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Active Implantable cardioverter-defibrillators in Continuous-flow Left Ventricular Assist Device Recipients

Electrophysiology Collaborative Consortium for Metaanalysis – ELECTRAM Investigators

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Abstract

Introduction: Implantable cardioverter-defibrillator (ICD) in patients with heart failure with reduced ejection fraction reduces mortality secondary to malignant arrhythmias. Whether end-stage heart failure (HF) with continuous-flow left ventricular assist device (cf-LVAD) derive similar benefits remains controversial.

Methods: We performed a systematic literature review and meta-analysis of all published studies that examined the association between active ICDs and survival in advanced HF patients with cf LVAD. We searched PubMed, Medline, Embase, Ovid, and Cochrane for studies reporting the association between ICD and all-cause mortality in advanced HF patients with cfLVAD. Mantel-Haenszel risk ratio (RR) random-effects model was used to summarize data.

Results: Ten studies (9 retrospective and one prospective) with a total of 7,091 patients met inclusion criteria. There was no difference in all-cause mortality (RR 0.84, 95% CI 0.65–1.10, p=0.20, I^2=62.40%), likelihood of survival to transplant (RR 1.07, 95% CI 0.98–1.17, p= 0.13, I^2 =0%), RV failure (RR 0.74, 95% CI 0.44–1.25, p = 0.26, I^2=34%) between Active ICD and inactive/no ICD groups, respectively. Additionally, 27.5% received appropriate ICD shocks, while 9.5% received inappropriate ICD shocks. No significant difference was observed in terms of any complications between the two groups.

Conclusion: All-cause mortality, the likelihood of survival to transplant, and worsening RV failure were not significantly different between active ICD and inactive/no ICD in cf-LVAD recipients. A substantial number of patients received appropriate ICD shocks suggesting a high-arrhythmia burden. The risks and benefits of ICDs must be carefully considered in patients with cf-LVAD.

Key Words

Implantable Cardioverter-Defibrillator, Continuous-Flow LVAD, Mortality

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Introduction

Continuous flow left ventricular assist devices (cf-LVAD) are being increasingly utilized in patients with end-stage heart failure (on guideline-directed medical therapy) as a bridge to transplant or destination therapy, with improved overall survival[1,2]. Similarly, implantable cardioverter-defibrillator (ICD) is indicated in heart failure patients (New York Heart Association functional class I, II,

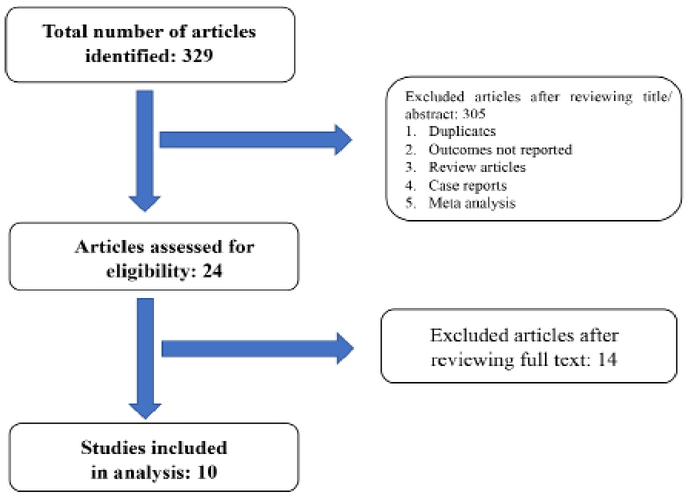


Figure 1: Flow Diagram illustrating systematic search of studies

III) for primary/secondary prevention of sudden cardiac death caused by ventricular arrhythmias.

Patients with cf-LVAD are at increased risk of ventricular arrhythmias either due to worsening underlying disease substrate, scarring around the inflow cannula, or arrhythmias resulting from suction events due to underfilling of the left ventricle[3,4]. However, it remains controversial if ICD offers any survival benefit in advanced heart failure patients with cf-LVAD. Patients with cf-LVAD have been able to tolerate prolonged periods of ventricular arrhythmias with minimal or no neurological sequelae, and are rarely associated with sudden cardiac death[5]. Based on the currently available literature, there are no strict guidelines on ICD utilization in advanced heart failure patients with cf-LVAD. Therefore, we performed a systematic review and meta-analysis of all the clinical studies examining the role of active ICD in end-stage heart failure patients with cf-LVAD.

Methods

Search strategy

The reporting of this systematic review and meta-analysis complies with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines(SupplementTable 1) [6].

