Clinical Outcomes Following Continuous-Flow Left Ventricular Assist Device: A Systematic Review

McIlvennan et al: Continuous-Flow LVAD Outcomes

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Abstract

**Background**—Conveying the complex trade-offs of continuous-flow left ventricular assist devices (CF LVAD) is challenging, and made more difficult by absence of an evidence summary for the full range of possible outcomes. We aimed to summarize the current evidence on outcomes of CF LVAD.

**Methods and Results**—PubMed and Cochrane Library were searched from January 2007–December 2013, supplemented with manual review. Three reviewers independently assessed each study for saliency regarding patient-centered outcomes. Data were summarized in tabular form. Overall study characteristics encouraged inclusion of all indications (destination therapy and bridge to transplant) and prevented meta-analysis. The electronic search identified 465 abstracts, of which 50 met inclusion criteria; manual review added 2 articles in press. The articles included 10 industry-funded trials and registries, 10 multi-center reports, and the remainder single-center observational experiences. Estimated actuarial survival after CF LVAD ranged from 56-87% at 1-year, 43-84% at 2-years, and 47% at 4-years. Improvements in functional class and quality of life were reported, but missing data complicated interpretation. Adverse events were experienced by the majority of patients, but estimates for bleeding, stroke, infection, right heart failure, arrhythmias, and rehospitalizations varied greatly.

**Conclusions**—The totality of data for CF LVADs show consistent improvements in survival and quality of life counterbalanced by a range of common complications. While this summary should provide a practical resource for health care provider-led discussions with patients, it highlights the critical need for high-quality patient-centered data collected with standard definitions.

**Key Words:** heart-assist device, heart failure, left ventricular assist device, health outcomes
Left ventricular assist devices (LVADs) are becoming an increasingly viable treatment option for patients with end-stage heart failure. Newer generation continuous-flow (CF) LVADs have taken the place of the first generation pulsatile-flow (PF) LVADs due to their smaller size and greater durability. Ideal informed consent and shared decision making for LVADs should be grounded in a thorough review of expected risks and benefits.\(^1\) This process should compare and contrast LVAD therapy to alternative approaches, and include not only estimates of survival but also major adverse events, health-related quality of life (HRQoL), symptom burden, functional limitations, and obligations for caregivers.\(^2\)

Although a variety of trial and registry data are available to complement individual clinician experience and patient testimonials, there is currently no comprehensive systematic review of CF LVADs that attempts to summarize and organize available information into a practical format. Existing guidelines and standard consent forms do not provide such summary data with any degree of detail.\(^3\) This absence of accurate and easily accessible information from which to anchor risk-benefit communication leads to a potentially non-standardized and variable informed consent and decision-making process around LVADs that may be incomplete, confusing, or biased.\(^4\)^\(^5\)

Therefore, we aimed to summarize the current evidence on risks and benefits of CF LVADs. Our objectives were to: 1) capture contemporary clinical data regarding outcomes for patients offered CF LVADs; 2) describe the nature and quality of this evidence; 3) organize the data in a way that conveys the full range of expected outcomes for CF LVADs, with direct comparisons to outcomes without implantation; and 4) identify critical gaps in the scientific data that should be a priority of future research. Our primary goal was to provide a practical
document that could guide a more standardized informed consent process and future development of decision aids for CF LVADs.

Methods

Search Strategy

Our methods directly adhered to the guidelines set forth in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. We searched PubMed (MEDLINE) and the Cochrane Library full text databases for English-language studies concerning human subjects published between January 1, 2007 and December 13, 2013 related to CF LVAD outcomes. The year 2007 was chosen, as this was the time when data on contemporary CF LVADs started to become available. The search algorithm, developed and then replicated for accuracy by four members of the study team (CKM, KHM, JST, LAA), included a combination of Medical Subject Headings and free-text terms related to LVAD, CF, and associated outcomes such as survival, HRQoL, bleeding, stroke, or infection (see Supplemental Material: Figure 1). The original intent was to summarize data for LVAD used as destination therapy (DT); however, due to the complexities around indication reporting and because many aspects of LVAD therapy are applicable across indications, studies including both bridge to transplant (BTT) and DT were included. Where possible, care was taken to clearly identify and separate BTT-only and DT-only data within the review. We included all forms of research, such as meta-analyses, trials, retrospective and prospective studies and expert opinion papers without restriction by journal. The reference lists of selected studies were manually reviewed to identify any relevant studies that were potentially missed in the database search.
Study Selection

Eligible articles were presented in English and provided primary data about outcomes of CF LVADs. Two study team members independently reviewed all titles and abstracts for initial selection for inclusion (AVA, LAA). When the title and abstract provided insufficient information to determine study relevance, a full text copy of the article was retrieved and reviewed. For final selection, full text copies of all initially selected articles were examined for study eligibility.

The following exclusion criteria were applied: studies that included less than 50 patients with CF devices, reviews or editorials on CF LVADs, studies that were non-human or focused on imagine with CF LVADs, studies that focused on surgical techniques, studies restricted to pediatric populations, studies that reported outcomes on temporary devices or partial support, studies with a transplant focus, studies that did not separate data based on CF versus PF device, studies reporting on other devices such as intra-aortic balloon pumps, studies reporting data on risk modeling and CF LVADs, studies that were updated by newer publications, and sub-analyses of previously reported results. Additionally, for serial publications updating longitudinal registry findings, we included only the most recent publication that addressed a specific outcome. We also excluded papers focused on risk modeling for which the overall outcome frequency for the same population was published elsewhere. Exceptions were made for evidence sources that were frequently referenced by more contemporary publications. See Figure 1 for a summary of evidence search and selection. For each article excluded, a single most obvious exclusion criterion was chosen, even though many articles met multiple exclusion criteria.
Data Extraction and Quality Assessment

From each study, two independent reviewers (KHM, JST) extracted total patients, total CF patients, type of device (CF, PF), specific model of device (e.g. Thoratec HeartMate II (HMII), HeartWare HVAD), duration of follow-up or defined time at risk, population characteristics (BTT, DT), and outcome measures (survival, functional status, HRQoL, bleeding, neurological events, infection, device malfunction, right heart failure, arrhythmia, aortic insufficiency, renal failure, and rehospitalization). These outcomes were chosen by a group of clinicians, patients, and families as most important to CF LVAD therapy. Definitions for each outcome are included in Supplemental Material: Figure 2. A third reviewer (CKM) independently reviewed and confirmed all data abstracted. Disagreements were resolved through discussion by the entire study team. We aimed to include all relevant studies that reported outcomes for CF devices that met our stated inclusion and exclusion criteria. Assessment of quality was based on study design. The studies were categorized in the order of rigor: 1) industry-funded trials and related prospective registries, which included all controlled trials related to CF devices; 2) multicenter registries; and 3) single center reports and case series.

Data Synthesis

Data was summarized in tabular form. The resulting tables were organized according to the prospectively identified key patient-centered outcome domains of interest: survival, HRQoL and functional status, and adverse events. Where necessary, we manually calculated cumulative numbers when data was only reported separately for subgroups. When relevant data was only presented in graphic form, quantitative estimates were extracted and reported. Narrative syntheses of data were added to supplement the tables, incorporate nuanced information about
data generation and quality, and provide a holistic summary. In order to create a clinically useful synopsis that may help facilitate communication with patients and families, we performed a crude analytic summary of the existing data. After reviewing the literature for all reported outcomes, we solicited feedback from physicians, physician assistants, nurse practitioners, nurses, a social worker, patients, and their families about which outcomes should be included in a summary figure. We consolidated hospitalization, bleeding, stroke, and infections, where appropriate, for ease of understanding. Event rates at 1-year were chosen as many studies did not report events past 1-year. Final outcomes are reported in Figure 2. We first collated the data from all studies for each outcome and subsequently removed redundant data. We excluded studies that did not report percentage data. Second, we applied the weighted average method based on total study sample and percentage reported. The weighted average method provides a summary treatment effect that more heavily emphasizes data reported from a registry with a large number of patients than a small single center study. It assumes fixed effects of CF LVAD across studies. The resultant weighted average included all trial, registry, and single-center studies and is reported as an estimated mean for all data. Finally, we applied the weighted average method to calculate the time period reported for each outcome. We were unable to calculate the summary effect sizes due to a variety of barriers, including the clinically diverse nature of the studies and lack of reporting standards.

Results

The electronic search identified 465 titles and abstracts. An additional 2 studies related to pump thrombosis that were currently in press7-8 and not identified in the search were added. After
inclusion and exclusion criteria were applied, a total of 52 full-text articles were included and reviewed (see Supplemental Material: Table 1).

The majority of studies were non-randomized, observational, small power, or single center. The studies included 10 industry-funded trials, 10 multi-center reports (many were different analyses of the same ongoing registry), and the remainder single-center observational experiences. A number of the multi-center registry publications that highlighted particular outcomes of interest were sub-analyses or post-hoc analyses of existing databases. Similarly, ongoing registries tended to be used for serial publications regarding individual outcomes.

Based on the data extracted, we identified 10 relevant patient-centered outcomes for which data was reported: survival, HRQoL, functional status, bleeding, neurological events, infection, device malfunction, right heart failure, arrhythmias, and rehospitalizations. All single-center studies and those with less than 100 CF LVAD patients are summarized in Supplemental Material: Tables 2-4. A summary of simplified one-year outcomes using weighted averages, including all data is provided in Figure 2. A pictograph was developed according to accepted patient communication methods and feedback from clinicians, nurses and patients was provided on content and readability.

**Survival** (6 Industry Funded Trials and Related Registries; 6 Multicenter Registries; 9 Single Center Reports or Case Series. See Supplemental Material for all single-center studies and those with less than 100 CF LVAD patients.)

Survival is the outcome of dominant importance to the majority of patients. Extending life is a primary goal of LVADs, and therefore communicating statistics around mortality is critical. Although survival is an objective measure, characterizing long-term survival after LVAD
implantation is complicated by a number of factors, including finite study time periods, patient loss to follow-up, and censoring of patients at the time of transplantation. Even in the DT population, a significant minority of patients will later become transplant eligible (approximately 10% in DT trial populations). Therefore, estimated actuarial survival is most often reported.

