JACC: HEART FAILURE
VOL. 4, NO. 10, 2016

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2016.05.003

Implantable Cardioverter-Defibrillator Use in Patients With Left Ventricular Assist Devices

A Systematic Review and Meta-Analysis

Kairav Vakil, MD,[a,b] Felipe Kazmirczak, MD,[b] Neeraj Sathnur, MD,[b] Selcuk Adabag, MD, MS,[a,b] Daniel J. Cantillon, MD,[c] Erich L. Kiehl, MD,[c] Ryan Koene, MD,[b] Rebecca Cogswell, MD,[b] Inderjit Anand, MD, DPHIL (OXON),[d] Henri Roukoz, MD[b]

ABSTRACT

OBJECTIVES This study evaluated the impact of implantable cardioverter-defibrillators (ICDs) on mortality in patients with left ventricular assist devices (LVADs) by conducting a systematic review and meta-analysis of published studies.

BACKGROUND The burden of ventricular arrhythmias in patients with LVADs is high. Prior studies assessing the impact of ICD on survival of patients with LVADs have yielded conflicting results.

METHODS Relevant studies from January 2000 through October 2015 were identified in the databases PubMed and OVID. Weighted relative risks were estimated using random effects meta-analysis techniques.

RESULTS Six observational studies (n = 937) were included. Patients were 53 ± 12 years of age, and 80% were male. Bridge-to-transplantation was the indication for LVAD use in 93% of the patients. A continuous-flow (CF) LVAD was present in 39% of patients. Mean left ventricular ejection fraction was 16 ± 6%. An ICD was present in 355 patients (38%). During a mean follow-up of 7 months, 241 patients (26%) died (16% in the ICD group vs. 32% in the no-ICD group). Presence of an ICD was associated with a 39% relative risk reduction in all-cause mortality (RR: 0.61; 95% confidence interval [CI]: 0.46 to 0.82; $p < 0.01$). Among subgroup of patients with CF-LVAD (n = 361), ICD use was associated with a statistically nonsignificant trend toward improved survival (RR: 0.76; 95% CI: 0.51 to 1.12; $p = 0.17$).

CONCLUSIONS ICD use was associated with a significant reduction in mortality in LVAD patients, however, this effect was not significant in patients with CF-LVADs. Although these data support the use of ICDs, larger randomized trial data are strongly warranted to evaluate ICD effectiveness in patients with current generation LVADs.
(J Am Coll Cardiol HF 2016;4:772–9) © 2016 by the American College of Cardiology Foundation.

Permanently implantable left ventricular assist devices (LVADs) significantly improve survival in patients with end-stage heart failure who are either awaiting or are ineligible for cardiac transplantation (1–3). Despite the increasing use of LVADs and the advancing device technology (4), the estimated actuarial survival in LVAD-supported patients ranges from 56% to 87% at 1 year, and ~47% at 4 years (5). Device thrombosis, sustained ventricular arrhythmias, driveline infections, neurologic events, and right ventricular failure are the most important risk factors for mortality in these patients (5,6).

Although ventricular arrhythmias are common and frequently associated with increased mortality in patients with LVADs (7), it is suggested that sudden cardiac death is an uncommon mode of death in these

From the [a]Division of Cardiology, Veterans Affairs Medical Center, Minneapolis, Minnesota; [b]Division of Cardiology, University of Minnesota, Minneapolis, Minnesota; [c]Division of Cardiology, Cleveland Clinic Foundation, Cleveland, Ohio; and the [d]Division of Cardiology, Veterans Affairs Medical Center, San Diego, California. Dr. Cantillon is a consultant for and has received grants from St. Jude Medical and Boston Scientific. Dr. Vakil has received a grant from Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Vakil and Kazmirczak contributed equally to this work.

Manuscript received April 12, 2016; revised manuscript received May 2, 2016, accepted May 5, 2016.

patients. In previous studies, patients with LVADs have been reported to survive for days to months despite being in rapid ventricular arrhythmias (8–11). As such, it is postulated that mortality in these patients with ventricular arrhythmias is primarily related to right heart failure and renal dysfunction. Hence, the benefit of implantable cardioverter-defibrillators (ICDs) in patients with LVADs has remained unclear.

SEE PAGE 780

Although prior observational studies have reported a high burden of appropriate and inappropriate ICD therapies, data for the effect of ICD on survival of patients with LVADs have been conflicting (12–17). The aim of this study was to assess the impact of ICD on survival of patients with LVADs through a comprehensive systematic review and meta-analysis of published studies.