The initial search strategy was developed by two authors (KS and RC). Systematic search, without language restriction, using PubMed, EMBASE, SCOPUS, Google Scholar, and Clinical Trials.gov from inception to November 10th, 2020, for studies comparing clinical outcomes between active ICD versus inactive ICD and/or no ICD in advanced heart failure patients with cf-LVAD was performed. We used the following keywords and medical subject heading: "continuous-flow left ventricular assist device,""implantable cardioverter-defibrillator," "end-stage heart failure."

Study Selection and data extraction

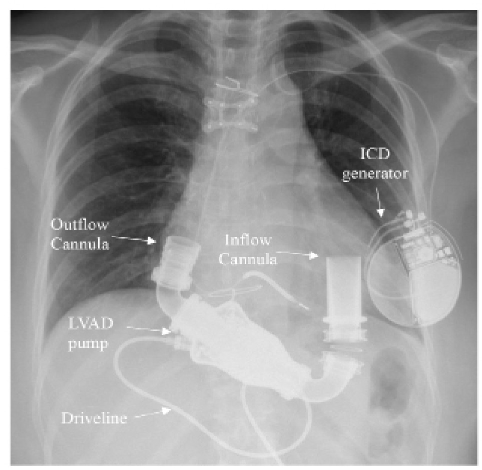
The eligibility criteria for our systematic review and meta-analysis included: (1) all studies reporting clinical outcomes comparing active ICD vs. inactive ICD/no ICD in end-stage heart failure patients with cf-LVAD and (2) studies that included human subjects aged ≥ 18 years. We included studies only published in the English language. Studies involving pulsatile flow LVAD (pf-LVAD), single-arm studies, case reports, editorial, or systematic reviews were excluded. Two investigators (KS and RC) independently performed the literature search and screened all titles and full-text versions of all relevant studies that met study inclusion criteria. The references of all identified articles were also reviewed for relevant studies meeting the eligibility criteria.

The data from included studies were extracted using a standardized protocol and a data extraction form. Any discrepancies between the two investigators were resolved with a consultation with the senior investigator (JG). Two independent reviewers (KS and RC) extracted the following data from the eligible studies: author name, study design, publication year, follow-up duration, number of patients, age, gender, body mass index, diabetes, smoking, etiology of cardiomyopathy, indications of cf-LVAD, medications, INTERMACS score. The Newcastle Ottawa Risk bias assessment tool was used to appraise the included studies' quality (Supplement Table 2).

Outcomes

Clinical outcomes

The primary outcome of our study was - (1) All-cause mortality. Secondary outcomes were the likelihood of survival to transplant, right ventricular (RV) failure, and ICD therapies (appropriate or inappropriate). Adverse events included were infectious complications (sepsis or bacteremia or driveline infections), LVAD related complications (pump thrombosis or driveline malfunction or



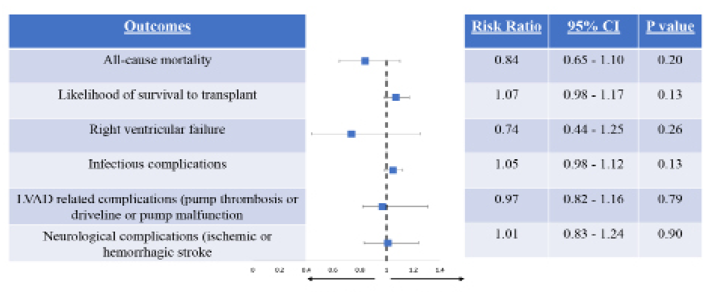


Figure 2: Active ICD versus inactive ICD/no ICD in end-stage heart failure patients with cf-LVAD

