Clinical effectiveness of therapy with continuous-flow left ventricular assist devices in nonischemic versus ischemic cardiomyopathy: a systematic review and meta-analysis

Christopher Wavell, BSc
Andrew Sokolowski, BSc
Michelle L. Klingel, MSc
Charles Yin, PhD
A. Dave Nagpal, MD MSc

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Correspondence to:
D. Nagpal
B6-104 University Hospital
339 Windermere Rd
London ON N6A 5A5
dave.nagpal@lhsc.on.ca

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Background: Clinicians may be less inclined to consider long-term left ventricular assist device (LVAD) therapy in end-stage heart failure (ESHF) as a result of nonischemic cardiomyopathy (NICM) versus ischemic cardiomyopathy (ICM) owing to potentially greater right ventricular involvement in the former; however, it is unknown whether the cause of heart failure has a clinically meaningful effect on outcomes following LVAD implantation. In this systematic review, we aimed to determine whether ischemic versus nonischemic etiology has any impact on patient-relevant outcomes.

Methods: We searched MEDLINE, Embase, PubMed and the Cochrane Library for studies published in English between Jan. 1, 2000, and Nov. 22, 2018, that examined survival and transplantation rates following LVAD implantation in patients with NICM or ICM. Randomized clinical trials, cohort studies, case–control studies, cross-sectional studies and case series with a sample size of at least 8 patients were eligible for inclusion. To be included in the meta-analysis, outcomes had to include at least death reported at 30 days or 1 year after LVAD implantation. Quality of included studies was assessed by 2 independent reviewers using the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) quality-assessment tool was used to assess outcomes (30-d survival, 1-yr survival and cardiac transplantation following LVAD therapy) across studies.

Results: From a total of 2843 citations identified, 7 studies met all inclusion criteria. Studies were generally of good quality, but reporting of patient demographic characteristics, outcomes and complications was heterogeneous. We found no significant difference in 30-day or 1-year survival or in cardiac transplantation rates after device implantation between the NICM and ICM groups. Patients in the 2 groups had similar outcomes up to 1 year with LVAD therapy.

Conclusion: Early outcomes of LVAD therapy do not appear to be affected by heart failure etiology. Ongoing investigation is required to determine the long-term outcomes of LVAD therapy in ICM and NICM.

Systematic review registration: PROSPERO register, record ID 76483.

Contexte : Les professionnels de la santé peuvent être moins enclins à envisager un traitement à long terme par dispositif d’assistance ventriculaire gauche (DAVG) en cas d’insuffisance cardiaque terminale résultant d’une myocardiopathie non ischémique plutôt que d’une myocardiopathie ischémique, en raison du risque potentiellement accru d’atteinte du ventricule droit dans le premier cas. Cependant, on ne sait pas si la cause de l’insuffisance cardiaque a un effet clinique significatif sur les issues après l’implantation d’un DAVG. Dans cette revue systématique, nous avons voulu déterminer si l’étiologie ischémique ou non ischémique a une incidence sur les issues pour les patients.

Méthodes : Nous avons interrogé MEDLINE, Embase, PubMed et la Bibliothèque Cochrane pour trouver les études publiées en anglais entre le 1er janvier 2000 et le 22 novembre 2018 qui examinaient la survie et le taux de greffe après l’implantation d’un DAVG chez les patients atteints d’une insuffisance cardiaque ischémique ou non ischémique. Les essais cliniques randomisés, les études de cohorte, les études cas–témoins, les études transversales et les séries de cas ayant un échantillon d’au moins 8 patients étaient admissibles pour inclusion. Pour qu’une publication soit incluse dans la méta-analyse, les issues à l’étude devaient comprendre au minimum les décès...
The advent of continuous-flow left ventricular assist devices (LVADs), with increased reliability and fewer complications than older-generation pulsatile devices, has led to a rise in the use of LVADs for medically refractory end-stage heart failure (ESHF). Long-term survival data are emerging in the literature as LVADs remain implanted for longer periods, with patients routinely surviving over 5 years with LVAD support. In a multicentre study of 156 patients surviving for at least 4 years on LVAD support, the mean survival duration was 7.1 years, with the majority of patients retaining good function (New York Heart Association Classification class I or II).