METHODS

DATA SOURCES AND SEARCH STRATEGY. We searched PubMed and OVID for studies published from January 2000 through October 2015, using the medical subject heading terms "implantable cardioverter-defibrillator or ICD," "ventricular assist device or VAD," "left ventricular assist device or LVAD," "mortality," and "outcomes." We limited our search to studies published in English and those involving humans only. We also searched the ClinicalTrials.gov website and the reference list of relevant articles and used the Science Citation Index to cross-reference any articles that met our selection criteria. The methodology used in this study was previously used and validated (18–20).

STUDY SELECTION. To be eligible, studies had to fulfill the following inclusion criteria: 1) they were randomized controlled trials or observational studies; 2) they compared LVAD-supported patients with ICDs to those without ICDs; 3) they reported information for all-cause mortality for both ICD and no-ICD groups; and 4) they reported the estimate of relative risk (RR) with 95% confidence interval (CI), or different measures of RR such as hazard ratio or odds ratio, or they provided data such that RR could be calculated. Presence of biventricular assist devices (BIVAD) or right ventricular assist device (RVAD) alone was acceptable. Studies with fewer than 20 patients and abstracts were excluded. The final inclusion consisted of 6 studies (12–17). Our search strategy is shown in **Figure 1**.

DATA EXTRACTION. Two reviewers (F.K. and N.S.) independently examined the study titles, abstracts, and full-length articles identified by the described search strategy to determine study inclusion and exclusion. These reviewers also independently abstracted the study characteristics, patient characteristics, design, methods, and relevant outcomes. Discrepancies between the reviewers were infrequent and were resolved by consensus or consultation with a third reviewer (K.V.).

QUALITY OF STUDIES IN ANALYSIS. Assessment of bias was conducted as described by Downs and Black (21), with 2 independent reviewers (F.K. and N.S.) assessing the studies. High, medium, and low risks of bias in reporting, external validity, internal validity bias, internal validity-confounding, and power were quantified as previously described (22). A funnel plot was constructed to assess publication bias.

PATIENT GROUPS AND OUTCOMES. Patients who had an ICD at the time of LVAD implantation and those who received an ICD after LVAD implantation were included in the ICD group. Patients who did not have an ICD and those who had the ICD inactivated after LVAD implantation were included in the no-ICD group. Primary outcome was all-cause mortality. Secondary outcome, which was reported by only 5 of the 6 studies (except for Enriquez et al. [14]), was the incidence of blood stream or device-related infections.

STATISTICAL ANALYSIS. Continuous variables are mean ± SD and were accumulated using single-arm continuous variable random effects meta-analysis. Categorical variables are percentages and accumulated using standard weighted proportions. Baseline variables were compared using *t* test for means and *z* test for proportions. RR and 95% CI were calculated by creating contingency tables. The natural logarithms of the study-specific RR and CI from individual studies were combined using random-effects meta-analytic model (23). Given that the study by Cantillon et al. (13) contributed nearly one-half the patients to the meta-analysis and had a significant proportion of patients with BIVADs, sensitivity analysis for primary outcome was performed for the remaining 5 studies after excluding the study by Cantillon et al. (13).

Subgroup analysis was also performed to assess the impact of ICDs on mortality in patients with continuous flow (CF)-LVADs. Four of the 6 studies included only patients with CF-LVADs (12,14–16); the study by Refaat et al. (17) included only patients with pulsatile flow (PF)-LVADs, whereas Cantillon et al. (13) included patients with both CF- and PF-LVADs. To facilitate such subgroup analysis, the primary author for the study from the Cleveland Clinic Foundation

ABBREVIATIONS AND ACRONYMS

BIVAD = biventricular assist device

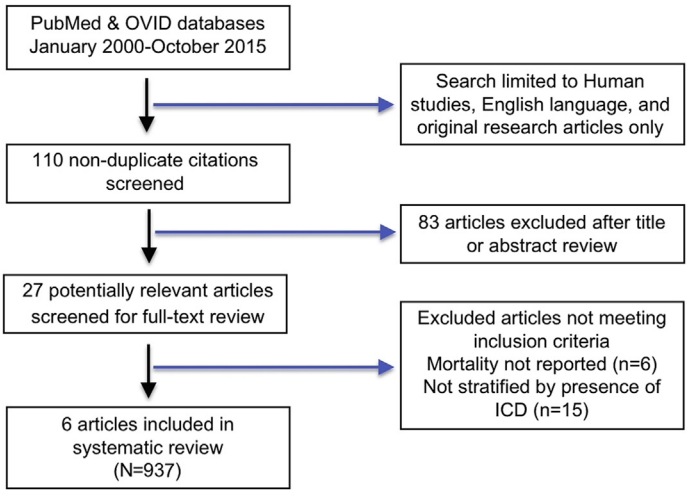
ICD = implantable cardioverter-defibrillator

LVAD = left ventricular assist device

RR = relative risk

RVAD = right ventricular assist device

FIGURE 1 Studies Included in the Review



Selection of clinical studies included in the systematic review and meta-analysis.