Table 1: Baseline characteristics of studies included in our meta-analysis

Study	Anderson et al	Enriquez et al	Garan et al	Lee et al	Clerkin et al. INTERMACS	Clerkin et al. UNOS	Kutyifa et al	Alvarez et al	Cikes et al	Simsek et al
Design	Retrospective	Retrospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Study period	2006-2008	2008-2012	2012	2004-2013	2006-2016	2004-2014	2008-2014	2004-2017	2006-2018	2010-2016
Sample size	ICD: 17 No ICD: 6	ICD: 62 No ICD: 36	ICD: 77 No ICD: 17	ICD: 63 No ICD: 31	ICD: 2209 No ICD: 2209	ICD: 506 No ICD: 506	ICD: 129 No ICD: 62 Of 62, 31 had ICD implanted after cf-LVAD	ICD: 387 No ICD: 99 Of 99, 52 had ICD after cf-LVAD	ICD: 240 No ICD: 208	ICD: 104 No ICD: 123
Follow up	ICD: 214 days No ICD: 52 days	253 ± 194 days	12.7 ± 12.3 months	364 ± 295 days	12.4 months (median)	ICD: 287.5 days (median) No ICD: 305Days (median)	2.1 ± 1 years	401 days (median)	1.1 years (median)	16.5 ± 11.8 months
Patient age mean ± SD (years)	-	ICD: 56.7 No ICD: 56.3	ICD: 63.1 No ICD: 58.1	ICD: 53.9 No ICD: 42.9	ICD: 59 No ICD: 59	ICD: 51 No ICD: 52	ICD: 57.4 No ICD: 54.9	ICD: 57 No ICD: 48.4	ICD: 54±12 No ICD: 50±14	ICD: 51.3 ± 12.2 No ICD: 49.3± 13.9
Bridge to transplant	19 total	ICD: 55 No ICD: 33	ICD: 37 No ICD: 9	ICD: 56 No ICD: 28	ICD: 512 No ICD: 512	ICD: 506 No ICD: 506	ICD: 98 No ICD: 23	ICD: 257 No ICD: 24	ICD: 168 No ICD: 137	ICD: 91 No ICD: 103
Device type	HeartMate II	HeartMate II	-	Ventrassist, Heartware	-	HeartMate II, Heartware	HeartMate II	-	HeartMate II HeartWare HVAD HeartMate3	Heartmate II, HeartMate III, HeartWare, HeartAssist5
Diabetes	-	-	-	ICD: 17.46% No ICD: 12.90 %	ICD: 4.5 % No ICD: 4.2%	ICD: 27.9% No ICD: 29.1%	ICD: 43% No ICD: 29%	ICD: 158 No ICD: 29	ICD: 22.1% No ICD: 17.8%	ICD: 26.9 % No ICD: 29.3 %
Body mass index	-	-	-	-	ICD: 27.7 No ICD: 27.8	ICD: 27.5 No ICD: 27.4	ICD: 29.8 No ICD: 29.9	ICD: 28.5 No ICD: 27.2	ICD: 26.2 ± 4.8 No ICD: 25.3 ± 4.4	-
INTERMACS profile ≤ 2	-	ICD: 45.2% No ICD: 66.7%	ICD: 67.5% No ICD: 88.2%	ICD: 73% No ICD: 74.19%	ICD: 59.7 % No ICD: 57.8%	-	ICD: 52.7% No ICD: 79%	ICD: 12.1% No ICD: 49.49%	ICD:31.6% No ICD: 56.7%	ICD: 27.9 % No ICD: 36.6 %
Ischemic cardiomyopathy	-	ICD: 30.7% No ICD: 58.3%	ICD: 50.6% No ICD: 58.8%	ICD: 31.74 % No ICD: 35.48%	ICD: 50.7% No ICD: 48.6 %	ICD: 42.5% No ICD: 42.1%	ICD: 47% No ICD: 74.19%	ICD: 39.8% No ICD: 48.48%	ICD: 42.5% No ICD: 50%	ICD: 46.2 % No ICD: 52.8 %
Medications	-	-				-		-		
Beta-blockers			ICD: 96.1% No ICD: 52.9%	ICD: 71.4% No ICD: 67.74%	ICD: 70.1% No ICD: 72.3%		ICD: 84% No ICD: 56.45 %		ICD: 78.3% No ICD: 43.5%	ICD: 73.1 % No ICD: 71.5 %
ACE Inhibitors /ARB			-	ICD: 65.07% No ICD: 67.74%	-		ICD: 30% No ICD: 22.58 %		ICD: 49.3% No ICD: 49.7%	ICD: 31.7 % No ICD: 33.3 %
Antiarrhythmic medications			ICD: 37.7 % No ICD: 52.9 %	ICD: 41.26% No ICD: 38.70%	ICD: 40.4% No ICD: 41.4%		-		-	ICD: 25 % No ICD:12.2%

device malfunction), and neurological complications (hemorrhagic or ischemic).

Statistical Analysis

Mantel-Haenszel risk ratio (RR) random-effects model (DerSimonian and Laird method) was used to summarize data between the two groups[7]. For single arm proportion we used the Logit method to establish variance of raw proportions and then used random effects model (Der Simonian and Laird method) to combine the transformed proportions. The data of the pooled analysis was plotted on forest plots. Higgins I-squared (I^2) statistic was used to assess the test ofheterogeneity[8]. A value of I^2 of 0–25% represented insignificant heterogeneity, 26–50% represented low heterogeneity, 51–75% represented moderate heterogeneity, and more than 75% represented high heterogeneity. Publication bias was visually assessed using funnel plots and Egger's linear regression test of funnel plot asymmetry. A two-tailed $p < 0.05$ was considered statistically significant. Statistical analysis was performed using Comprehensive Meta-Analysis version 3.0 (Biostat Solutions, Inc. [BSSI], Frederick, Maryland).