Most studies reported survival rates at times post-implantation ranging from 1 to 24 months, with less data beyond 2 years (Table 1). The pivotal HMII DT Trial showed estimated actuarial survival at 2 years of 58%. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Fifth Annual Report showed 1, 12, 24, 36, and 48-month survival at 95%, 80%, 70%, 59% and 47%, respectively. These values represent some of the most recent data as well as some of the highest rates of survival for CF LVAD patients. The ADVANCE: HVAD BTT Trial Continued Access Protocol (CAP) also illustrated improved survival 6 months and 1 year after device implantation compared with trials performed in earlier years. However, to what extent progressive improvements in survival represent true improvements in the use of the device versus patient selection into less sick populations is unclear.

**HRQoL and Functional Status** (6 Industry Funded Trials and Related Registries\(^{10-14,21}\), 1 Multicenter Registry\(^{19}\))

One of the main goals of LVAD implantation is to improve the HRQoL and functional capacity for patients with symptomatic heart failure. Improvements in New York Heart Association functional class are common after LVAD implantation. Approximately 80% of patients improved from New York Heart Association class IIIB or IV at baseline to New York Heart Association class I or II symptoms after LVAD in the HMII BTT and DT trials.\(^{10,12}\) In addition,
instruments commonly used to assess HRQoL in heart failure patients that are often prospectively collected in LVAD studies include heart failure disease-specific measures such as the Minnesota Living with Heart Failure Questionnaire\textsuperscript{22}, the Kansas City Cardiomyopathy Questionnaire\textsuperscript{23}, as well as general measures such as the European Quality of Life-5 Dimensions.\textsuperscript{24} In addition to subscales of HRQoL questionnaires, functional status is most commonly assessed through 6-minute walk distance. Among patients who survive with LVADs, HRQoL measures improve markedly from baseline (Table 2). The collective HMII studies demonstrated significant improvements in Minnesota Living with Heart Failure Questionnaire and Kansas City Cardiomyopathy Questionnaire scores, as well as 6-minute walk distance from before surgery to all time points assessed after device implantation.\textsuperscript{10-12,21} Additionally, the most recent INTERMACS Annual Report demonstrated overall improvements in the European Quality of Life-5 Dimensions visual analog scale, and fewer patients identified themselves as having “extreme problems” with self-care and usual activities.\textsuperscript{19}

It should be noted that HRQoL and functional status data has typically censored patients at the time of death, which can progressively enrich for a “healthier” population. Additionally, missing data for HRQoL and functional status measures are more common than for an outcome like survival, with 13-38% of patients unable to complete health status or functional assessments at a given time point.\textsuperscript{10,12} However this failure to complete health status assessments can itself be informative, with worse outcomes commonly seen in these patients.\textsuperscript{10,12} Finally, the HRQoL measures developed in patients with chronic heart failure may not perform as intended when applied to the LVAD population, given that many heart failure-related symptoms are traded for other unique symptoms and burdens.\textsuperscript{25}
Common Adverse Events

Although LVADs offer patients the potential for improved survival, HRQoL, and functional status, there are also several risks associated with LVAD therapy. Some of the most commonly studied and reported major adverse events following LVAD implantation are bleeding, neurological events, and infection. Definitions for all adverse events are included in Supplemental Material: Figure 2.

**Bleeding.** (7 Industry Funded Trials and Related Registries\(^{10-14}\), 3 Multicenter Registries\(^{16,18-19}\); 14 Single Center Reports or Case Series. See Supplemental Material for all single-center studies and those with less than 100 CF LVAD patients.) Bleeding is the most commonly recorded adverse event of CF LVADS\(^{11-12,19}\), with the majority of patients in all published cohorts experiencing some type of bleeding. When possible, bleeding rates are reported by \(<30 \text{ days (early)}\) and \(>30 \text{ days (late)}\) in order to help differentiate post-operative bleeding from non-surgical bleeding. A recent study of 139 HMII patients showed the greatest risk of bleeding was within the first 2 weeks post-operatively and early bleeding was associated with decreased survival.\(^{26}\) Later gastrointestinal bleeding is reported with rates as high as 13\% in the ADVANCE: HVAD BTT Trial CAP.\(^{14}\) A single-center study of 86 HMII patients reported gastrointestinal bleeding as a frequent source of morbidity for patients but not a factor that significantly impacts survival.\(^{27}\)

**Neurological Events.** (7 Industry Funded Trials and Related Registries\(^{10-14}\), 4 Multicenter Registries\(^{15-16,18,19}\); 9 Single Center Reports or Case Series. See Supplemental Material for all single-center studies and those with less than 100 CF LVAD patients.) Neurological events, including ischemic stroke, hemorrhagic stroke, and transient ischemic attack, are relatively common and often severe complications following LVAD placement. In the INTERMACS
Annual Report, there was a 3% risk of stroke at 1 month, 5% at 3 months, 7% at 6 months, 11% at 12 months, 17% at 24 months, and 19% at 36 months post-implant.\textsuperscript{19} Similarly, the HMII DT Trial showed rates of ischemic and hemorrhagic stroke as high as 8% and 11%, respectively, in the first 2 years after LVAD placement, with hemorrhagic stroke being the leading cause of death among patients with a CF LVAD.\textsuperscript{12} The reported rates of stroke from other reports is quite variable and likely reflects differences in study follow-up time and the patient population studied; however, the overall annual risk of stroke in CF LVAD patients appears to be substantial.

\textit{Infection. (7 Industry Funded Trials and Related Registries}^{10-14}; 4 Multicenter Registries\textsuperscript{16,18-19,28}; 9 Single Center Reports or Case Series. See Supplemental Material for all single-center studies and those with less than 100 CF LVAD patients.) Patients are at increased risk of bacterial infections following LVAD implantation, occurring at the driveline, pump pocket, or systemically. Driveline infections in the International HVAD Trial are reported at 18% at 1-year\textsuperscript{29}, while the HMII BTT trial and trial registry report rates as high as 14% at 6 months.\textsuperscript{10-11} Developing any type of infection is associated with decreased survival and quality of life;\textsuperscript{28} in one cohort, 2-year cumulative survival rate was 67% for patients with infections and 81% in those without.\textsuperscript{30}

A summary of these outcomes, including all trial and registry data with greater than 100 CF LVAD patients, is provided in Table 3.
Other Adverse Events

Although bleeding, neurological events, and infection are dominant in adverse events reporting, there are additional complications with CF LVAD therapy that can be equally devastating or have an impact on HRQoL (Table 4).

Device Malfunction. (7 Industry Funded Trials and Related Registries \textsuperscript{10-14}; 7 Multicenter Registries \textsuperscript{7-8,12,16,18,31-32}; 4 Single Center Reports or Case Series. See Supplemental Material for all single-center studies and those with less than 100 CF LVAD patients.) Device malfunction is a serious adverse event of LVADs, as treatment usually requires reoperation and its attendant risks. There are several causes of device malfunction, including thrombus formation with hemolysis, mechanical failure of the impeller, and driveline lead fractures with electrical failure.

In earlier reports, the highest rate of thrombosis requiring pump exchange was in the International HVAD Trial at 8\% at 2 years.\textsuperscript{29} However, a recent study from three high volume centers, including 837 HMII patients, shows an increase in the rate of confirmed pump thrombosis at 3 months post-implant from 2.2\% before March 2011 to 8.4\% by January 2013.\textsuperscript{32} Analysis of the multicenter INTERMACS registry also confirmed a temporal increase in the rates of HMII thrombosis.\textsuperscript{7} Temporal changes in thrombosis rates were not seen in a recent analysis of the HeartWare HVAD.\textsuperscript{8} These recent studies illustrate the dynamic potential for rates of adverse events over time, possibly reflecting changes in device technology, patient selection, surgical technique, and post-implantation management.

Right Heart Failure. (8 Industry Funded Trials and Related Registries \textsuperscript{10-14,33}; 3 Multicenter Registries \textsuperscript{16,18-19}; 7 Single Center Reports or Case Series. See Supplemental Material for all single-center studies and those with less than 100 CF LVAD patients.) Right heart failure following LVAD implantation contributes to increased post-operative morbidity and mortality.
Outcomes of LVAD patients are dependent on right heart function due to the necessity of adequate flow through the pulmonary circuit to the left heart. In the HMII DT Trial, 20% of patients received extended inotropic therapy for persistent right heart failure and 4% required placement of a right ventricular assist device. In the ADVANCE: HVAD BTT Trial CAP, 25% of patients became dependent on inotropic therapy and 3% required a right ventricular assist device. The HMII BTT Trial-Registry and an analysis of 484 patients enrolled in the HMII BTT Trial reported right heart failure post-LVAD implantation is associated with a marked reduction in rates of survival and longer hospital length of stay.

Cardiac Arrhythmias. (6 Industry Funded Trials and Related Registries; 3 Multicenter Registries; 5 Single Center Reports or Case Series. See Supplemental Material for all single-center studies and those with less than 100 CF LVAD patients.) Cardiac arrhythmias, both ventricular and supraventricular, can develop after LVAD implantation. A study of 184 HMII devices showed an incidence of ventricular arrhythmias up to 32% post-LVAD. Studies have reported conflicting associations of ventricular arrhythmias with survival. A study of 61 patients reported patients with post-LVAD ventricular arrhythmias had a significantly increased risk of mortality. In contrast, another cohort of 61 patients showed post-LVAD ventricular arrhythmias had no association with survival but did have greater morbidity, as patients with post-LVAD ventricular arrhythmias had greater rehospitalization rates. In addition, patients with post-LVAD ventricular arrhythmias had higher rates of appropriate (31%) and inappropriate (15%) defibrillator shocks.

Rehospitalizations. (4 Industry Funded Trials and Related Registries; 1 Multicenter Registries; 7 Single Center Reports or Case Series. See Supplemental Material for all single-center studies and those with less than 100 CF LVAD patients.) Recurrent hospital admissions
are a common occurrence in LVAD patients. One trial reported readmission rates as high as 94%\(^1\), and another reports up to 1.2 admissions per patient year.\(^2\) One study of 71 CF LVAD patients found that patients are most often readmitted within 6 months of discharge, with gastrointestinal bleeding as the most common cause.\(^3\)

Additional Adverse Events. Renal function, neurocognitive function, and aortic insufficiency are additional patient-centered outcomes identified in our electronic search. There are limited studies that report this data; therefore, the outcomes were not included in the tables. Remaining patient-centered outcomes included the following: 1) one study of 107 HMII patients found that 15\% required some form of renal replacement therapy post-LVAD implantation;\(^4\) 2) one study of 96 HMII patients showed no change or improvement in neurocognitive testing post-LVAD implantation;\(^5\) and 3) one study of 58 HMII patients showed that aortic insufficiency of the native valve progresses with the duration of LVAD support.\(^6\)

A summary of these outcomes, including all trial and registry data with greater than 100 CF LVAD patients, is provided in Table 4.