(D.C.) provided de-identified mortality data stratified by ICD use for CF-LVAD patients alone (n = 46) from their cohort of 478 patients. All tests were 2-tailed, and a p value of <0.05 was considered significant. Analyses were performed by using Stata version 10.1 software (Stata Corp., College Station, Texas). This study was exempt from Institutional Review Board approval.

RESULTS

INCLUDED STUDIES. A total of 6 studies reporting data for 937 patients (range: 23 to 478 patients) were included in the analysis (**Table 1**). All studies were observational and were published between 2009 and 2015. One study was conducted in Europe (12), 4 in the United States (13-15,17), and 1 in Australia (16). Characteristics of each study, including design, follow-up, and quality, are shown in **Table 1**. Risk of bias assessment for each individual study is illustrated in **Figure 2**. A funnel plot illustrating publication bias is shown in **Figure 3**.

PATIENT CHARACTERISTICS. Overall, patients were 53 ± 12 years of age, and a majority (80%) were male (**Table 2**). All patients (except for 39 patients with RVAD alone in the study by Cantillon et al. [13]) had an LVAD. Patients with RVAD alone comprised 4% of the entire cohort, whereas 17% patients had BIVADs. A total of 361 patients (39%) had a CF-LVAD. Bridge-to-cardiac transplantation was the indication for LVAD placement in 870 patients (93%). Mean LV ejection fraction (LVEF) and LV end-diastolic dimension were 16 ± 6% and 6.8 ± 1.2 cm, respectively. A significant proportion of patients were taking beta-blockers (59%), angiotensin-converting enzyme (ACE) inhibitors (65%), and aldosterone receptor antagonists (44%). Clinical characteristics of patients included in each individual study are shown in Online Table 1.

An ICD was present in 355 patients (38%). **Table 2** shows the pooled clinical characteristics of the patients with an ICD vs. those without an ICD. Patients in the ICD group were more often male and had a higher incidence of diabetes but a lower incidence of ischemic cardiomyopathy. Those patients were more likely to be taking beta-blockers and aldosterone receptor antagonists.

ICD USE AND OUTCOMES. A total of 241 patients (26%) died during a mean follow-up of 7 months, consisting of 16% (57 of 355 patients) in the ICD group and 32% (184 of 582) in the no-ICD group. Thus, use of an ICD was associated with a 16% absolute risk reduction and a 39% relative risk reduction (RR: 0.61; 95% CI: 0.46 to 0.82; p < 0.01) in all-cause mortality (**Figure 4**). Approximately 6 patients (95% CI: 4.8 to 9.9) needed to be treated with an ICD for an average of 7 months to prevent 1 death. The effect of ICDs on mortality was unchanged on sensitivity analyses after excluding the study by Cantillon et al. (13) (RR: 0.61; 95% CI: 0.41 to 0.89; p = 0.011) that contributed nearly one-half of the patients (n = 478) in this systematic review.

Five studies (except for that by Enriquez et al. [14]) provided information on secondary outcome (i.e., data on infection was available for 839 of the 937 patients). The incidence of infection was significantly lower in patients with ICDs (18 of 293 patients) than in patients without an ICD (96 of 546 patients), 6% vs. 18% (p <0.01).

SUBGROUP ANALYSIS OF PATIENTS WITH CF-LVADs. Of the total 937 patients, 361 patients (39%) had a CF-LVAD. In this subgroup, an ICD was present in 245 patients (68%), whereas 116 patients (32%) did not have an ICD. Mortality in the ICD group was 14% compared to 25% in the no-ICD group. Thus, use of an ICD was associated with an 11% absolute risk reduction and a 24% relative risk reduction (RR: 0.76; 95% CI: 0.51 to 1.12; p = 0.17) in mortality in the CF-LVAD subgroup (**Figure 5**), however, this trend towards improved survival with ICD use was not statistically significant.