Results

Search results

A total of 329 citations were identified (Figure 1) during the initial search. Three hundred five records were excluded. After a detailed evaluation of these studies,ten studies (9 retrospective and oneprospective) ultimately met the inclusion criteria (N=7,091

Table 2: Baseline characteristics of studies included in our meta-analysis evaluating ICD shocks (appropriate or inappropriate)

Study ID	Anderson et al	Lee et al	Enriquez et al	Kutyifa et al	Alvarez et al	Cikes et al	Oswald et al	Brenyo et al
Design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Prospective	Retrospective
Study period	2006-2008	2004-2013	2008-2012	2008-2014	2004-2017	2006-2018	2005-2008	2006-2010
Sample size	ICD: 17 No ICD: 6	ICD: 63 No ICD: 31	ICD: 62 No ICD: 36	ICD: 129 No ICD: 62 Of 62, 31 had ICD after cf-LVAD	ICD: 387 No ICD: 99 Of 99, 52 had ICD after cf-LVAD	ICD: 240 No ICD: 208	ICD only: 61	ICD only: 61
Follow up	ICD: 214 days No ICD: 52 days	364 ± 295 days	253 ± 194 days	2.1 ± 1 years	401 days (median)	1.1 years (median)	365 + 321 days.	622 days
Patient age mean ± SD (years)	-	ICD: 53.9 No ICD: 42.9	ICD: 56.7 No ICD: 56.3	ICD: 57.4 No ICD: 54.9	ICD: 57 No ICD: 48.4	ICD: 54±12 No ICD: 50±14	ICD only: 50+12	ICD only: 55.75
Bridge to transplant	19 total	ICD: 56 No ICD: 28	ICD: 55 No ICD: 33	ICD: 53 No ICD: 17	ICD: 226 No ICD: 55	ICD: 73% No ICD: 68.8%	-	ICD only: 72%
Device type	HeartMate II	Ventrassist, Heartware	HeartMate II	HeartMate II	-	HeartMate II HeartWare HVAD HeartMate 3	HeartMate II HeartWare	HeartMate II Jarvik
Diabetes	-	ICD: 17.46% No ICD: 12.90 %	-	**ICD: 43%** **No ICD: 29%**	ICD: 158 No ICD: 29	ICD: 22.1% No ICD: 17.8%	-	ICD only: 361%
Body mass index	-	-	-	ICD: 29.8 No ICD: 29.9	ICD: 28.5 No ICD: 27.2	ICD: 26.2 ± 4.8 No ICD: 25.3 ± 4.4	-	-
INTERMACS profile ≤ 2	-	ICD: 73% No ICD: 74.19%	ICD: 45.2% No ICD: 66.7%	ICD: 52.7% No ICD: 79%	ICD: 12.1% No ICD: 49.49%	ICD:31.6% No ICD: 56.7%	-	-
Ischemic cardiomyopathy	-	ICD: 31.74 % No ICD: 35.48%	ICD: 30.7% No ICD: 58.3%	ICD: 47% No ICD: 74.19%	ICD: 39.8% No ICD: 48.48%	ICD: 42.5% No ICD: 50%	ICD only: 49%	ICD only: 60.6%
Medications			-		-			
Beta-blockers		ICD: 71.4% No ICD: 67.74%		ICD: 84% No ICD: 56.45 %		ICD: 78.3% No ICD: 43.5%	**ICD only: 69%**	**ICD only: 90%**
ACE Inhibitors /ARB		ICD: 65.07% No ICD: 67.74%		ICD: 30% No ICD: 22.58 %		ICD: 49.3% No ICD: 49.7%	**ICD only: 67%**	**ICD only: 63.9%**
Antiarrhythmic medications		ICD: 41.26% No ICD: 38.70%		-		-	**ICD only: 71%**	**ICD only: 32.78%**

Table 3: Adverse events reported in studies included in our meta-analysis

	Garan et al		Enriquez et al		Lee et al		Clerkin et al. INTERMACS		Alvarez et al		Simsek et al		Cikes et al	
	ICD (72)	No ICD (22)	ICD (62)	No ICD (36)	ICD (64)	No ICD (36)	ICD (2209)	No ICD (2209)	ICD (439)	No ICD (47)	ICD (104)	No ICD (123)	ICD	No ICD
Infection	1	1	NR	NR	0	4	1046	992	110	9	5	11	risk ratio (separate events not reported)	
LVAD complications	NR	NR	43	25	NR	NR	487	497	23 Pump thrombosis: 20 Driveline malfunction: 2 Device malfunction: 1	0	2 Pump thrombosis: 2	8 Pump thrombosis: 8	NR	NR
Neurological complications	1	0	NR	NR	NR	NR	509	473	4	7	6	11	NR	NR