Given the increasing utility of LVADs to prolong life in patients with ESHF, a better understanding of factors influencing patient outcomes following LVAD implantation becomes more important. Patients with ESHF as a result of ischemic cardiomyopathy (ICM) may have better long-term clinical outcomes with LVAD therapy than patients with ESHF as a result of nonischemic cardiomyopathy (NICM) owing to a typically greater degree of right ventricular involvement in the latter. On the other hand, patients with NICM are typically younger, with fewer comorbidities. There have been contradictory reports in the literature on outcomes following LVAD implantation in patients with NICM and those with ICM.

The objective of this systematic review was to determine whether there is a difference in survival and rates of patient-relevant complications with LVAD therapy between patients with ESHF as a result of NICM versus ICM.

Methods

This systematic review and meta-analysis followed the guidelines presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. The study protocol is in the PROSPERO register under record ID 76483.

Search strategy

We performed a search of the MEDLINE, Embase, PubMed and Cochrane Library databases. We also conducted a grey literature search using Clinicaltrials.gov. Search results were restricted by date from Jan. 1, 2000, to the date the search was run (Nov. 22, 2018) and to articles published in English. Before 2000, the literature offered clinical data only on older-generation pulsatile LVADs, which were excluded from our study. We searched databases using the following search terms: “cardiomyopathy,” “heart failure,” “systolic dysfunction,” “left ventricular assist device” and “continuous flow,” and their variants.

Study selection

Two reviewers (C.W. and A.S.) independently screened records identified through the search using a 2-stage strategy of an initial title and abstract review, and then a full-text review of pertinent articles identified. Disagreements were resolved through discussion and consultation with a third reviewer (C.Y.). Randomized clinical trials, cohort studies, case–control studies, cross-sectional studies and case series with a sample size of at least 8 patients were eligible for inclusion. Studies included were those that examined clinical outcomes, with mortality as a required inclusion criterion, following LVAD implantation in defined NICM and ICM patient populations. Studies that used pulsatile-flow LVADs, those in pediatric (< 18 yr) populations, and those in acute myocarditis or compaction were excluded.
Data extraction

Two reviewers (C.W. and A.S.) independently extracted the data from included studies using a standardized form. Disagreements were resolved by review by a third reviewer (C.Y.).

To be included in the meta-analysis, outcomes had to include at least death reported at 30 days or 1 year after LVAD implantation. The other commonly reported outcome was whether patients underwent heart transplantation following LVAD therapy or continued with LVAD support as destination therapy.

Where possible, we extracted data on age, gender, certain comorbidities (diabetes, hypertension, chronic renal insufficiency, dialysis, chronic obstructive pulmonary disease, previous stroke or transient ischemic attack, peripheral arterial disease), length of stay in hospital and in the intensive care unit, and certain major complications (major bleeding, right ventricular failure, infection, stroke/transient ischemic attack or readmission to hospital).

Quality assessment

The quality of included studies was assessed by 2 independent reviewers (C.W. and A.S.) using the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies. Author disclosure statements were also examined when available for financial and other conflicts of interest. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) quality-assessment tool was used to assess outcomes (30-d survival, 1-yr survival and cardiac transplantation) following LVAD therapy across studies.

Statistical analysis

All statistical analyses were performed in Stata 14.0 (StataCorp). Heterogeneity, as defined by the $I^2$ statistic, was determined a priori to be above the threshold for pooling at 40%. In addition, studies were pooled only if the reviewers believed them to be clinically similar and did not have concerns with pooling. We summarized pooled data with descriptive statistics, using means and standard deviations with normally distributed data, and medians with interquartile ranges where necessary. When pooling was determined to be appropriate, odds ratios (ORs) and 95% confidence intervals (CIs) were reported. We decided a priori that, owing to the expected clinical heterogeneity in studies, random-effects models would be most appropriate.