DISCUSSION

Results of this meta-analysis highlight several important findings. First, use of ICDs in this cohort of patients with end-stage heart failure and LVAD

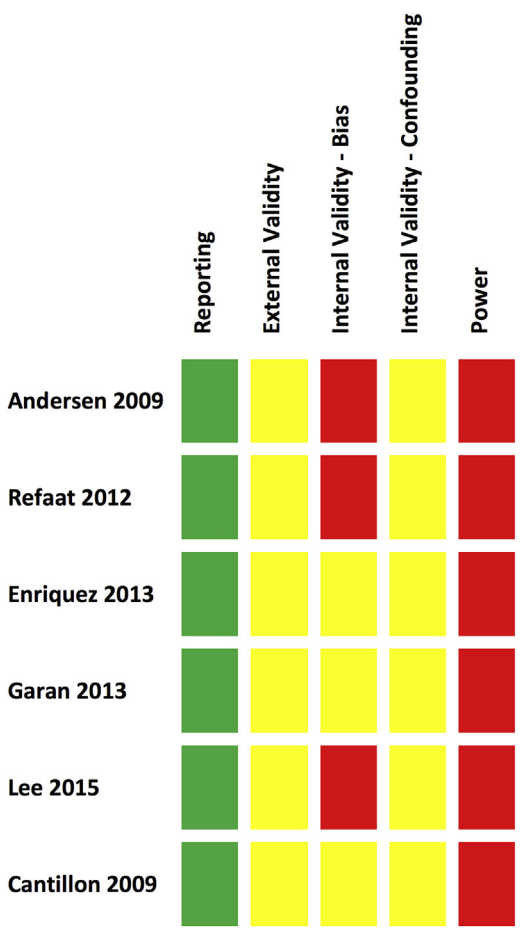
TABLE 1 Clinical Studies of ICD vs. No ICD in LVAD Patients

First Author (Ref. #)	Patient Enrollment Years	Publication Year	n	Participants	Design	Mean Follow-Up
Andersen et al. (12)	2006–2008	2009	23	CF-LVAD only	Retrospective observational	9 months
Refaat et al. (17)	1996–2003	2012	144	PF-LVAD plus BIVAD	Retrospective observational	12 months
Enriquez et al. (14)	2008–2012	2013	98	CF-LVAD plus BIVAD	Retrospective observational	7 months
Garan et al. (15)	2012	2013	94	CF-LVAD only	Retrospective observational	13 months
Lee et al. (16)	2004–2013	2015	100	CF-LVAD plus BIVAD	Retrospective observational	12 months
Cantillon et al. (13)	1991–2008	2009	478	CF-LVAD plus PF-LVAD plus BIVAD plus RVAD	Retrospective observational	3 months

BIVAD = biventricular assist device; CF = continuous flow; ICD = implantable cardioverter-defibrillator; LVAD = left ventricular assist device; PF = pulsatile flow; RVAD = right ventricular assist device.

implantation was relatively low at 38%. This may be related to inclusion of a larger number of patients from the study by Cantillon et al. (13), who were enrolled before ICD implantation guidelines were available. Second, ICD use was associated with a 39% relative reduction in mortality in patients with LVADs. However, when the analysis was limited to patients with CF-LVADs only, the trend toward improved survival with ICD use did not reach statistical significance. Finally, the rate of blood stream or device-related infections was lower in the ICD group than in the no-ICD group. Given the lack of patient-level data reasons for such a finding are unclear but may reflect a selection bias of not implanting ICDs in patients thought to be at a relatively higher risk for infections.

FIGURE 2 Risk of Bias Assessment

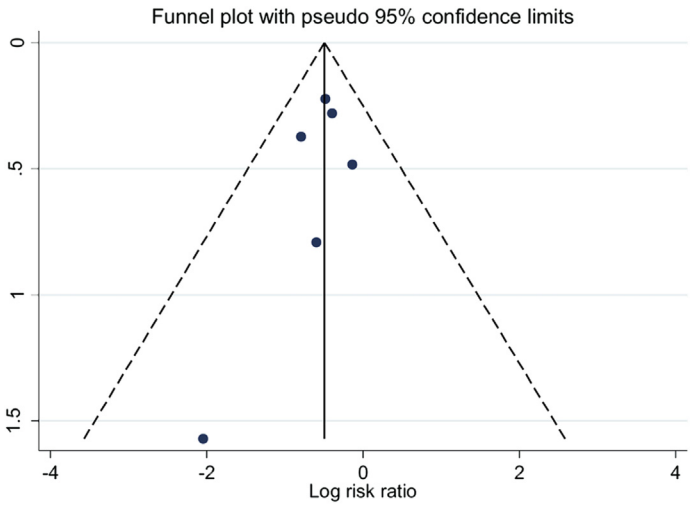


Green indicates low-risk of bias; **yellow** indicates medium-risk of bias; and **red** indicates high-risk of bias.