N.R = not reported, ICD = Implantable cardioverter defibrillator

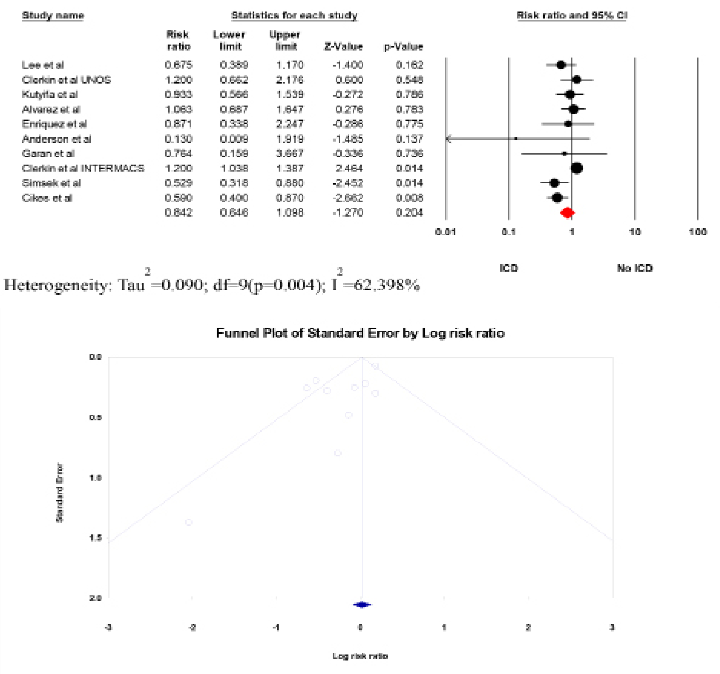


Figure 3: **All-cause mortality.** The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favor active ICD. The funnel plot demonstrates publication bias

patients)[9-18]. The follow-up duration for the studies ranged from 52 days to 3.1 years. Table 1 summarizes the study characteristics of the included trials.

Study characteristics

The study by Cantillon et al. evaluated outcomes of ICD in both pf-LVAD (n=354) and cf-LVAD patients; however, the baseline characteristics and outcomes of patients with cf-LVAD could not be delineated from those who underwent pf-LVAD. Hence, we excluded from our analysis [19]. In studies by Kutyfia et al., Alvarezet al., and Cikes et al., a total of 103 patients received ICD post-cf-LVAD implantation; and were therefore included in the ICD group[15-17]. In a study by Cikes et al.,[20] patients received ICD post-cf-LVAD, while 45 patients had their ICD deactivated or extracted post-cf-LVAD implantation, 34 of which underwent heart transplantation[17]. Studies by Clerkin et al. (INTERMACS and UNOS data) were propensity score-matched in order to ensure comparable groups (and similar baseline characteristics). This accounted for more than two-thirds (76.5%) of our study population (n=5,430)[13,14].

Overall, the patients' mean agewas 50.34 years in active ICD and 47.09 years in the inactive/no ICD group. Bridge to transplantation was the indication for LVAD placement in 3,174 patients (44.70%). Table 1 summarizes the study characteristics of the included trials.

Clinical Outcomes (Figure 2)

All-cause mortality

The data for all-cause mortality was available in all ten trials[9-18]. Active ICD was not associated with any difference in all-cause mortality as compared to Inactive/No ICD (RR 0.84, 95% 0.65-1.10, p = 0.20). Moderate heterogeneity was observed between trials (I^2 =62.40%). Publication bias was observed (Figure3).

Likelihood of SurvivaltoTransplant

The data for the likelihood of heart transplant was available in sixtrials[10-14,18]. No significant difference was observed between the two groups in the likelihood of survival to transplant (RR 1.07, 95% CI 0.98 – 1.17, p=0.13). No significant heterogeneity was observed between trials (I^2 =0%). No publication bias was observed (Figure4).

Right ventricular failure

The data for right ventricular (RV) failure was available in five trials[10-12,16,18]. No significant difference was observed in terms of RV failure between the two groups(RR 0.74, 95% CI 0.44 – 1.25, p=0.26). Mild heterogeneity was observed between trials (I^2 =34.44%). No publication bias was observed (Figure5).