Discussion

Permanent mechanical circulatory support in the form of a CF LVAD offers the potential to fundamentally change the clinical course of severe heart failure. Existing evidence shows that, for populations of carefully selected patients, LVADs improve survival, HRQoL, and functional status. Because outcomes in these domains are so dismal without an LVAD, the absolute benefit is marked, with number needed to treat that dwarfs most existing medical therapies. However, despite these dramatic improvements in survival and heart failure symptoms, LVAD therapy remains associated with a significant residual risk of mortality after implantation and the
potential for major adverse events in a significant percentage of patients. Thus, for eligible patients, whether to pursue these therapies should involve a careful assessment of the totality of expected risks and benefits over time and how these may relate to a patient’s values, goals, and preferences.

Given the complex tradeoffs of LVAD therapy, necessary components for shared decision making around CF LVAD must include optimal patient selection, extensive informed consent, and adequate time to review expected risks, benefits, and burdens. To ensure this, LVAD programs are required by the Joint Commission to have a process around education, decision making, and informed consent. While the ethical mandate surrounding informed consent is clear, achieving true informed consent in this setting is challenging. Additionally, providing accurate information to patients in an understandable format to facilitate shared-decision making is complicated.

There have been other reviews regarding LVAD outcomes, however, there has been no major attempt at systematically reviewing this data according to accepted scientific standards in a patient-focused manner. Several studies have found that graphical presentation of risks and benefits enhances understanding of statistics for patients and families of varying numeracy and literacy skills. The pictograph developed from this systematic review (Figure 2) provides patients, their families, and clinicians an estimate of the full range of CF LVAD outcomes based on weighted averages of all trial, registry, and single-center data published to date. Research has shown that patients differ in their decision-making processes, with some patients viewing survival and quality of life as paramount while others weigh risks and burdens more heavily. In response to this, the pictograph provides both benefits and risks; therefore, patients can weigh those outcomes they feel are most important to them. This pictograph could
be easily incorporated into existing educational materials and informed consent documents. While the pictograph does not provide tailored risk estimates and does not show measures of uncertainty for individual patients, we feel it is a significant improvement over existing educational materials.43

The importance of considering tradeoffs for LVAD therapy is particularly salient to the subgroup of patients with a DT indication, who should expect to live the remainder of their life dependent on an LVAD and for whom the reasons making them transplant ineligible will usually persist (advanced age, comorbidity, and frailty). As such, the initial goal of this systematic review was to summarize the risks and benefits of DT LVAD therapy. However, the overall paucity of studies reporting outcomes confined to patients implanted with a DT indication—and the intermixing of DT and BTT patients in some reporting—led to the inclusion of data from BTT populations as well. This allowed for a wider range of evidence; however, the data for BTT patients is not ideal data for informed decision making around DT LVAD. The two indications yield different populations and different outcomes for a variety of reasons, including the temporary nature of BTT and the younger age and lower comorbidity of the BTT-eligible population. This limitation is not peculiar to the systematic review, but rather to the state of LVAD research and reporting. Where reported, we have recognized the DT versus BTT indication to help refine interpretation.

As only one device is currently approved in the United States for the DT indication, and only one large high-quality trial (HMII DT Trial) was conducted to describe outcomes in this setting, clinicians and patient educational materials for DT often default to the event rates reported from this study.12 This approach is reasonable given possible threats to scientific validity from lower quality observational data. However, the HMII DT Trial has a number of
limitations that encourage supplementation from other sources. Although a randomized controlled trial, the study compared CF DT LVAD to the older PF LVAD, not to a control group of optimal medical therapy patients (OMT). Additionally, this comparison was un-blinded. The trial included only 133 patients in the HMII CF device arm, such that estimates of rare events are potentially unstable. Further, the randomized controlled trial setting, with highly selected patients treated at a limited number of participating centers, may not be particularly generalizable to the usual care setting. Recent reports of higher than expected pump thrombosis rates illustrate these potential concerns.\textsuperscript{7,32} Therefore, systematically reviewing all of the published literature for individual outcomes and then summarizing those estimates in tabular form hopefully offers a more complete picture of the expected range of risks and benefits that clinicians can convey to patients considering LVAD.

In addition to summarizing existing data, the conduct of this systemic review also clarifies deficiencies in the sum of existing data. Data regarding survival for DT eligible patients who decline LVAD and continue with OMT are relatively sparse and dated. All studies showed a higher survival rate at every increment of time for patients who received an LVAD as compared to patients who were treated with OMT.\textsuperscript{44-46} Further, the COSI trial showed a dismal 6\% survival at one year for patients with end-stage heart failure managed with continuous inotropic support.\textsuperscript{46} With ranges in 2-year survival of 60-70\% for CF DT LVAD\textsuperscript{12} and 6-8\% for OMT\textsuperscript{44}, the number needed to treat to save one life over a 2-year span is less than 2 patients. Although survival is significantly improved with LVAD implantation, the absolute rates of death remain relatively high with less than half of patients still alive 4 years after implantation.\textsuperscript{19} With improvements in technology, surgical technique, peri-operative care, and patient selection,\textsuperscript{47} summary data suggest that for the near term, CF DT LVAD patients should expect actuarial survival rates in the
2-years after implantation on the order of 65-75%. BTT survival rates are better, with 2-year survival reported as high as 79-84%. In a perfect world, studies would randomly compare DT LVADs to OMT. While randomizing patients to this comparison is essentially unfeasible in most contexts, obtaining additional data on outcomes among OMT populations is possible. The recently launched Medical Arm of INTERMACS (MEDAMACS) and Randomized Evaluation of VAD InterVEntion before Inotropic Therapy (REVIVE-IT) studies should provide additional data regarding the outcomes of OMT in a group of non-inotrope dependent advanced heart failure patients. Additionally, due to variation in outcomes by indication, future studies should aim to separate data collection and outcomes reporting based on BTT versus DT implantation status. Patients who decline DT LVAD may also provide important comparator information.

Furthermore, lack of rigorous standard methodology decreases the utility of study information. The non-uniform reporting of event rates limits the ability to pool data across studies. While events per patient time may be statistically sound, it complicates interpretation for patients with lower numeracy. Similarly, there is no standardized or patient-centered method for accounting for loss to follow up (e.g. death during longitudinal measures of quality of life) or alternative end points (e.g. transplantation when calculating survival in DT). Additionally, with standardized reporting, summarizing data for longitudinal outcomes reporting would be less problematic. Finally, due to the rapid evolution of mechanical circulatory support, flexible and efficient systems must be developed to help patients and their health care providers stay updated on contemporary rates of outcomes. Ultimately, not only is there a desperate need for additional high-quality data, but this data must be collected using standard event definitions, such as the set used by the INTERMACS registry, and reported in units that are mostly clinically meaningful.
Limitations

In addition to the above issues with mixing of BTT and DT, data quality, and non-standardized reporting, there are several additional limitations that deserve recognition. First, the vast amount of data was difficult to present in a complete and simultaneously understandable format, such that some detail was sacrificed for ease of interpretation, both in terms of excluding smaller studies and in simplifying the studies that were included. Second, we included all data on outcomes of CF LVADs without a rigorous exclusion process based on the quality of the study; therefore, interpretation of the data should be guided by the categorized rigor of the study. In depth review of individual studies may ultimately be required by individual health care providers to better answer nuanced clinical questions.

Conclusion

The totality of data for CF LVADs show consistent improvements in survival and quality of life counterbalanced by a range of common complications. While this summary of outcomes data for CF LVAD should help frame consent, education, and decision making around durable mechanical circulatory support, future action is required to remedy the lack of high quality data for CF LVAD, particularly in the DT setting. Additional randomized controlled trials with larger patient populations are needed to further examine survival, HRQoL and frequency of complications. Supplementary trials that report outcomes for a timeline that mirrors the lifespan of DT patients are also necessary. Further, registries for patients on OMT who decline LVAD therapy are critical. An exponential expansion in LVAD use without such information is likely to diminish the overall value that patients and society can derive from this remarkable therapy.
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Disclosures

None.

References


42. McIlvennan CK, Allen LA, Newels CT, Cleveland JC, Brieke A, Matlock DD. Decision making for destination therapy left ventricular assist devices: “There was no choice” versus “I thought about it an awful lot.”. *Circ Cardiovasc Outcomes*. 2014;7:374-80.


### Table 1. Estimated Actuarial Survival of CF LVAD - All Trial and Registry Data with Greater Than 100 CF Patients

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<thead>
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<th>Year</th>
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<td>2007</td>
<td>133</td>
<td>133</td>
<td>0</td>
<td>89%</td>
<td>75%</td>
<td>68%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HMII BTT Trial Registry</td>
<td>Pagani</td>
<td>2009</td>
<td>281</td>
<td>281</td>
<td>0</td>
<td>92%</td>
<td>82%</td>
<td>73%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HMII DT Trial</td>
<td>Slaughter</td>
<td>2009</td>
<td>133</td>
<td>0</td>
<td>133</td>
<td>-</td>
<td>-</td>
<td>68%</td>
<td>58%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ADVANCE: HVAD BTT Trial</td>
<td>Aaronson</td>
<td>2012</td>
<td>140</td>
<td>140</td>
<td>0</td>
<td>99%</td>
<td>94%</td>
<td>86%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ADVANCE: HVAD BTT Trial CAP</td>
<td>Slaughter</td>
<td>2013</td>
<td>332</td>
<td>332</td>
<td>0</td>
<td>97%</td>
<td>91%</td>
<td>-</td>
<td>84%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Multicenter Registries</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INCOR Analysis</td>
<td>Schmid</td>
<td>2008</td>
<td>216</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>56%</td>
<td>43%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>64 European Institutions</td>
<td>Lahpor</td>
<td>2010</td>
<td>411</td>
<td>300</td>
<td>86</td>
<td>-</td>
<td>74%</td>
<td>72%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>U of Minnesota, Pittsburgh, &amp;</td>
<td>Boyle</td>
<td>2011</td>
<td>101</td>
<td>86</td>
<td>15</td>
<td>77%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Columbia</td>
<td>John</td>
<td>2011</td>
<td>1496</td>
<td>1496</td>
<td>0</td>
<td>-</td>
<td>89%</td>
<td>85%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>John INTERMACS</td>
<td>Kirklin</td>
<td>2013</td>
<td>5436</td>
<td>3742</td>
<td>1694</td>
<td>95%</td>
<td>-</td>
<td>80%</td>
<td>70%</td>
<td>59%</td>
<td>47%</td>
</tr>
<tr>
<td>INTERMACS 2013</td>
<td>Kirklin</td>
<td>2014</td>
<td>6910</td>
<td>-</td>
<td>-</td>
<td>95%</td>
<td>87%</td>
<td>80%</td>
<td>69%</td>
<td>58%</td>
<td>46%</td>
</tr>
<tr>
<td>INTERMACS Thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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* See Supplemental Material for all single-center studies or those with less than 100 continuous flow patients.