The evidence supporting ICD use in patients with LVADs is limited to a few, relatively small studies. Current practice guidelines supporting ICD use in LVAD patients are therefore predominantly based on expert consensus and observational studies (24). To the best of our knowledge, this is the first comprehensive systematic review in an area that currently lacks prospective cohort studies or randomized trials. Although the overall results from this meta-analysis support ICD use in VAD patients, the beneficial effect of ICDs lost statistical significance when the analysis was limited to only CF-LVAD patients, despite an 11% absolute risk reduction in mortality noted in the ICD arm. While the reasons for this are not immediately clear, one could speculate that a significantly smaller sample size might have caused the RR to cross the line of identity in this subgroup. To the contrary, given that outcomes and hemodynamic stability with CF-LVADs are significantly better than with older PF-LVADs, ICDs may not offer survival benefit to CF-LVAD patients. Based on these findings, however, we believe that ICDs should continue to be used in patients with CF-LVADs until further randomized clinical trial data become available.

The reported prevalence of ventricular arrhythmias after LVAD implantation has been shown to range from 22% to 59% and depends on several

FIGURE 3 Funnel Plot for Assessment of Publication Bias



Each **dot** represents a study; the y-axis represents the size of the study, and the x-axis shows the study results.

factors such as the presence of ventricular arrhythmias prior to LVAD implant, LVAD type, and presence of ischemic heart disease (25). Although the burden of ventricular arrhythmias is the highest in the first 30 days following LVAD implantation (12,26,27), late ventricular arrhythmias have also been reported (15). Although ventricular arrhythmias commonly lead to sudden cardiac death in non-LVAD patients, patients with LVADs have been reported to survive for prolonged periods of time while being in sustained ventricular arrhythmias (8–11). Despite that, several studies have reported a higher mortality in LVAD patients who have ventricular arrhythmias. In a study by Bedi et al. (7), a 15% higher absolute risk of mortality was observed in patients with ventricular arrhythmias, with overall mortality being highest among those who developed arrhythmias within 1 week of LVAD implantation. In another study, Brenyo et al. (28) found a nearly 10-fold increase in mortality in LVAD patients who had ventricular arrhythmias compared to those who did not. Interestingly, the median time from first ventricular arrhythmia event to death in that study was ~1 year, suggesting that causality between arrhythmic events and mortality may be difficult to prove; and ventricular arrhythmias may be a marker of overall clinical deterioration rather than the cause of death (25).

Furthermore, in a study of 94 patients, Garan et al. (15) reported that ICDs in CF-LVAD patients appeared to be beneficial only in those who had ventricular arrhythmias prior to LVAD implantation. The authors asserted it might be reasonable to not implant ICDs in those LVAD patients who did not have a history of ventricular arrhythmias. However, Ziv et al. (27), in a retrospective study of 91 patients, showed that 28 patients (31%) without pre-LVAD ventricular arrhythmias developed de novo ventricular arrhythmias after LVAD implantation. Unfortunately, the absence of patient-level data limits our ability to differentiate between the utility of ICDs among those

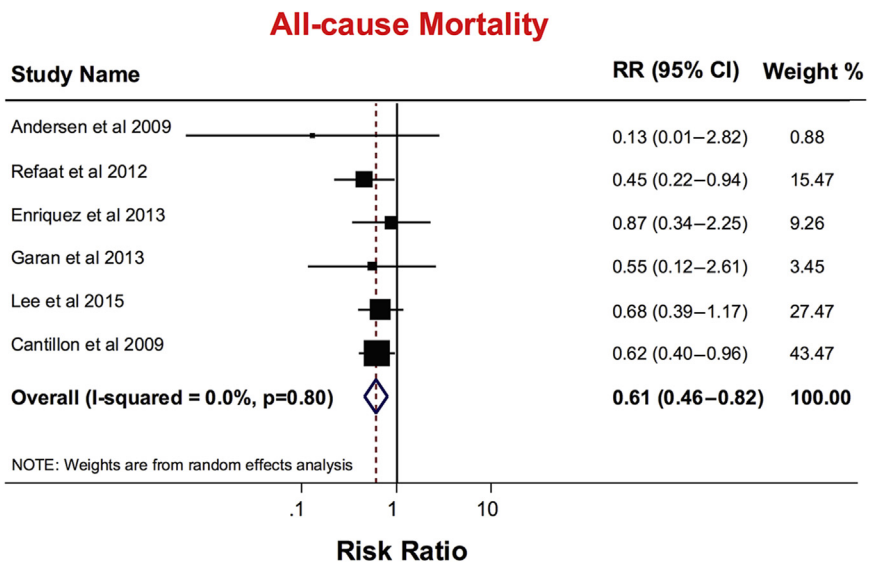
TABLE 2 Pooled Clinical Characteristics of the Entire Cohort Stratified by the Presence of an ICD*