ICD shocks

We conducted a separate literature search in PUBMED, MEDLINE, EMBASE, EBSCO, CINAHL, Web of Science, and Cochrane (March 10th, 2020) to identify eligible studies assessing ICD shocks (both appropriate and inappropriate) in end-stage heart failure patients with cf-LVAD. After a detailed evaluation of these studies, eightstudies (7 retrospective and oneprospective) clinical studies ultimately met the inclusion criteria (N=970 patients). Follow-up duration for the studies ranged from 52 days to 3 years. Table 2 summarizes the study characteristics of the included trials[9,10,12,15-17,20,21]. Studies by Oswald et al.[21] and Brenyo et al.[20] were only included to assess the incidence of ICD shocks (since both studies did not have any comparator arm).

The data for appropriate ICD shock was available in all eight trials

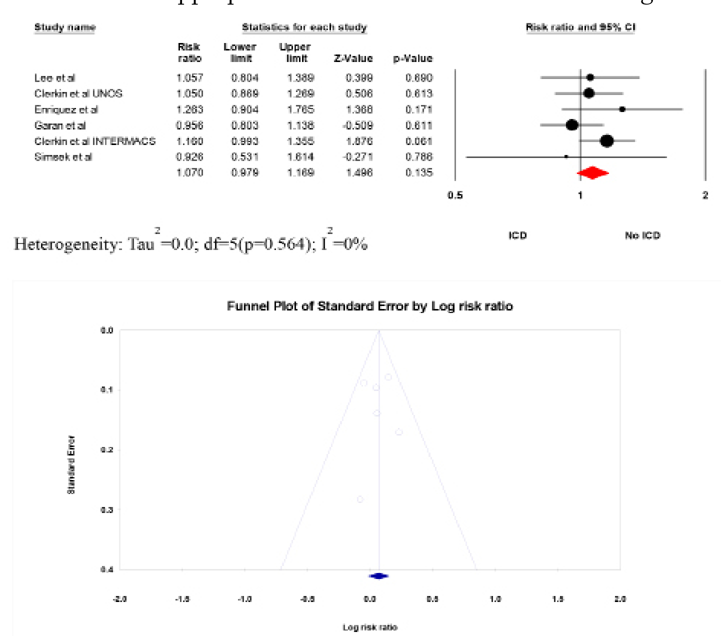


Figure 4: **Likelihood of Survival to Transplant.** The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favor active ICD. The funnel plot demonstrates no publication bias

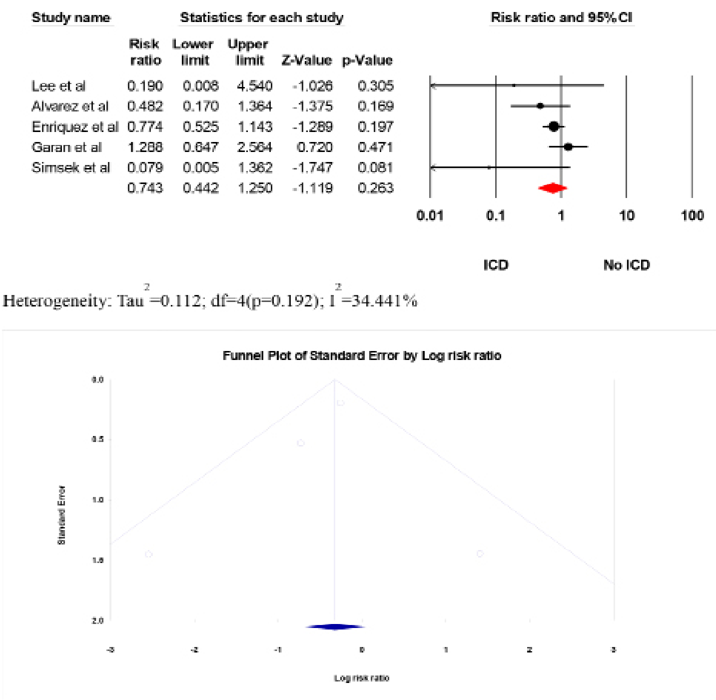


Figure 5: Right ventricular failure. The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favor active ICD. The funnels plot demonstrates no publication bias

[9,10,12,15-17,20,21]that included 970 patients, with an incidence of 27.5% (95% CI 0.22-0.33, I^2=61.36%) during the follow-up period (Figure6).

Inappropriate ICD shock was reported in sixtrials[9,10,12,16,20,21] that included 704 patients with an incidence rate of 9.5% (95% CI 0.05-0.18, I^2=81.69%) during the follow upperiod (Figure7).