Results

Our search strategy identified 2843 citations, of which 7 met the inclusion criteria: 6 full-text manuscripts and 1 conference abstract. Our search and selection strategy is summarized in Figure 1. Agreement between reviewers on which studies to include was fair (Cohen $\kappa = 0.25$). One additional conference abstract was identified upon which studies to include was fair (Cohen $\kappa = 0.25$). One additional conference abstract was identified that met the inclusion criteria; however, the authors did not provide data on mortality after LVAD implantation in a usable format (only the OR was stated), and we were unable to contact the investigators.

Characteristics of the included studies are provided in Table 1. Five studies were conducted at centres in the United States, and 2...
were conducted at Japanese centres.20,21 Six studies were single-centre observational studies or case series, and 1 study was a multicentre study that examined patient records from 31 centres in the US.11 The HeartMate II (Thoratec Corporation) was the most commonly used device (96.4%), with the HeartWare (HeartWare International) (2.4%) and Jarvik 2000 (Jarvik Heart) (1.2%) being more rarely used.11,12,17–21

The demographic characteristics of the patient population included are summarized in Table 2, although reporting of patient demographics was heterogeneous. A total of 674 patients (mean sample size 96, median sample size 33) were enrolled across all included studies. Study sample sizes varied greatly, from 8 patients in a study reporting a single-centre experience with LVAD therapy21 to 468 patients in a study detailing a multicentre prospective cohort trial.11 Patients had their devices implanted between 2003 and 2012.

A summary of the outcomes reported in included studies is provided in Table 3, although this reporting was also heterogeneous. Most studies were retrospective cohorts or case series that were interested primarily in rates of death and of major complications. Only John and colleagues11 reported a prospective cohort study that examined the impact of duration of LVAD support on survival rates after heart transplantation. Most studies reported mortality rates 30 days and 1 year after device implantation or transplantation. Studies typically reported whether patients underwent transplantation and also indicated whether LVAD therapy was being used as bridge-to-transplantation or destination therapy. There did not appear to be any major differences in the proportion of patients who received LVAD support as bridge-to-transplantation or destination therapy between patients with NICM and those with ICM, nor were there major differences in rates of major complications and the average length of intensive care unit and hospital stays between the 2 groups.

### Quality of included studies

All included studies reported data on mortality after LVAD implantation or after implantation following LVAD support. Data included in the meta-analysis were obtained only from studies in which the authors compared mortality rates directly between NICM and ICM patient groups.

Characteristics of the patient population in the included studies tended to be fairly homogeneous. To be considered for LVAD therapy, patients had to have a diagnosis of medically intractable ESHF. Therefore, for cohort studies, we found that patient selection was adequately free of bias, with study participants being representative of the typical population that would require device support. Whether patients belonged to the NICM or ICM group was ascertained through patient records in all studies. Most studies controlled for patient age and sex, the 2 most important demographic factors that could affect study outcomes (older patients generally have worse overall outcomes, and women are at greater risk for cerebrovascular complications after LVAD implantation than men22). In all cases, 30-day mortality or 1-year mortality, or both, was reported for all patients included in the studies.

Study quality as assessed with the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies is shown in Table 4. Although we included the result from Kumar and colleagues17 in our review, it was not possible to complete proper quality assessment on this study because only the abstract was available to us. We therefore excluded this study from the meta-analysis since we could not be confident in its quality.

All included studies with the exception of that of Segura and colleagues19 had a published disclosure statement. In
the study by John and colleagues, which examined posttransplantation survival following LVAD support with HeartMate II devices, 3 of 11 investigators disclosed previous financial support from the manufacturer. In the study by Maltais and colleagues, the principal investigator disclosed previous financial support from the company that manufactures the device used in their study. None of the authors of the other studies reported potential conflicts of interest. It was not possible to determine whether any disclosures were reported by Kumar and colleagues.