	Number of Data Available (n Studies)† (N = 937)	ICD Group Weighted Mean or Frequency (n Patients) (n = 355)	No ICD Group Weighted Mean or Frequency (n Patients) (n = 582)	p Value‡
Mean age, yrs	914 (5)	56 ± 11 (338)	53 ± 12 (576)	0.12
Males	816 (4)	86% (238/276)	77% (416/540)	0.002
Diabetes mellitus	722 (3)	12% (24/199)	7% (39/523)	0.049
Ischemic cardiomyopathy	914 (5)	43% (144/338)	58% (336/576)	<0.001
LVEF, %	816 (4)	16.4 ± 5.3 (276)	15.5 ± 0.5 (540)	0.092
LVEDD, cm	436 (4)	7.1 ± 0.9 (248)	6.3 ± 1.2 (188)	<0.001
Beta-blockers	816 (4)	67% (184/276)	54% (290/540)	<0.001
ACE inhibitors	722 (3)	70% (139/199)	66% (344/523)	0.28
Aldosterone antagonist	722 (3)	51% (102/199)	42% (222/523)	0.03
Antiarrhythmic therapy	816 (4)	40% (111/276)	37% (202/540)	0.64
CF-LVAD	937 (6)	69% (245/355)	20% (116/582)	<0.001
BIVAD	816 (4)	9% (25/276)	13% (68/540)	0.14
Creatinine, mg/dl	244 (2)	1.4 ± 0.6 (109)	1.3 ± 0.5 (135)	0.09

Values are n (%), mean ± SD (N), or % (n/N). *Study by Andersen et al. (12) (n = 23) did not stratify clinical characteristics of patients based on the presence of an ICD. †Number of studies providing the mentioned clinical variable. ‡p value of *t* test or *z* test, as appropriate, comparing the ICD patient group to the no ICD patient group.

ACE = angiotensin-converting enzyme; BIVAD = biventricular assist device; ICD = implantable cardioverter-defibrillator; LVEDD = left ventricular end diastolic dimension; LVEF = left ventricular ejection fraction.

FIGURE 4 Forest Plot and Pooled Analysis

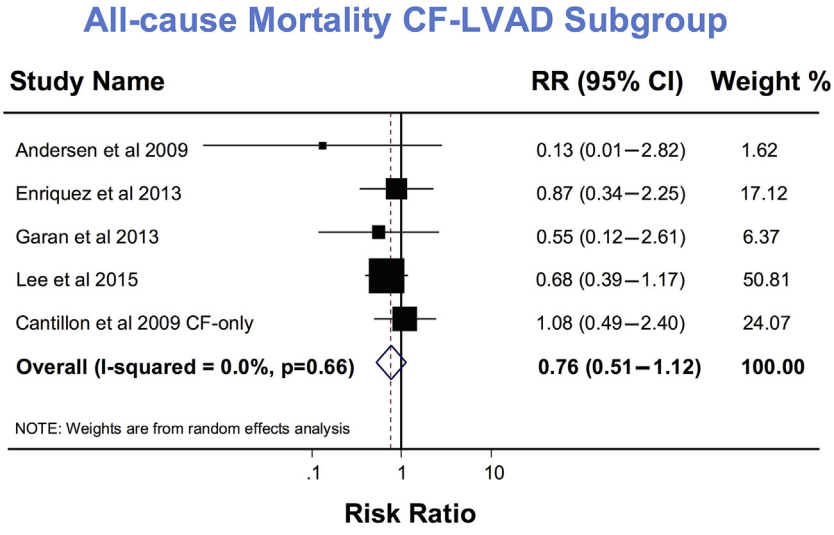


Forest plot and pooled analysis for all-cause mortality (N = 937). RR = relative risk; CI = confidence interval.

who had pre-implant ventricular arrhythmias and those who did not.