** Study includes alternative indications for implant (e.g. bridge to decision, bridge to candidacy).

BTT=bridge to transplant; CAP=continued access protocol; CF=continuous-flow; DT=destination therapy; HMII=HeartMate II; HVAD=HeartWare ventricular assist device; INCOR=INCOR left ventricular assist device; INTERMACS=Interagency Registry for Mechanically Assisted Circulatory Support; mo=month; LVAD=left ventricular assist device.
### Table 2. HRQoL and Functional Status of CF Devices

**KCCQ - Scores range from 0 to 100. A higher score illustrates a better health status.**

<table>
<thead>
<tr>
<th>Study</th>
<th>First Author</th>
<th>Year</th>
<th># CF</th>
<th>Baseline*</th>
<th># CF</th>
<th>3 Mo*</th>
<th># CF</th>
<th>6 Mo*</th>
<th># CF</th>
<th>12 Mo*</th>
<th># CF</th>
<th>24 Mo*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMII BTT Trial10</td>
<td>Miller</td>
<td>2007</td>
<td>113</td>
<td>33±19</td>
<td>77</td>
<td>57±20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HMII BTT Trial Registry11</td>
<td>Pagani</td>
<td>2009</td>
<td>90</td>
<td>36±21</td>
<td>-</td>
<td>-</td>
<td>90</td>
<td>63±23</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HMII DT Trial12</td>
<td>Slaughter</td>
<td>2009</td>
<td>115</td>
<td>27±16</td>
<td>89</td>
<td>63±19</td>
<td>-</td>
<td>-</td>
<td>76</td>
<td>66±20</td>
<td>47</td>
<td>70±19</td>
</tr>
<tr>
<td>HMII BTT DT Trial Registry21</td>
<td>Rogers</td>
<td>2010</td>
<td>226</td>
<td>26(m)</td>
<td>167</td>
<td>58(m)</td>
<td>119</td>
<td>60(m)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ADVANCE: HVAD BTT Trial13</td>
<td>Aaronson</td>
<td>2012</td>
<td>128</td>
<td>35±19</td>
<td>-</td>
<td>-</td>
<td>70</td>
<td>67±21</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ADVANCE: HVAD BTT Trial CAP14</td>
<td>Slaughter</td>
<td>2013</td>
<td>169</td>
<td>37±22</td>
<td>-</td>
<td>-</td>
<td>169</td>
<td>68±19</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**MLHFQ - Scores range from 0 to 105. A lower score illustrates a better quality of life.**

<table>
<thead>
<tr>
<th>Study</th>
<th>First Author</th>
<th>Year</th>
<th># CF</th>
<th>Baseline</th>
<th># CF</th>
<th>3 Mo</th>
<th># CF</th>
<th>6 Mo</th>
<th># CF</th>
<th>12 Mo</th>
<th># CF</th>
<th>24 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMII BTT Trial10</td>
<td>Miller</td>
<td>2007</td>
<td>114</td>
<td>73±25</td>
<td>77</td>
<td>45±25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HMII BTT Trial Registry11</td>
<td>Pagani</td>
<td>2009</td>
<td>92</td>
<td>69±23</td>
<td>-</td>
<td>-</td>
<td>92</td>
<td>41±25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HMII DT Trial12</td>
<td>Slaughter</td>
<td>2009</td>
<td>116</td>
<td>75±18</td>
<td>89</td>
<td>37±22</td>
<td>-</td>
<td>76</td>
<td>34±22</td>
<td>44</td>
<td>30±22</td>
<td></td>
</tr>
<tr>
<td>HMII BTT DT Trial Registry21</td>
<td>Rogers</td>
<td>2010</td>
<td>224</td>
<td>75(m)</td>
<td>164</td>
<td>42(m)</td>
<td>115</td>
<td>38(m)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**EQ-5D VAS - Scores range from 0 to 100, 0 representing the worst possible health state and 100 representing the best.**

<table>
<thead>
<tr>
<th>Study</th>
<th>First Author</th>
<th>Year</th>
<th># CF</th>
<th>Baseline</th>
<th># CF</th>
<th>3 Mo</th>
<th># CF</th>
<th>6 Mo</th>
<th># CF</th>
<th>12 Mo</th>
<th># CF</th>
<th>24 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE: HVAD BTT Trial13</td>
<td>Aaronson</td>
<td>2012</td>
<td>130</td>
<td>40±24</td>
<td>-</td>
<td>-</td>
<td>72</td>
<td>70±20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ADVANCE: HVAD BTT Trial CAP14</td>
<td>Slaughter</td>
<td>2013</td>
<td>178</td>
<td>44±25</td>
<td>-</td>
<td>-</td>
<td>178</td>
<td>72±19</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>INTERMACS 201319</td>
<td>Kirklin</td>
<td>2013</td>
<td>852</td>
<td>41(m)</td>
<td>528</td>
<td>69(m)</td>
<td>466</td>
<td>73(m)</td>
<td>281</td>
<td>72(m)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**6MWD - Evaluates an individual’s functional exercise capacity by measuring the distance, in meters, he or she can walk in six minutes.**

<table>
<thead>
<tr>
<th>Study</th>
<th>First Author</th>
<th>Year</th>
<th># CF</th>
<th>Baseline</th>
<th># CF</th>
<th>3 Mo</th>
<th># CF</th>
<th>6 Mo</th>
<th># CF</th>
<th>12 Mo</th>
<th># CF</th>
<th>24 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMII BTT Trial10</td>
<td>Miller</td>
<td>2007</td>
<td>25</td>
<td>42±97</td>
<td>56</td>
<td>292±212</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HMII BTT Trial Registry11</td>
<td>Pagani</td>
<td>2009</td>
<td>14</td>
<td>201±140</td>
<td>-</td>
<td>-</td>
<td>109</td>
<td>347±179</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HMII DT Trial12</td>
<td>Slaughter</td>
<td>2009</td>
<td>50</td>
<td>182±140</td>
<td>77</td>
<td>319±191</td>
<td>61</td>
<td>318±164</td>
<td>36</td>
<td>372±191</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMII BTT DT Trial Registry21</td>
<td>Rogers</td>
<td>2010</td>
<td>38</td>
<td>214±215</td>
<td>-</td>
<td>-</td>
<td>97</td>
<td>372±199</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>BTT</td>
<td></td>
<td></td>
<td>129</td>
<td>204±150</td>
<td>-</td>
<td>-</td>
<td>199</td>
<td>350±198</td>
<td>-</td>
<td>-</td>
<td>75</td>
<td>360±210</td>
</tr>
</tbody>
</table>

* Time was reported variably among studies: mean/SD (x ± y), mean (x(m))
#=number; 6MWD=6 minute walk distance; BTT=bridge to transplant; CAP=continued access protocol; CF=continuous-flow; DT=destination therapy; EQ-5D=European Quality of Life-5 Dimensions; HRQoL=health-related quality of life; HMII=HeartMate II; HVAD=HeartWare ventricular assist device; INTERMACS=Interagency Registry for Mechanically Assisted Circulatory Support; KCCQ=Kansas City Cardiomyopathy Questionnaire; MLHFQ=Minnesota Living with Heart Failure Questionnaire; mo=month; VAS=Visual Analogue Scale.
### Table 3. Common Adverse Events of CF LVAD - All Trial and Registry Data with Greater Than 100 CF Patients*

<table>
<thead>
<tr>
<th>Study</th>
<th>First Author</th>
<th>Year</th>
<th>Total CF</th>
<th>BTT</th>
<th>DT</th>
<th>Defined Time at Risk</th>
<th>Early ≤30 days (%)</th>
<th>Late &gt; 30 days (%)</th>
<th>GI</th>
<th>Ischemic</th>
<th>Hemorrhagic</th>
<th>TIA</th>
<th>Other</th>
<th>Local</th>
<th>Driveline</th>
<th>Pocket</th>
<th>Sepsis</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMII BTT Trial†</td>
<td>Miller</td>
<td>2007</td>
<td>133</td>
<td>133</td>
<td>0</td>
<td>6 mo</td>
<td>75%</td>
<td>8%</td>
<td>-</td>
<td>6%</td>
<td>2%</td>
<td>4%</td>
<td>6%</td>
<td>28%</td>
<td>14%</td>
<td>0%</td>
<td>20%</td>
<td>-</td>
</tr>
<tr>
<td>HMII BTT Trial Registry‡</td>
<td>Pagani</td>
<td>2009</td>
<td>281</td>
<td>281</td>
<td>0</td>
<td>6 mo</td>
<td>69%</td>
<td>23%</td>
<td>-</td>
<td>5%</td>
<td>5%</td>
<td>3%</td>
<td>2%</td>
<td>5%</td>
<td>30%</td>
<td>14%</td>
<td>2%</td>
<td>17%</td>
</tr>
<tr>
<td>HMII DT Trial‡</td>
<td>Slaughter</td>
<td>2009</td>
<td>133</td>
<td>0</td>
<td>133</td>
<td>24 mo</td>
<td>111%</td>
<td>8%</td>
<td>11%</td>
<td>-</td>
<td>22%</td>
<td>49%</td>
<td>-</td>
<td>36%</td>
<td>35%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ADVANCE: HVAD BTT Trial†‡</td>
<td>Aaronson</td>
<td>2012</td>
<td>140</td>
<td>140</td>
<td>0</td>
<td>6 mo</td>
<td>26%</td>
<td>11%</td>
<td>11%</td>
<td>7%</td>
<td>6%</td>
<td>4%</td>
<td>-</td>
<td>-</td>
<td>12%</td>
<td>-</td>
<td>11%</td>
<td>-</td>
</tr>
<tr>
<td>ADVANCE: HVAD BTT Trial CAP‡</td>
<td>Slaughter</td>
<td>2013</td>
<td>332</td>
<td>332</td>
<td>0</td>
<td>3-36 mo</td>
<td>12%</td>
<td>14%</td>
<td>13%</td>
<td>8%</td>
<td>8%</td>
<td>5%</td>
<td>-</td>
<td>-</td>
<td>17%</td>
<td>-</td>
<td>17%</td>
<td>-</td>
</tr>
<tr>
<td>INCOR Analysis§</td>
<td>Schmid</td>
<td>2008</td>
<td>216</td>
<td>-</td>
<td>-</td>
<td>48 mo</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>18%</td>
<td>8%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>64 European Institutions§§</td>
<td>Lahpor</td>
<td>2010</td>
<td>184</td>
<td>-</td>
<td>-</td>
<td>8±7 mo</td>
<td>52%</td>
<td>-</td>
<td>-</td>
<td>4%</td>
<td>2%</td>
<td>4%</td>
<td>-</td>
<td>20%</td>
<td>22%</td>
<td>5%</td>
<td>30%</td>
<td>-</td>
</tr>
<tr>
<td>John INTERMACS§§</td>
<td>John</td>
<td>2011</td>
<td>1496</td>
<td>1496</td>
<td>0</td>
<td>9±7 mo</td>
<td>36%</td>
<td>10%</td>
<td>4%</td>
<td>2%</td>
<td>-</td>
<td>4%</td>
<td>-</td>
<td>13%</td>
<td>2%</td>
<td>3%</td>
<td>26%</td>
<td>-</td>
</tr>
<tr>
<td>Goldstein INTERMACS§§§</td>
<td>Goldstein</td>
<td>2012</td>
<td>2006</td>
<td>830</td>
<td>291</td>
<td>12 mo</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>23%</td>
<td>19%</td>
<td>-</td>
<td>20%</td>
<td>-</td>
</tr>
<tr>
<td>INTERMACS 2013§§</td>
<td>Kirklin</td>
<td>2013</td>
<td>5358</td>
<td>-</td>
<td>-</td>
<td>12 mo</td>
<td>9.5/100 pt-mo</td>
<td>1.8/100 pt-mo</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8.0/100 pt-mo</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Adverse events definitions in Supplemental Material: Figure 2.

