centers that utilize the two different strategies could help us learn how to optimize anticoagulation in this challenging population. In this era of heightened awareness of pump thrombosis and its negative impact on survival, it would not be surprising to learn that circumstances may dictate the optimal strategy with perhaps differing anticoagulation protocols.

Unfortunately, suspected device thrombosis continues to be a common clinical problem in the CF-LVAD population. The gold standard for known thrombosis would be device removal (either device exchange with replacement or transplantation), but efforts to treat medically have been advocated by some. Methods include GPIIb/IIIa inhibitors and thrombolytics each with a significant risk of severe and/or catastrophic intracranial bleeding [25,26]. On the other hand, patients are often asymptomatic and reluctant to undergo device exchange, particularly if soon after their initial implant. Medical comorbidities may also contribute to high (or prohibitive) risk of device replacement. In this context, it is not surprising that the results of our survey show an overwhelming first line usage of medical therapy.

A promising alternative in reducing morbidity and mortality of pump exchange has been the advent of minimally invasive pump exchange through a subcostal approach [27]. Considering the limited success of medical therapy in achieving lasting resolution of pump thrombosis, more widespread application of minimally invasive pump exchange could improve overall outcome of patients affected by pump thrombosis and make this more mainstream. However, it is noteworthy that the minimally invasive technique cannot be applied to situations where pump thrombosis occurs in association with inflow cannula malposition - which is the most commonly seen scenario in late (>1 year) presentation. Although it might be tempting to persevere with medical therapy in these cases to avoid a high risk exchange operation, it is ironic that these are often the cases which respond the least to non-surgical approaches because of the anatomical substrate responsible for pump thrombosis.



## Conclusions

It is only through honest dialogue regarding our collective experiences in the mechanical support community that we can hope to have more fruitful discussions with our patients and ourselves regarding best care practices. While some complications are indeed rare, difficult clinical scenarios are unfortunately too common. The dissemination of information amongst all centers will help clinicians discuss not only the current trends in practice but will enable the clinician to have a more insightful conversation with alternatives and indications with their patients of a specified therapy. LVAD technology will continue to change and improve with the next set of pumps on the horizon. Undoubtedly, the current state of LVADs is for better access for patients to these devices with less adverse events. These will be coupled with the search for better hemocompatibility, smaller devices with less surgical morbidity, longer battery life, more user friendly controllers and transcutaneous power. Progress in these fields cannot be made independently without pausing to understand the current state of technology, practice patterns and patient determinants of success with LVAD therapy. It is no longer enough to merely have better machines for better results. This survey underscores the lack of consensus regarding best practice principles. A great deal of time, energy and resources are invested in looking in the future to the next, new device without a clear understanding of optimal care practices after implant. The LVAD guidelines are dominated by “level of evidence C” recommendations, with most extrapolated from single institutional studies [28]. There needs to be an increased focus on care management for LVAD patients with collaborative, multi-institutional studies. We must hold each other accountable for getting away from institutional dogma and have more cross talk to get better results for our complex patients suffering from advanced heart failure.



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