**Evidence synthesis**

From data sets obtained from the studies included, we were able to perform a meta-analysis of 30-day \((I^2 = 21\%)\) and 1-year \((I^2 = 38\%)\) survival, as well as likelihood of undergoing transplantation \((I^2 = 4\%)\) for patients with NICM versus ICM. Owing to the heterogeneity in the data presented by each study, only data from 3 studies could be included for each analysis.

We first examined differences in survival after LVAD implantation in patients with NICM versus ICM. Data included in this analysis were from John and colleagues and Tsiouris and colleagues. Despite observing a trend of increased survival in patients with NICM, we did not find significant differences in survival rates between the 2 patient groups 30 days (Fig. 2A) (OR 1.82, 95% CI 0.67–4.97) and 1 year (Fig. 2B) (OR 1.00, 95% CI 0.47–2.12) after LVAD implantation. Interestingly, Kumar and colleagues observed a trend toward increased survival in patients with NICM at both 30 days and 1 year after device implantation, and Tsiouris and colleagues observed a trend toward increased survival in patients with NICM at 1 year. However, John and colleagues observed slightly increased survival in patients with ICM at both 30 days and 1 year after implantation.

In addition, we did not identify any significant differences in risk of transplantation after LVAD implantation between patients with NICM and those with ICM (Fig. 3) (OR 0.47, 95% CI 0.16–1.39). Data included in this analysis were from Tsiouris and colleagues and Yoshioka and colleagues.

### Table 2. Demographic characteristics of patient populations

| Characteristic                              | Nonischemic cardiomyopathy | Ischemic cardiomyopathy |
|--------------------------------------------|----------------------------|-------------------------|
| No. of studies reporting                   | Range across studies, %*   | No. of studies reporting | Range across studies, %* |
| Age, yr                                    | 5                         | 33.5–53.9               | 4                   | 59.5–73       |
| Male sex                                   | 5                         | 25–86                   | 4                   | 0–85          |
| Length of follow-up, d                     | 4                         | 143–426                 | 3                   | 152–414       |

**Comorbidities**

- Diabetes: 2, 8–30, 2, 18–74
- Hypertension: 2, 8–85, 1, 91
- Chronic renal insufficiency: 3, 11–29, 3, 0–70
- Dialysis: 1, 2, 1, 6
- Chronic obstructive pulmonary disease: 1, 12, 1, 32
- Previous stroke/transient ischemic attack: 1, 17, 0, 12
- Peripheral arterial disease: 1, 11, 1
- History of cardiac surgery: 4, 10–14, 3, 43–100
- Creatinine level, mg/dL: 3, 0.8–1.35, 2, 0.8–1.49
- Mechanically ventilated: 1, 3, 1, 9

*Except where noted otherwise.

### Table 3. Outcomes

| Outcome                          | Nonischemic cardiomyopathy | Ischemic cardiomyopathy |
|----------------------------------|----------------------------|-------------------------|
| No. of studies reporting         | Total patients included    | Range across studies    | No. of studies reporting | Total patients included | Range across studies |
| Survival 30 d                    | 6                          | 258, 85–100             | 5                       | 198, 83–100             |
| Survival 6 mo                    | 4                          | 94, 89–100              | 2                       | 35, 85–100              |
| Survival 1 yr                    | 6                          | 258, 64–100             | 5                       | 198, 61–100             |
| Latest reported survival, yr     | 4                          | 171, 1.5–4.4            | 2                       | 108, 1.1–1.7            |
| Underwent transplantation        | 6                          | 258, 11–100             | 5                       | 198, 0–100              |
| Destination therapy              | 5                          | 192, 0–0.89             | 4                       | 164, 0–0.100            |
| Explanted/recovery               | 5                          | 192, 0–0.25             | 4                       | 164, 0–0.0              |
| Length of stay, d                |                            |                         |                         |                         |
| Intensive care unit admission    | 2                          | 73, 5.0–11.5            | 2                       | 35, 3.0–13.0            |
| Hospital admission               | 2                          | 75, 21.3–68.4           | 2                       | 67, 18.0–24.9           |
| Complications                    |                            |                         |                         |                         |
| Major bleeding                   | 2                          | 75, 5–11                | 2                       | 67, 15–64              |
| Right ventricular failure        | 3                          | 82, 11–14               | 1                       | 34, 9                  |
| Infection                        | 3                          | 82, 14–22               | 2                       | 67, 12–24              |
| Stroke/transient ischemic attack  | 3                          | 82, 14–22               | 3                       | 68, 12–24              |
| Readmission                      | 2                          | 73, 26–29               | 1                       | 34, 21                 |