* See Supplemental Material for all single-center studies or those with less than 100 continuous flow patients
† Study uses HeartMate II definitions for adverse events.
‡ Study uses INTERMACS definitions for adverse events.
§ Study includes alternative indications for implant (i.e. bridge to decision, bridge to candidacy).
Il Time at risk was variable among studies: truncated time point (x mo), mean/SD (x ± mo), range (x-y mo).

BTT=bridge to transplant; CAP=continued access protocol; CF=continuous-flow; DT=destination therapy; GI=gastrointestinal; HMII=HeartMate II; HVAD=HeartWare ventricular assist device; INCOR=INCOR left ventricular assist device; INTERMACS=Interagency Registry for Mechanically Assisted Circulatory Support; mo=month; TIA=transient ischemic attack
Table 4. Other Adverse Events of CF LVAD - All Trial and Registry Data with Greater Than 100 CF Patients*

| Industry-Funded Trials and Related Registries | | | | | |
|---|---|---|---|---|---|---|
| Study | First Author | Year | Total CF Pts | BTT | DT | Defined Time at Risk | Device Malfunction | Right Heart Failure | Arrhythmia |
| HMII BTT Trial10† | Miller | 2007 | 133 | 133 | 0 | 6 mo | 2% | 2% | 13% | 4% | 24% | - | 41% |
| HMII BTT Trial Registry11† | Pagani | 2009 | 281 | 281 | 0 | 18 mo | 2% | 3% | 13% | 6% | 20% | - | 68% |
| HMII DT Trial12† | Slaughter | 2009 | 133 | 0 | 133 | 24 mo | 2% | 8% | 20% | 4% | 56% | - | 94% |
| HMII BTT Trial Registry-RVF33† | Kormos | 2010 | 484 | 484 | 0 | 12 mo | - | - | 14% | 6% | - | - | - |
| ADVANCE: HVAD BTT Trial13‡ | Aaronson | 2012 | 332 | 332 | 0 | 3-36 mo | 4% | 5% | 25% | 3% | 21% | 20% | - |
| Multicenter Registries | | | | | | | | | | | | |
| 64 European Institutions16§ | Lahpor | 2010 | 184 | - | - | 8-7 mo | 2% | - | - | 20% | 32% | - | - |
| John INTERMACS18‡ | John | 2011 | 1496 | 1496 | 0 | 9-7 mo | 10% | - | - | 12% | 1% | 28% | - | 50% |
| Holman INTERMACS31‡ | Holman | 2013 | 2816 | 36 mo | 0.9% | 0.8% | - | - | - | - | - | - | - |
| INTERMACS 201319‡ | Kirklin | 2013 | 5358 | - | - | 12 mo | - | 1.6/100 pt-mo | 1.8/100 pt-mo | 4.7/100 pt-mo | - | - | - |
| INTERMACS Thrombosis‡ | Kirklin | 2014 | 6910 | - | - | 12 mo | 5% | - | - | - | - | - | - | - |
| Najjar ADVANCE BTT & CAP8‡ | Najjar | 2014 | 382 | 382 | - | 12 mo | 5% | - | - | - | - | - | - | - |
| Cleveland Clinic, Barnes-Jewish, & Duke32 | Starling | 2014 | 837 | - | - | 8-11 mo | 4% | - | - | - | - | - | - | - |

Adverse events definitions in Supplemental Material: Figure 2.
* See Supplemental Material for all single-center studies or those with less than 100 continuous flow patients
† Study uses HeartMate II definitions for adverse events.
‡ Study uses INTERMACS definitions for adverse events.
§ Study includes alternative indications for implant (i.e. bridge to decision, bridge to candidacy)
II Time at risk was variable among studies: truncated time point (x mo), mean/SD (x ± y mo), range (x-y mo), mean (x mo(m))
Figure Legends

**Figure 1.** Search Flow Diagram

**Figure 2.** Simplified One-Year Outcomes Using Weighted Averages for Left Ventricular Assist Device (Combined Bridge-to-Transplant and Destination Therapy)
465 articles identified through MEDLINE search

2 articles identified through other sources

467 records screened

415 records excluded
<50 continuous-flow = 102
Review/editorial = 103
Technical, imaging or non-human = 35
Surgical technique = 29
Pediatric = 29
Temporary device/partial support = 28
Transplant focus = 21
Pulsatile flow = 18
Other devices = 15
Risk model = 13
Updated by newer publication = 12
Sub-analysis reported results = 10

52 articles included in systematic review
Industry-funded trials and related registries = 10
Multicenter registries = 10
Single center reports and case series = 32
Figure 2. Simplified One-Year Outcomes Using Weighted Averages for Left Ventricular Assist Device (Combined Bridge-to-Transplant and Destination Therapy)

<table>
<thead>
<tr>
<th>Benefits</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0%</td>
<td>1 year after LVAD = 70</td>
<td>100</td>
<td>Worst</td>
<td>Best</td>
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<table>
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<tr>
<th>Quality of Life*</th>
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<tr>
<td>80%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>1 year after LVAD = 70</td>
<td>100</td>
<td>Worst</td>
<td>Best</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Risks</th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rehospitalized for Any Cause</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>55%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0%</td>
<td>1 year after LVAD = 70</td>
<td>100</td>
<td>Worst</td>
<td>Best</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Bleeding†</th>
<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>0-1 month after LVAD (typically surgical)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>30%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0%</td>
<td>1 year after LVAD = 70</td>
<td>100</td>
<td>Worst</td>
<td>Best</td>
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<table>
<thead>
<tr>
<th>Stroke‡</th>
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<tbody>
<tr>
<td>10%</td>
<td></td>
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<tr>
<td>0%</td>
<td>1 year after LVAD = 70</td>
<td>100</td>
<td>Worst</td>
<td>Best</td>
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</table>

<table>
<thead>
<tr>
<th>Serious Device-Related Infection§</th>
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<th></th>
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<tr>
<td>20%</td>
<td></td>
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</tr>
<tr>
<td>0%</td>
<td>1 year after LVAD = 70</td>
<td>100</td>
<td>Worst</td>
<td>Best</td>
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</table>

<table>
<thead>
<tr>
<th>Device Malfunction Due to Clotting¶</th>
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<tbody>
<tr>
<td>5%</td>
<td></td>
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<tr>
<td>0%</td>
<td>1 year after LVAD = 70</td>
<td>100</td>
<td>Worst</td>
<td>Best</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ongoing Heart Failure‖</th>
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<tbody>
<tr>
<td>18%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>1 year after LVAD = 70</td>
<td>100</td>
<td>Worst</td>
<td>Best</td>
</tr>
</tbody>
</table>

Shaded=Affected; White=Not affected. All timeframes are time since LVAD implant. LVAD=left ventricular assist device. *Kansas City Cardiomyopathy Questionnaire score; †Requiring transfusion or urgent medical attention; ‡ischemic=5%±5, Hemorrhagic=5%±4; §Driveline=18%±2, Pump Pocket=2%±2; ¶Typically requiring surgery to replace the device; ‖Requiring inotropes >2 weeks after implant=15%±7, Requiring right ventricular assist device=3%±2.

Standard Deviations (not reported above): Survival=80%±10; Quality of Life baseline=28±27, 1 year=70±0; Rehospitalized=55%±2; Bleeding 0-1 month=30%±5, 1-12 months=20%±6; Device Malfunction=5%±2.