Adverse events

The major adverse event rates were reported in six clinical trials (Table 3). There was no significant difference in terms of infectious complications (RR 1.05, 95% CI 0.98-1.12, p = 0.13, I^2=0%) (Figure 8)[11-13,16-18], LVAD related complication (19.72% vs 21.94%; RR 0.97, 95% CI 0.82-1.16, p=0.79, I^2=19.76%) (Figure 9)[10,13,16,18] and neurological complications (ischemic or hemorrhagic stroke) (19.68% vs 20.44%; RR 1.01, 95% CI 0.83-1.24, p=0.90, I^2=6.1%) (Figure 10)[11,13,16,18] between the two groups. The test of heterogeneity was not significant for either outcomes. No publication bias was observed.

Sensitivity analysis

A sensitivity analysis was performed to investigate the significant heterogeneity observed between the trials for all-cause mortality. Studies by Clerkin et al. (INTERMACS and UNOS data) [13,14] were propensity score-matched in order to ensure comparable groups (and similar baseline characteristics). This accounted for more than two-thirds (76.5%) of our study population (n=5,430), of which Clerkin eta l (INTERMACS) contributed 81.36% patients (n=4,418). While Clerkin et al. (UNOS) included all patients as bridge to transplant, only 23.17% of patients were as bridge to transplant in the Clerkinet al. (INTERMACS) trial. There was a significant reduction in all-cause mortality in cf-LVAD recipients with active ICD (RR 0.77, 95% CI 0.61-0.98, p = 0.03), with no significant heterogeneity (P forheterogeneity = 0.22, I^2 = 24.86%) after excluding Clerkin et al (INTERMACS) trial.

Finally, we performed a sensitivity analysis after excluding both Clerkin et al. trials (UNOS and INTERMACS). There remained a significant reduction in all-cause mortality in cf-LVAD with active ICD (RR 0.73, 95% CI 0.58 – 0.92, p = 0.01, I^2 = 15.12%, P for heterogeneity = 0.31).

Discussion

The main findings in this analysis are: (1) All-cause mortality and likelihood of survival to transplant did not differ between the Active ICD and Inactive/no ICD groups in end-stage heart failure patients with cf-LVAD; (2) the incidence rate of appropriate ICD shock was 27.5%, while inappropriate ICD shock was 9.5%; (3)no significant increase in the incidence of RV failure; and finally, there was no difference in the adverse events between the two groups. These findings have important clinical implications, and therefore, the risks and benefits of active ICD must be carefully considered (Figure 2).

This is the largest study assessing the role of active ICD in end-stage heart patients with cf-LVAD (either as destination therapy or bridge to transplant). Our findings strengthen the results of the previously reported trials and metanalyses, demonstrating no net clinical benefit of ICD in advanced heart failure patients with cf-LVAD[22,23]. Since then, new clinical trials and more contemporary data mandated an update to the prior meta-analyses. There are several potential explanations for the findings observed in our study. First, given the lack of randomized clinical trials (and exclusion of healthier patient population), no mortality benefit with ICD is a mere reflective of selection bias towards sicker patient population. Second, end-stage heart failure patients with

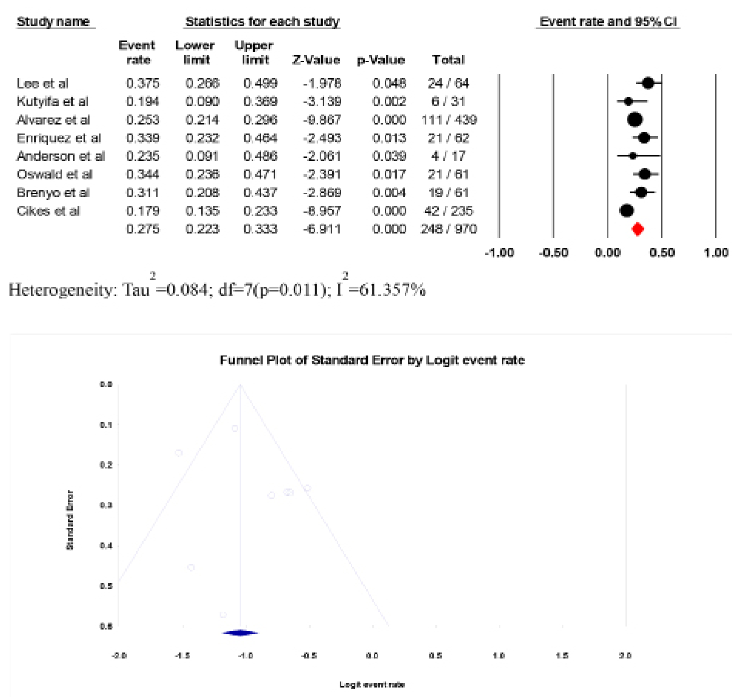


Figure 6: Forest Plot of the Incidence of Appropriate ICD shock in patients with cf-LVAD