The study by Cantillon et al. (13) contributed the largest number of patients to this systematic review (n = 478) and also included 84 patients with BIVADs and 36 patients with RVAD alone. Patients in this study were enrolled over 2 decades (1991 to 2008) and had a much lower prevalence of ICD use and a significantly worse overall survival than those in the other studies, perhaps due to the use of

FIGURE 5 Forest Plot and Pooled Analysis for All-Cause Mortality



Forest plot and pooled analysis for all-cause mortality in CF-LVAD patients (N = 361). Data for mortality for CF-LVAD subgroup patients stratified by ICD use was obtained from personal communication (D.C., Cleveland Clinic Foundation). CF-LVAD = continuous-flow left ventricular assist device; ICD = implantable cardioverter-defibrillator; other abbreviations are shown in Figure 4.

predominantly older generation PF-LVADs. When sensitivity analyses were performed after excluding that study, the prevalence of ICD use increased from 38% to 58%. Importantly, the beneficial effect of ICDs on mortality persisted even after excluding this study.

STUDY LIMITATIONS. First, all included studies reported retrospective observational data, which are subject to bias. Particularly, we cannot exclude the possibility of selection bias when clinicians made decisions about ICD implantation. Second, this cohort was enriched with patients (93%) who received an LVAD as bridge-to-transplantation. As such, these results cannot be generalized to patients receiving destination therapy LVADs, who are known to be relatively sicker than those awaiting transplantation. Third, information on the burden of ventricular arrhythmias and its relationship to timing of LVAD implantation, ICD therapies, and ICD programming was unavailable and cannot be accounted for. Fourth, given the lack of patient level data, we could not exclude all patients with BIVADs (17%) and RVADs (4%). However, in the subgroup analysis of CF-LVAD only patients (**Figure 5**), the percentage of patients with BIVADs drops to 4%, and those with RVADs drops to 0%. Fifth, the cause of death (sudden vs. nonsudden) could not be ascertained.

CONCLUSIONS

ICD use is associated with a significant reduction in all-cause mortality in LVAD patients and has a nonsignificant trend toward improved survival in patients with CF-LVADs. These findings support and strengthen the current guideline recommendations regarding the use of ICDs in LVAD patients. Randomized trial data are strongly warranted that can address the utility, optimal device programming, and timing of ICD implantation in the current generation CF-LVAD patients with and without ventricular arrhythmias.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Kairav Vakil, Division of Cardiology, Department of Medicine, Veterans Affairs Medical Center and University of Minnesota, 111C, One Veterans Drive, Minneapolis, Minnesota 55417. E-mail: vakil012@umn.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Results from this meta-analysis are the largest to date highlighting the importance of ICD use in patients with LVADs and suggest that ICD use may be associated with improved survival in this population. Given that LVADs provide strong hemodynamic support, sudden death is a rare in these patients. Although the mechanism of survival benefit from ICDs in LVAD patients remains unclear, one could speculate that the beneficial effects may be related to reduction in deleterious effects of ventricular arrhythmias on right ventricular function, thereby leading to reduction of heart failure deaths as opposed to sudden death. Further, although the current analysis may be underpowered to examine the effectiveness of ICDs in CF-LVAD patients, there was still a nonsignificant trend toward improved survival and an 11% absolute reduction in mortality in this subgroup suggesting that ICDs may be beneficial in patients with the newer generation CF-LVADs as well.

TRANSLATIONAL OUTLOOK: Despite the improved outcomes of patients with mechanical circulatory support systems over the last decade, survival for patients with LVADs is relatively poor. Whether ICDs improve survival in patients with LVADs has been a matter of controversy. Although the findings from the current systematic review favor the use of ICDs in patients with LVADs, randomized control clinical trials addressing this very important question are strongly warranted to improve future patient outcomes. It would be ideal for future randomized studies to examine the utility and timing of ICD implantation in patients with newer generation CF-LVADs when used for both, bridge-to-transplantation and destination therapy.

REFERENCES

1. Jorde UP, Kushwaha SS, Tatooles AJ, et al. Results of the destination therapy post-food and drug administration approval study with a continuous flow left ventricular assist device: a prospective study using the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support). J Am Coll Cardiol 2014;63:1751–7.

2. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med 2001;345:1435–43.

3. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241–51.

4. Kirklin JK, Naftel DC, Kormos RL, et al. Fifth INTERMACS annual report: risk factor analysis from more than 6,000 mechanical circulatory support patients. J Heart Lung Transplant 2013;32:141–56.

5. McIlvennan CK, Magid KH, Ambardekar AV, Thompson JS, Matlock DD, Allen LA. Clinical outcomes after continuous-flow left ventricular assist device: a systematic review. Circ Heart Fail 2014;7:1003–13.

6. Mancini D, Colombo PC. Left ventricular assist devices: a rapidly evolving alternative

to transplant. J Am Coll Cardiol 2015;65:2542–55.