For more information, go to www.patientdecisionaid.org
Clinical Outcomes Following Continuous-Flow Left Ventricular Assist Device: A Systematic Review
Colleen K. McIlvennan, Kate H. Magid, Amrut V. Ambardekar, Jocelyn S. Thompson, Daniel D. Matlock and Larry A. Allen

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Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2014/10/07/CIRCHEARTFAILURE.114.001391.DC1

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http://circheartfailure.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL
Figure 1. Search Algorithm

PubMed / MEDLINE Search Algorithm:

((heart-assist devices* OR left ventricular assist device[tiab] OR lvad[tiab] OR mechanical circulatory support[tiab])

AND


AND

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Localized Non-Device Infection</strong></td>
<td>Infection localized to any organ system or region without evidence of systemic involvement which requires treatment or is ascertained by standard clinical methods and either associated with evidence or bacterial, viral, fungal, and protozoal infection, by standard clinical pathologic/laboratory methods. This definition includes positive blood cultures that are not considered to be septic in etiology.</td>
</tr>
<tr>
<td><strong>Percutaneous Site Infection</strong></td>
<td>Infection of the percutaneous drive line site evidenced by the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, and or leukocytosis. This definition includes any positive cultures identified at the time of pump explant.</td>
</tr>
<tr>
<td><strong>Pump Pocket Infection</strong></td>
<td>Infection of the pump pocket area evidence by the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, and or leukocytosis. This definition includes any positive cultures identified at the times of pump explant.</td>
</tr>
<tr>
<td><strong>Sepsis</strong></td>
<td>A systematic response to a serious infection, usually manifested by fever, tachycardia, tachypnea, leukocytosis and vasodilation requiring use of IV antimicrobial therapy. It may or may or may not be associated with a localized site of infection. It may of or may not be accompanied by a positive microbiological culture from the blood, the localized site of infection, or other evidence of bacterial, viral, fungal, or protozoal infection using standard clinical pathologic/laboratory methods. This definition excludes routine prophylactic treatment with IV antimicrobial therapy.</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>An episode of internal of external bleeding that causes death, re-operation, permanent injury, or necessitates transfusion of &gt; 2 units of red blood cells within 24 hours.</td>
</tr>
<tr>
<td><strong>Neurologic Event</strong></td>
<td>Any new, temporary or permanent, focal or global, neurological deficit including TIA, metabolic encephalopathy, seizure, etc. The event must be subcategorized to document the type of neurologic event.</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>A neurologic deficit lasting more than 24 hours, or lasting 24 hours or less with a brain imaging study showing new infarction. A TIA is a neurological deficit lasting 24 hours and if an imaging study is performed, shows no evidence of new infarction. Each stroke must be subcategorized as either ischemic or hemorrhagic.</td>
</tr>
<tr>
<td><strong>RHF</strong></td>
<td>Symptoms of RHF (e.g. drop in right ventricular ejection associated with right sided congestion including hepatic congestion, peripheral edema, jugular venous distension, etc. requiring either RVAD implantation at any time, or inotropic therapy &gt; 14 days following implant.</td>
</tr>
<tr>
<td><strong>Cardiac Arrhythmias</strong></td>
<td>Any symptomatic or asymptomatic arrhythmia that requires intervention. The investigator should distinguish four types of events: 1) cardiac arrest, 2) VA, 3) supraventricular arrhythmia, 4) atrial arrhythmia.</td>
</tr>
<tr>
<td><strong>Renal Failure</strong></td>
<td>Abnormal kidney function requiring dialysis in patients who did not require this procedure prior to the implant.</td>
</tr>
<tr>
<td><strong>Respiratory Failure</strong></td>
<td>Impairment of respiratory function requiring reintubation and/or tracheostomy at any time or the inability to discontinue ventilator support after six days (144 hours) of device support.</td>
</tr>
<tr>
<td><strong>Suspected Device Malfunction/Failure</strong></td>
<td>An instance when any component of the system fails to perform its intended function. Losses of the display, inability to operate on batteries, or pump stoppage are examples. Event consequences can be captured on the case report form and will include: hemodynamic compromise, re-operation, death, urgent transplant or initiation of inotropes.</td>
</tr>
<tr>
<td><strong>INTERNMACS</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Localized Non-Device Infection</strong></td>
<td>Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.</td>
</tr>
<tr>
<td><strong>Percutaneous Site and/or Pocket Infection</strong></td>
<td>A positive culture from the skin and/or tissue surrounding the drive line or from the tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis.</td>
</tr>
<tr>
<td><strong>Internal Pump Component or Outflow Tract Infection</strong></td>
<td>Infection of blood-contacting surfaces of the LVAD documented by positive site culture.</td>
</tr>
<tr>
<td><strong>Sepsis</strong></td>
<td>Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.</td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>An episode of suspected internal or external bleeding that results in one or more of the following: death, re-operation, hospitalization, transfusion of PRBCs as follows: 1) during first 7 days post implant = ≥ 4 units PRBC within any 24 hour period or 2) after 7 days post implant any transfusion of PRBCs</td>
</tr>
<tr>
<td><strong>Neurological Dysfunction</strong></td>
<td>Any new, temporary or permanent, focal or global neurologic deficit, including TIA that resolves within 24 hours, and ischemic or hemorrhagic intracranial CVA that persists beyond 24 hours or less than 24 hours with infarction on an image study.</td>
</tr>
<tr>
<td><strong>Right Heart Failure</strong></td>
<td>Symptoms and signs of persistent right ventricular dysfunction [central venous pressure &gt; 18 mmHg with a cardiac index &lt;2.3 L/min/m² in the absence of elevated left atrial/pulmonary capillary wedge pressure (greater than 18 mmHg), tamponade, ventricular arrhythmias or pneumothorax] requiring RVAD; implantation; or requiring inhaled nitric oxide or inotropic therapy for a duration of more than 1 week at any time after LVAD implantation.</td>
</tr>
<tr>
<td><strong>Device Malfunction</strong></td>
<td>Denotes a failure of one or more of the components of the device system which either directly causes or could potentially induce a state of inadequate circulatory support (low cardiac output state) or death.</td>
</tr>
<tr>
<td><strong>Cardiac Arrhythmia</strong></td>
<td>Any documented arrhythmia that results in clinical compromise (e.g., diminished LVAD flow, oliguria, pre-syncpe or syncpe) that requires hospitalization or occurs during a hospital stay.</td>
</tr>
<tr>
<td><strong>American College of Chest Physicians and Society of Critical Care Medicine (ACCP/SCCM)</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Sepsis</strong></td>
<td>Defined as a systemic inflammatory response syndrome (two or more of: 1) temperature 38°C or 36°C; 2) heart rate 90 beats/min; 3) respiratory rate 20 breaths/min or PaCO&lt;sub&gt;2&lt;/sub&gt; 32 mm Hg; or 4) white blood cell count 12,000 cells/mm&lt;sup&gt;3&lt;/sup&gt;, 4,000 cells/mm&lt;sup&gt;3&lt;/sup&gt; or 10% immature bands) resulting from a confirmed infectious process.</td>
</tr>
<tr>
<td><strong>Schmid et al., 2008</strong>&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Stroke was a clinical diagnosis, defined as cerebral ischemia with consecutive neurologic symptoms persisting for 24 hours, irrespective of findings in cranial CT.</td>
</tr>
<tr>
<td><strong>Cerebral Bleeding</strong></td>
<td>Cerebral bleeding, caused either by spontaneous rupture of a blood vessel within the head or after stroke, mandated confirmation by CT scan, regardless of present symptoms.</td>
</tr>
<tr>
<td><strong>Lahner et al., 2009</strong>&lt;sup&gt;7&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>RHF</td>
<td>The post-operative need for temporary right ventricular mechanical support or inotropic support for more than 14 days following the implantation.</td>
</tr>
<tr>
<td>---</td>
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</tr>
<tr>
<td>Confirmed Pump Thrombosis</td>
<td>Confirmed pump thrombosis was defined as a thrombus found on the blood-contacting surfaces of the HeartMate II, its inflow cannula, or its outflow conduit at pump replacement, urgent transplantation, or autopsy.</td>
</tr>
<tr>
<td>Suspected Pump Thrombosis</td>
<td>Suspected pump thrombosis was defined as a clinical diagnosis of pump-related malfunction in which the clinical or device variables suggested a thrombus on the blood-contacting surfaces of the pump, cannulae, or grafts.</td>
</tr>
<tr>
<td>Crow et al., 2009$^9$</td>
<td>GI Bleeding Defined as a guaiac-positive stool and a hemoglobin drop requiring transfusion of at least 2 units of PRBCs.</td>
</tr>
<tr>
<td>Martin et al., 2010$^{10}$</td>
<td>Infection Defined as 1) a positive bacterial or fungal culture taken from the bloodstream attributable to the device, and/or from the driveline site, and/or the operative bed, that was treated with antimicrobial agents by the clinicians caring for the patient, or 2) a clinically suspected infection of the device that was surgically debrided and treated with antimicrobial therapy regardless of culture data.</td>
</tr>
<tr>
<td>Tonkara et al., 2010$^{11}$</td>
<td>Driveline/Pump Pocket Infection Defined as those that required treatment with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, and/or leukocytosis.</td>
</tr>
<tr>
<td>Local Infections</td>
<td>Defined as those limited to any organ system or region without evidence of systemic involvement that requires treatment or is ascertained by standard clinical method.</td>
</tr>
<tr>
<td>Uriel et al., 2010$^{12}$</td>
<td>Minor Bleeding Defined as observable blood loss without the need for transfusion.</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>Defined as need for blood transfusion 7 days after device insertion.</td>
</tr>
<tr>
<td>Stroke</td>
<td>Defined as any neurologic event lasting 24 hours and categorized as having a hemorrhagic or thromboembolic etiology according to the results of intracranial imaging.</td>
</tr>
<tr>
<td>Pump Thrombosis</td>
<td>Pump thrombosis was defined as any thrombus within the device or its conduits associated with clinical signs of impaired pump performance.</td>
</tr>
<tr>
<td>Demirozu et al., 2011$^{13}$</td>
<td>GI Bleeding Patients were considered to have GI bleeding if they had 1 or more of the following symptoms: guaiac-positive stool; hematemesis; melena; active bleeding at the time of endoscopy or colonoscopy; and blood within the stomach at endoscopy or colonoscopy. The symptom(s) had to be accompanied by a decrease of 1 g/dl in the patient’s hemoglobin level, which was considered to necessitate the transfusion of 2 units PRBCs.</td>
</tr>
<tr>
<td>Schaffer et al., 2011$^{14}$</td>
<td>Driveline/Pump Pocket Infection Defined as either: 1) purulent drainage from the drive-line exit site (or device pocket); 2) organisms isolated from an aseptically obtained culture of fluid or tissue from the driveline exit site (or device pocket); or 3) an abscess or other evidence of infection involving the drive-line tract (or device pocket) found on direct examination, during re operation or by histopathologic or radiologic examination.</td>
</tr>
<tr>
<td>Schaffer et al., 2011$^{15}$</td>
<td>GI Bleeding Defined as bleeding with an identifiable GI source by esophagogastroduodenoscopy, colonoscopy, or tagged red blood cell scan.</td>
</tr>
<tr>
<td>Aggarwal et al., 2012$^{16}$</td>
<td>GI Bleeding Defined as bleeding above the ligament of Treitz and bleeding from the GI tract distal to the ligament of Treitz, respectively.</td>
</tr>
<tr>
<td>Device Infection</td>
<td>Defined as a culture-positive specimen obtained from any part of the device, including driveline or pocket infections.</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bloodstream Infection</td>
<td>Must meet at least 1 of the following criteria: 1) a recognized pathogen cultured from 1 or more blood cultures and organism cultured from blood is not related to an infection at another site, 2) at least 1 of the following signs or symptoms: fever (&gt;38°C), chills, or hypotension and signs and symptoms and positive laboratory results are not related to an infection at another site and common skin contaminant is cultured from 2 or more blood cultures drawn on separate occasions.</td>
</tr>
<tr>
<td>VA</td>
<td>Defined as the first ICD therapy for VA after the start of follow-up.</td>
</tr>
<tr>
<td>GI Bleeding</td>
<td>Defined as melena, hematochezia or hematemesis along with a drop in hemoglobin requiring transfusion.</td>
</tr>
<tr>
<td>Sustained VA Event</td>
<td>Defined as a single episode of ventricular tachycardia lasting at least 30 seconds or a VA necessitating termination via antitachycardia pacing or defibrillation.</td>
</tr>
<tr>
<td>RHF</td>
<td>Symptoms of RHF requiring RVAD implantation at any time or inotropic support ≥14 days following LVAD implantation</td>
</tr>
<tr>
<td>Device Failure</td>
<td>All types of device malfunction, including mechanical failure, electrical failure, and device thrombosis</td>
</tr>
<tr>
<td>RHF</td>
<td>Defined as the need for inotropic support for more than 1 week or the need for RVAD support</td>
</tr>
<tr>
<td>RVF</td>
<td>Defined as the need for IV inotropes for more than 168 hours after the initial surgery</td>
</tr>
<tr>
<td>VA</td>
<td>Defined as ventricular tachyarrhythmia (ventricular tachycardia or ventricular fibrillation) that received appropriate therapy (antitachycardia pacing or shock) from an ICD or was sustained for &gt;30 s in the absence of effective treatment.</td>
</tr>
<tr>
<td>RVF</td>
<td>Defined as the need for IV inotropes for &gt;14 days post-operatively or an RVAD</td>
</tr>
<tr>
<td>VA</td>
<td>Defined as more than 30 seconds of documented ventricular tachycardia or ventricular fibrillation as seen on a rhythm strip, electrocardiographic tracing, or implantable cardiac defibrillator readout.</td>
</tr>
<tr>
<td>GI Bleeding</td>
<td>Defined as heme-positive stool or hematemesis and a decrease in hemoglobin &gt;1 g/dl.</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>Defined as an episode of suspected internal or external bleeding resulting in 1 of the following: death, surgical intervention, hospitalization, or transfusion of PRBCs as well as a documented decrease in hemoglobin ≥2g/dL.</td>
</tr>
</tbody>
</table>
Table 1. Summary of Evidence Sources