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toward more frequent transplantation in the NICM group, but this was not significant, even in their single study. John and colleagues\textsuperscript{11} specifically examined survival in patients who had undergone LVAD implantation and subsequently transplantation, so all patients in their study underwent transplantation and could not be included in the analysis of differences in transplantation rates.

**DISCUSSION**

Heart transplantation continues to be the gold standard treatment for patients with medically refractory ESHF. However, the availability of donor organs continues to be limited. Furthermore, some patients are deemed ineligible for transplantation. Durable LVAD support
has emerged as a viable strategy for both bridge-to-
transplantation and destination therapy. Despite the pre-
dicted increase in LVAD use, very little is known about
the impact of the cause of heart failure on outcomes fol-
lowing LVAD therapy. Etiology could reasonably be
expected to have a substantial impact on outcomes owing
to the observation that ICM typically affects the left ven-
tricle more significantly, whereas NICM more typically
shows biventricular involvement. Clinicians may there-
fore be somewhat more reluctant to offer long-term
LVAD therapy in patients with NICM. On a cellular
level, the cause of heart failure appears to be important in
cardiomyocyte remodelling. Wever-Pinzon and col-
leagues23 showed significant improvements in left ven-
tricular ejection fraction for both patients with ICM and
those with NICM following LVAD support. However,
only 5% of patients with ICM achieved a left ventricular
ejection fraction greater than 40%, compared to 21% of
patients with NICM.

There are conflicting reports on the impact of the
cause of heart failure on the outcome of LVAD ther-
apy. In a study among 100 patients with ICM or
NICM, mortality rates following device implantation
were not significantly different between the 2 groups.12
In contrast, Kumar and colleagues17 reported that ICM
was an independent predictor of death after LVAD
implantation. The matter is further complicated by
limited duration of follow-up and small samples, which
makes it difficult to determine whether the cause of
ESHF has a significant impact on patient outcomes
following LVAD therapy over a longer period. It is
possible that the subtype of NICM played a role in
some of the inconsistencies that we observed in our
meta-analysis. Neither Tsiouris and colleagues12 nor
John and colleagues11 reported the specific cause in
their NICM cohorts, which made it impossible to
determine whether NICM subtype had any affect on
outcomes.

Following the considerations on evidence quality put
forward by the GRADE Working Group,15 we found no
difference in survival rates between ICM and NICM
30 days and 1 year after LVAD implantation. This
allows us to make a very weak conclusion that the cause
of ESHF does not have a substantial impact on short-
and medium-term survival and cardiac transplantation
rates following LVAD implantation. Table 5 presents a
GRADE evidence profile of the 3 major outcomes exam-
ined in this meta-analysis (30-d survival, 1-yr survival
and cardiac transplantation). Given that patients with
NICM may be expected to have slightly worse outcomes
than those with ICM because of a greater degree of right
ventricular involvement in the former population,7,8 it
was surprising to see no differences in survival at 30 days
or 1 year. If more high-quality data had been available, it
is possible that this prediction would have been borne
out, but it is also possible that any expected survival ben-
efit for patients with ICM who have LVAD support is
offset by the fact that these patients tend to be older and
have more comorbidities.9,10 In addition, although we
did not formally include recovery of left ventricular
function as an outcome in our review, it should be noted
that only 1 of the 7 studies included reported left ven-
tricular recovery.19 In that study, 3 of 12 patients were
reported to have recovery of left ventricular function
device explantation.