7. Bedi M, Kormos R, Winowich S, McNamara DM, Mathier MA, Murali S. Ventricular arrhythmias during left ventricular assist device support. Am J Cardiol 2007;99:1151–3.

8. Fasseas P, Kutalek SP, Kantharia BK. Prolonged sustained ventricular fibrillation without loss of consciousness in patients supported by a left ventricular assist device. Cardiology 2002;97:210–3.

9. Oz MC, Rose EA, Slater J, Kuiper JJ, Catanese KA, Levin HR. Malignant ventricular arrhythmias are well tolerated in patients receiving long-term left ventricular assist devices. J Am Coll Cardiol 1994;24:1688–91.

10. Salzberg SP, Lachat ML, Zund G, Turina MI. Left ventricular assist device (LVAD) enables survival during 7 h of sustained ventricular fibrillation. Eur J Cardiothorac Surg 2004;26:444–6.

11. Sims DB, Rosner G, Uriel N, Gonzalez-Costello J, Ehlert FA, Jorde UP. Twelve hours of sustained ventricular fibrillation supported by a continuous-flow left ventricular assist device. Pacing Clin Electrophysiol 2012;35:e144–8.

12. Andersen M, Videbaek R, Boesgaard S, Sander K, Hansen PB, Gustafsson F. Incidence of ventricular arrhythmias in patients on long-term support with a continuous-flow assist device (HeartMate II). J Heart Lung Transplant 2009;28:733–5.

13. Cantillon DJ, Tarakji KG, Kumbhani DJ, Smedira NG, Starling RC, Wilkoff BL. Improved survival among ventricular assist device recipients with a concomitant implantable cardioverter-defibrillator. Heart Rhythm 2010;7:466–71.

14. Enriquez AD, Calenda B, Miller MA, Anyanwu AC, Pinney SP. The role of implantable cardioverter-defibrillators in patients with continuous flow left ventricular assist devices. Circ Arrhythm Electrophysiol 2013;6:668–74.

15. Garan AR, Yuzefpolskaya M, Colombo PC, et al. Ventricular arrhythmias and implantable cardioverter-defibrillator therapy in patients with continuous-flow left ventricular assist devices: need for primary prevention? J Am Coll Cardiol 2013;61:2542–50.

16. Lee W, Tay A, Subbiah RN, et al. Impact of implantable cardioverter defibrillators on survival of patients with centrifugal left ventricular assist devices. Pacing Clin Electrophysiol 2015;38:925–33.

17. Refaat MM, Tanaka T, Kormos RL, et al. Survival benefit of implantable cardioverter-defibrillators in left ventricular assist device-supported heart failure patients. J Cardiac Fail 2012;18:140–5.

18. Vakil K, Roukoz H, Sarraf M, et al. Safety and efficacy of the MitraClip system for severe mitral regurgitation: a systematic review. Catheter Cardiovasc Interv 2014;84:129–36.

19. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS 2009;6:e1000097.

20. Adabag S, Roukoz H, Anand IS, Moss AJ. Cardiac resynchronization therapy in patients with minimal heart failure: a systematic review and meta-analysis. J Am Coll Cardiol 2011;58:935–41.

21. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of epidemiology and community health 1998;52:377–84.

22. Galvagno SM Jr., Thomas S, Stephens C, et al. Helicopter emergency medical services for adults with major trauma. Cochrane Database Syst Rev 2013;3:CD009228.

23. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

24. Feldman D, Pamboukian SV, Teuteberg JJ, et al. The 2013 International Society for Heart and Lung Transplantation guidelines for mechanical circulatory support: executive summary. J Heart Lung Transplant 2013;32:157–87.

25. Nakahara S, Chien C, Gelow J, et al. Ventricular arrhythmias after left ventricular assist device. Circ Arrhythm Electrophysiol 2013;6:648–54.

26. Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. N Engl J Med 2007;357:885–96.

27. Ziv O, Dizon J, Thosani A, Naka Y, Magnano AR, Garan H. Effects of left ventricular assist device therapy on ventricular arrhythmias. J Am Coll Cardiol 2005;45:1428–34.

28. Brenyo A, Rao M, Koneru S, et al. Risk of mortality for ventricular arrhythmia in ambulatory LVAD patients. J Cardiovasc Electrophysiol 2012;23:515–20.

KEY WORDS implantable cardioverter-defibrillator, left ventricular assist device, mortality, systematic review, meta-analysis

APPENDIX For a supplemental table, please see the online version of this article.