<table>
<thead>
<tr>
<th>Industry-Funded Trials and Related Registries</th>
<th>Multicenter Registries</th>
<th>Single Center Reports and Case Series</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abbreviations</strong></td>
<td><strong>First Author</strong></td>
<td><strong>Year</strong></td>
</tr>
<tr>
<td>HMII BTT Trial</td>
<td>Miller</td>
<td>2007</td>
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<td>HMII BTT Trial Registry</td>
<td>Pagani</td>
<td>2009</td>
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<tr>
<td>HMII DT Trial</td>
<td>Slaughter</td>
<td>2009</td>
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<tr>
<td>HMII BTT Trial Registry RVEF</td>
<td>Kormos</td>
<td>2010</td>
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<tr>
<td>HMII BTT DT Trial Registry</td>
<td>Rogers</td>
<td>2010</td>
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<tr>
<td>International HVAD Trial</td>
<td>Struebel</td>
<td>2011</td>
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<tr>
<td>ADVANCE; HVAD BTT Trial CAP</td>
<td>Slaughter</td>
<td>2013</td>
</tr>
<tr>
<td><strong>Abbreviations</strong></td>
<td><strong>First Author</strong></td>
<td><strong>Year</strong></td>
</tr>
<tr>
<td>INCOR Analysis</td>
<td>Schmid</td>
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</tr>
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<td>64 European Institutions</td>
<td>Lahpor</td>
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</tr>
<tr>
<td>U of Minnesota, Pittsburgh, &amp; Columbia</td>
<td>Boyle</td>
<td>2011</td>
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<tr>
<td>John INTERMACS</td>
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<td>2011</td>
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<tr>
<td>Goldstein INTERMACS</td>
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</tr>
<tr>
<td>Hoiberg INTERMACS</td>
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<td>2013</td>
</tr>
<tr>
<td>INTERMACS 2013</td>
<td>Kirklin</td>
<td>2013</td>
</tr>
<tr>
<td>INTERMACS Thrombosis</td>
<td>Kirklin</td>
<td>2013</td>
</tr>
<tr>
<td>Najjar ADVANCE BTT &amp; CAP</td>
<td>Najjar</td>
<td>2013</td>
</tr>
<tr>
<td>Cleveland Clinic, Barnes-Jewish, &amp; Duke</td>
<td>Starling</td>
<td>2013</td>
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</table>

* includes bridge to recovery, bridge to decision, and bridge to candidacy. Study not included in Tables. BTT=bridge to transplant; CAP=continued access protocol; CF=continuous flow; DT=destination therapy; GI=gastrointestinal; HM-XV=HeartMate XV ventricular assist device; INTERMACS=Interagency Registry for Mechanically Assisted Circulatory Support; IVAD=implantable ventricular assist device; LVAD=left ventricular assist device; mo=month; NC=neurocognition; PVAD=Paracorporeal ventricular assist device; RRT=renal replacement therapy; RVEF=right ventricular failure.
## Table 2. Estimated Actuarial Survival of CF Devices - Single Center Studies or Those with Less Than 100 Continuous Flow Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>First Author</th>
<th>Year</th>
<th>Total CF</th>
<th>BTT</th>
<th>DT</th>
<th>1 Mo</th>
<th>6 Mo</th>
<th>12 Mo</th>
<th>24 Mo</th>
<th>36 Mo</th>
<th>48 Mo</th>
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<td></td>
</tr>
<tr>
<td>International HVAD Trial (8)</td>
<td>Strueber</td>
<td>2011</td>
<td>50</td>
<td>50</td>
<td>0</td>
<td>-</td>
<td>90%</td>
<td>84%</td>
<td>79%</td>
<td>-</td>
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</tr>
<tr>
<td><strong>Single Center Reports and Case Series</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Medical University of Vienna (25)</td>
<td>Sandner</td>
<td>2009</td>
<td>86</td>
<td>86</td>
<td>0</td>
<td>92%</td>
<td>61%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>German Heart Institute Berlin (45)</td>
<td>Drews</td>
<td>2011</td>
<td>111</td>
<td>0</td>
<td>111</td>
<td>-</td>
<td>-</td>
<td>71%</td>
<td>70%</td>
<td>49%</td>
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<tr>
<td>University of Minnesota (46)</td>
<td>John</td>
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<td>102</td>
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<td>95%</td>
<td>84%</td>
<td>79%</td>
<td>-</td>
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<td>Johns Hopkins (15)</td>
<td>Schaffer</td>
<td>2011</td>
<td>86</td>
<td>57</td>
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<td>-</td>
<td>-</td>
<td>72%</td>
<td>-</td>
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<tr>
<td>Henry Ford (19)</td>
<td>Morgan</td>
<td>2012</td>
<td>86</td>
<td>54</td>
<td>32</td>
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<td>-</td>
<td>87%</td>
<td>83%</td>
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</tr>
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<td>University of North Carolina (20)</td>
<td>Rassch</td>
<td>2012</td>
<td>61</td>
<td>27</td>
<td>34</td>
<td>-</td>
<td>87%</td>
<td>-</td>
<td>-</td>
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<tr>
<td>University of Münster (40)</td>
<td>Dell'Aquila</td>
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<td>50</td>
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<td>-</td>
<td>-</td>
<td>82%</td>
<td>-</td>
<td>78%</td>
<td>76%</td>
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<tr>
<td>University of Minnesota (25)</td>
<td>Deo</td>
<td>2013</td>
<td>126</td>
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<td>88%</td>
<td>-</td>
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</tr>
<tr>
<td>University of Virginia (26)</td>
<td>Mulloy</td>
<td>2013</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>98%</td>
<td>-</td>
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</tbody>
</table>

BTT = bridge to transplant; CF = continuous-flow; DT = destination therapy; HVAD = HeartWare ventricular assist device; mo = month
### Table 3. Common Adverse Events of CF LVAD – Single Center Studies or Those with Less Than 100 CF Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>First Author</th>
<th>Year</th>
<th>Total CF</th>
<th>BTT</th>
<th>DT</th>
<th>Defined Time at Risk</th>
<th>Early ≤ 30 days</th>
<th>Late &gt; 30 days</th>
<th>GI</th>
<th>Ischemic</th>
<th>Hemorrhagic</th>
<th>TIA</th>
<th>Other</th>
<th>Local</th>
<th>Driveline</th>
<th>Pocket</th>
<th>Sepsis</th>
<th>Other</th>
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<tr>
<td><strong>Industry-Funded Trials and Related Registries</strong></td>
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</tr>
<tr>
<td>International HVAD Trial[^37][*]</td>
<td>Strueber</td>
<td>2011</td>
<td>50</td>
<td>50</td>
<td>0</td>
<td>24 mo</td>
<td>20%</td>
<td>12%</td>
<td>-</td>
<td>4%</td>
<td>8%</td>
<td>4%</td>
<td>-</td>
<td>14%</td>
<td>18%</td>
<td>-</td>
<td>10%</td>
<td>-</td>
</tr>
<tr>
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<td>Moazami</td>
<td>2013</td>
<td>72</td>
<td>-</td>
<td>-</td>
<td>19±18 mo</td>
<td>9%</td>
<td>-</td>
<td>-</td>
<td>6%</td>
<td>-</td>
<td>-</td>
<td>-</td>
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### Single Center Reports and Case Series