Limitations

Our study is limited by a small sample size, differences in
causes of NICM, the older age of the ICM group and an
absence of any randomized controlled trials available to be
included in the analysis. Another major limitation is the
very small number of studies that were usable for our meta-
analysis, owing to limitations in how authors reported their
outcomes in the studies that met the inclusion criteria. As
more and longer-term outcomes following LVAD support
are published, sample sizes for review will increase, which
will help mitigate these limitations with statistical analysis.
In addition, third-generation centrifugal continuous-flow
pumps are beginning to be used clinically, with promising
early results. The recently published MOMENTUM 3 trial showed that the HeartMate III — a magnetically levitated
centrifugal pump — had a higher rate of survival free of
disabling strokes and reoperation or pump removal at 6
months (hazard ratio 0.46, 95% CI 0.31–0.69) and at 2
years, and a lower rate of pump thrombosis than the older
HeartMate II axial flow pumps. However, studies comparing
outcomes in NICM versus ICM with these next-
generation centrifugal-flow LVADs are still pending. Although LVADs may be on track to compete with heart transplantation, we are still far from the equipoise required to conduct a randomized controlled trial in this patient population. It is therefore relevant for future investigators to investigate and report the impact of specific causes of heart failure on patient outcomes over a longer period.

**CONCLUSION**

As LVADs for destination therapy become commonplace,
a more comprehensive understanding of the impact of the
cause of heart failure on patient outcomes following
LVAD therapy over longer periods is necessary to inform
decision-making. Although our findings suggest that there are no differences in short- or medium-term outcomes after LVAD therapy in patients with ICM versus NICM, the paucity of data beyond 1 year highlights the need for studies examining long-term patient outcomes following LVAD therapy.

### Table 5. Grading of Recommendations Assessment, Development and Evaluation (GRADE) evidence profile for use of left ventricular assist device therapy in patients with end-stage heart failure resulting from ischemic or nonischemic cardiomyopathy

| Outcome, no. of studies (no. of participants) | Quality assessment | Publication bias | Best estimate of ICM group rate, % | Best estimate of NICM group rate, % | Summary of findings | Quality |
|-----------------------------------------------|---------------------|-----------------|-----------------------------------|-----------------------------------|---------------------|---------|
| 30-d survival                                 |                     |                 |                                   |                                   |                     |         |
| 2 (350)                                        | Serious limitations | Explainable heterogeneity | Direct | Imprecision | Unlikely | 1.82 (0.67–4.97) | 79.6 | 88.9 | Very low |
| 1-yr survival                                 |                     |                 |                                   |                                   |                     |         |
| 2 (350)                                        | Serious limitations | Explainable heterogeneity | Direct | Imprecision | Unlikely | 1.00 (0.47–2.12) | 72.5 | 72.7 | Very low |
| Transplantation                               |                     |                 |                                   |                                   |                     |         |
| 2 (108)                                       | Serious limitations | Explainable heterogeneity | Direct | Imprecision | Unlikely | 0.47 (0.16–1.39) | 20.0 | 37.0 | Very low |

CI = confidence interval; ICM = ischemic cardiomyopathy; NICM = nonischemic cardiomyopathy; OR = odds ratio.
*Observational studies only (randomized controlled trials unavailable).
†One study examined outcomes following cardiac transplantation only; another used a different continuous-flow left ventricular assist device model from that used in the other studies.
‡Confidence interval includes possible survival advantage from use of left ventricular assist device in both patient groups.

**Affiliations:** From the Division of Cardiac Surgery, Department of Surgery, Schulich School of Medicine and Dentistry, Western University, London, Ont. (Wavell, Sokolowski, Yin); The Hospital for Sick Children, Toronto, Ont. (Klingel); Department of Microbiology and Immunology, Schulich School of Medicine and Dentistry, Western University, London, Ont. (Yin); and the Division of Critical Care Medicine, Department of Medicine, Schulich School of Medicine and Dentistry, Western University, London, Ont. (Nagpal).

**Competing interests:** None declared.

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