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<th>BTT</th>
<th>DT</th>
<th>Defined Time at Risk</th>
<th>Early ≤ 30 days</th>
<th>Late &gt; 30 days</th>
<th>GI</th>
<th>Ischemic</th>
<th>Hemorrhagic</th>
<th>TIA</th>
<th>Other</th>
<th>Local</th>
<th>Driveline</th>
<th>Pocket</th>
<th>Sepsis</th>
<th>Other</th>
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<tr>
<td>University of Minnesota[^3][‡]</td>
<td>Crow</td>
<td>2009</td>
<td>55</td>
<td>46</td>
<td>9</td>
<td>36 mo</td>
<td>-</td>
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<td>22%</td>
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<tr>
<td>Medical University of Vienna[^42][‡]</td>
<td>Sandner</td>
<td>2009</td>
<td>86</td>
<td>86</td>
<td>0</td>
<td>6 mo</td>
<td>26%</td>
<td>-</td>
<td>10%</td>
<td>12%</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>The Ohio State University[^10][§]</td>
<td>Martin</td>
<td>2010</td>
<td>64</td>
<td>-</td>
<td>18 mo</td>
<td>-</td>
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<tr>
<td>Washington University[^11][‡]</td>
<td>Topkara</td>
<td>2010</td>
<td>81</td>
<td>57</td>
<td>24</td>
<td>9±9 mo</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>37%</td>
<td>17%</td>
<td>5%</td>
<td>19%</td>
</tr>
<tr>
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<td>Uriel</td>
<td>2010</td>
<td>79</td>
<td>64</td>
<td>15</td>
<td>12±16 mo</td>
<td>44%</td>
<td>30%</td>
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<td>2011</td>
<td>172</td>
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<td>2±2 mo</td>
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<tr>
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<td>John</td>
<td>2011</td>
<td>102</td>
<td>102</td>
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<td>11±10 mo</td>
<td>17%</td>
<td>-</td>
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<td>22%</td>
<td>0%</td>
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<td>86</td>
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<td>-</td>
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<td>-</td>
<td>-</td>
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<td>26%</td>
<td>9%</td>
<td>64%</td>
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</tr>
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<td>Schaffer</td>
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<td>57</td>
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<td>12 mo</td>
<td>23%</td>
<td>-</td>
<td>28%</td>
<td>-</td>
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<tr>
<td>Advocate Christ Medical Center[^16][†]</td>
<td>Aggarwal</td>
<td>2012</td>
<td>101</td>
<td>7</td>
<td>94</td>
<td>0-70 mo</td>
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<td>Aggarwal</td>
<td>2012</td>
<td>87</td>
<td>-</td>
<td>-</td>
<td>19±14 mo</td>
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<td>9%</td>
<td>11%</td>
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<tr>
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<td>2012</td>
<td>61</td>
<td>44</td>
<td>17</td>
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<td>Kato</td>
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<td>140</td>
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<td>9±11 mo</td>
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<td>4%</td>
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<tr>
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<td>Morgan</td>
<td>2012</td>
<td>86</td>
<td>54</td>
<td>32</td>
<td>0-15 mo</td>
<td>-</td>
<td>-</td>
<td>22%</td>
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</tr>
<tr>
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<td>2012</td>
<td>143</td>
<td>56</td>
<td>87</td>
<td>11±11 mo</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>-</td>
<td>12%</td>
<td>6%</td>
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<tr>
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<td>Borgi</td>
<td>2013</td>
<td>100</td>
<td>68</td>
<td>32</td>
<td>0-12 mo</td>
<td>8%</td>
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<td>22%</td>
<td>9%</td>
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<td>-</td>
<td>10%</td>
<td>6%</td>
<td>1%</td>
<td>-</td>
<td>10%</td>
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</tr>
<tr>
<td>Cleveland Clinic[^23][‡][§]</td>
<td>Bunte</td>
<td>2013</td>
<td>139</td>
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<td>31</td>
<td>16 mo(m)</td>
<td>58%</td>
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<tr>
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<td>-</td>
<td>-</td>
<td>9 mo(m)</td>
<td>36%</td>
<td>20%</td>
<td>26%</td>
<td>26%</td>
<td>4%</td>
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<td>-</td>
<td>-</td>
<td>14%</td>
<td>-</td>
<td>28%</td>
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<tr>
<td>University of Virginia[^25][†]</td>
<td>Mulloy</td>
<td>2013</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>5-13 mo</td>
<td>-</td>
<td>-</td>
<td>8%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2%</td>
<td>14%</td>
<td>-</td>
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</tr>
<tr>
<td>Thomas Jefferson University[^26][†]</td>
<td>Sarosiek</td>
<td>2013</td>
<td>59</td>
<td>-</td>
<td>-</td>
<td>34±19 mo</td>
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<td>24%</td>
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</tr>
<tr>
<td>Utah Transplant Affiliated Hospitals[^27][‡][‡]</td>
<td>Weaver-Pinzon</td>
<td>2013</td>
<td>134</td>
<td>68</td>
<td>52</td>
<td>3 mo</td>
<td>25%</td>
<td>17%</td>
<td>-</td>
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</tr>
</tbody>
</table>

Adverse events definitions in Appendix 2.
* Study uses INTERMACS definitions for adverse events.
† Study uses HeartMate II definitions for adverse events.
‡ Study uses ISHLT consensus statement definitions for adverse events.
§ Study uses ACCP/SCCM consensus definition of sepsis.
‖ Study includes alternative indications for implant (i.e. bridge to decision, bridge to candidacy).
# Time at risk was variable among studies: truncated time point (x mo), mean/SD (x ± mo), range (x-y mo).

ACCP/SCCM=American College of Chest Physicians and Society of Critical Care Medicine; BTT=bridge to transplant; CF=continuous-flow; DT=destination therapy; GI=gastrointestinal; HMII=HeartMate II; HVAD=HeartWare ventricular assist device; INTERMACS=Interagency Registry for Mechanically Assisted Circulatory Support; ISHLT=International Society of Heart and Lung Transplant; mo=month; TIA=transient ischemic attack.
### Table 4. Other Adverse Events of CF Devices - Single Center Studies or Those with Less Than 100 Continuous Flow Patients

<table>
<thead>
<tr>
<th>Study</th>
<th>First Author</th>
<th>Year</th>
<th>Total CF</th>
<th>BTT</th>
<th>DT</th>
<th>Defined Time at Risk§</th>
<th>Device Malfunction</th>
<th>Right Heart Failure</th>
<th>Arrhythmia</th>
<th>Thrombosis Requiring Exchange</th>
<th>Other Requiring Exchange</th>
<th>Inotropic Support</th>
<th>RVAD</th>
<th>VA</th>
<th>Other</th>
<th>Rehospitalization</th>
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</thead>
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</tr>
<tr>
<td>International HVAD Trial</td>
<td>Strueber</td>
<td>2011</td>
<td>50</td>
<td>50</td>
<td>0</td>
<td>24 mo</td>
<td>8%</td>
<td>6%</td>
<td>6%</td>
<td>4%</td>
<td>-</td>
<td>1.2 adm/pt-yr</td>
<td></td>
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</tr>
<tr>
<td>* Study uses INTERMACS definitions for adverse events.</td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>HMII BTT DT Trial Replacement†</td>
<td>Moazami</td>
<td>2013</td>
<td>72</td>
<td>-</td>
<td>-</td>
<td>19±18 mo</td>
<td>2%</td>
<td>4%</td>
<td>9%</td>
<td>2%</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>† Study uses HeartMate II definitions for adverse events.</td>
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<td>Medical University of Vienna42</td>
<td>Sandner</td>
<td>2009</td>
<td>86</td>
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<td>6 mo</td>
<td>-</td>
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<td>John</td>
<td>2011</td>
<td>102</td>
<td>102</td>
<td>0</td>
<td>11±10 mo</td>
<td>1%</td>
<td>2%</td>
<td>-</td>
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<td>Brenyo</td>
<td>2012</td>
<td>61</td>
<td>44</td>
<td>17</td>
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<td>11%</td>
<td>-</td>
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<td>Raasch</td>
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<td>61</td>
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<td>34</td>
<td>0-12 mo</td>
<td>-</td>
<td>-</td>
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<td>Yuan</td>
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<td>133</td>
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<td>12%</td>
<td>-</td>
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<tr>
<td>Henry Ford22</td>
<td>Borgi</td>
<td>2013</td>
<td>100</td>
<td>68</td>
<td>32</td>
<td>0-12 mo</td>
<td>-</td>
<td>-</td>
<td>11%</td>
<td>5%</td>
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<tr>
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<td>Dell'Aquila</td>
<td>2013</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>9 mo(m)</td>
<td>-</td>
<td>-</td>
<td>24%</td>
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<td>2013</td>
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<td>Garan</td>
<td>2013</td>
<td>94</td>
<td>46</td>
<td>48</td>
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<td>-</td>
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<td>-</td>
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<td>2013</td>
<td>115</td>
<td>42</td>
<td>73</td>
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<td>-</td>
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<td>1.6 adm/pt-yr</td>
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<td>Henry Ford45</td>
<td>Morgan</td>
<td>2013</td>
<td>130</td>
<td>76</td>
<td>54</td>
<td>13 mo(m)</td>
<td>-</td>
<td>-</td>
<td>5%</td>
<td>4%</td>
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<tr>
<td>University of Virginia26</td>
<td>Mulloy</td>
<td>2013</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>5-13 mo</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>32%</td>
<td>-</td>
<td>20%</td>
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<tr>
<td>German Heart Institute Berlin53</td>
<td>Potapov</td>
<td>2013</td>
<td>225</td>
<td>-</td>
<td>-</td>
<td>8 mo(m)</td>
<td>5%</td>
<td>1%</td>
<td>-</td>
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</table>

Adverse events definitions in Supplemental Methods: Figure 2.
* Study uses INTERMACS definitions for adverse events.
† Study uses HeartMate II definitions for adverse events.
‡ Study includes alternative indications for implant (i.e. bridge to decision, bridge to candidacy).
§ Time at risk was variable among studies: truncated time point (x mo), mean/SD (x±y mo), range (x-y mo), mean (x mo(m)).
adm=admission; BTT=bridge to transplant; CF=continuous-flow; DT=destination therapy; HMII=HeartMate II; HVAD=HeartWare ventricular assist device; INTERMACS=Interagency Registry for Mechanically Assisted Circulatory Support; mo=month; pt=patient; RVAD=right ventricular assist device; RVF=right ventricular failure; VA=ventricular arrhythmia; yr=year.
SUPPLEMENTAL FIGURE LEGENDS

Figure 1. Search Algorithm

Figure 2. Adverse Event Definitions

Abbreviations:

ACCP/SCCM=American College of Chest Physicians and Society of Critical Care Medicine; CT=computed tomography; CVA=cerebrovascular accident; GI=gastrointestinal; ICD=internal cardioverter defibrillator; INTERMACS=Interagency Registry for Mechanically Assisted Circulatory Support; IV=intravenous; LVAD=left ventricular assist device; PRBC=packed red blood cell; RHF=right heart failure; RVAD=right ventricular assist device; TIA=transient ischemic attack; VA=ventricular arrhythmia
SUPPLEMENTAL REFERENCES