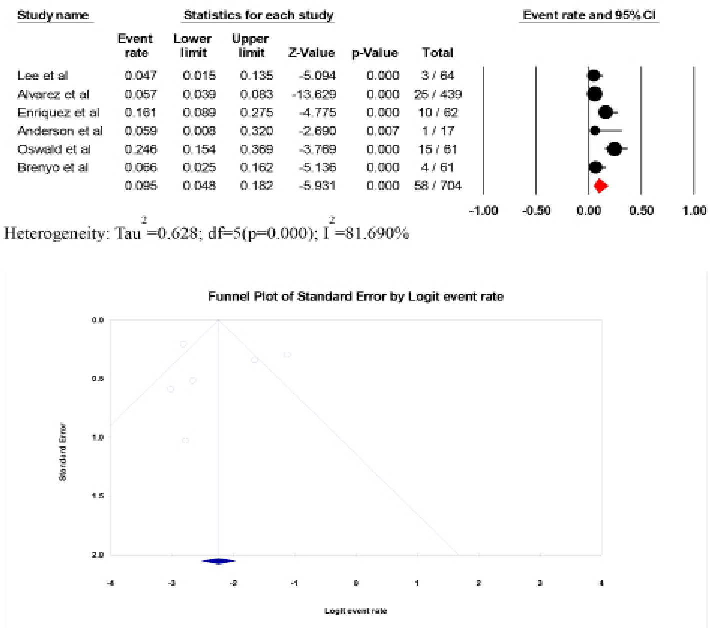


Figure 7: Forest Plot of the Incidence of Inappropriate ICD shock in patients with cf-LVAD

cf-LVAD are at increased risk of death from non-arrhythmic causes such as pump failure, infections, or device thrombosis, thus making it difficult to assess the net clinical benefit of ICD's. Third, patients with cf-LVAD may be less susceptible to unfavorable effects of ventricular arrhythmia (as noted in our study) [5,24]; consequently, are less likely to derive mortality benefit from ICD. Lastly, with improved cf-LVAD technology, patient management, and care transition teams, might have led to improved survival that counteracted the effect of ICD. This explains why there was no mortality benefit observed in our study in comparison to previously published meta-analysis assessing the role of ICD in advanced heart failure and pulsatile LVAD[22] (although results should be interpreted with caution given significant heterogeneity observed in our analysis).

The role of ICD in patients with cf-LVAD remains unclear, with no clear consensus from the American College of Cardiology/American Heart Association. The International Society of Heart and Lung Transplantation guidelines recommends the use of ICD [either reactivating previously implanted ICD (Class I, level of evidence A) or de novo implantation of ICD after cf-LVAD (Class IIa, level of evidence B)] [25]. This recommendation is solely based upon a single retrospective study in advanced heart failure patients with pulsatile LVAD[26]. Studies have shown pre-LVAD ventricular arrhythmia is a significant predictor of ventricular arrhythmias post-implant, with increased risk within the first 30 days following LVAD implant [27]. Mechanistically, pulsatile LVAD relies partially on intrinsic pump function, sustained and prolonged ventricular arrhythmias might, therefore, result in pump failure, hemodynamic decompensation, and unfavorable prognosis. On the contrary, cf-LVAD may permit preserved pump function and prevent hemodynamic decompensation during sustained ventricular arrhythmias. However, severe RV failure (due to unsupported RV) may result in adverse clinical outcomes (worst survival and increased heart failure hospitalizations) in 10-40% LVAD patients [28]. Therefore, termination of ventricular arrhythmias in cf-LVAD patients with unsupported RV might be a reasonable option. Besides, patients with cf-LVAD are also at increased risk of ventricular arrhythmias (from increased arrhythmogenic milieu from suction events) compared to pulsatile flow LVAD; therefore, having active ICD in situ seems logical. Furthermore, with a 27.5% incidence of appropriate ICD shocks (in contrast to 9.5% inappropriate ICD shocks), it appears more reasonable to activate ICD therapies following cf-LVAD implantation. Given increasing evidence of the decreased quality of life and increased mortality with ICD shocks, we, therefore, recommend delayed therapy approach (i.e., either prolonged detection time or higher rate cut-offs) in patients with cf-LVAD (Table 4 highlights proposed programming setting across different device vendors). We also recommend setting a lower VT monitor zone, and closer follow-up (either in electrophysiology clinic or remote monitoring) to look for arrhythmic burden.

In our study, no significant difference was observed in terms of infectious complications in cf-LVAD patients between the two groups. ICD related infections may disseminate locally (to cannula and pump) and systemically, requiring long-term suppressive antibiotics, and/or urgent heart transplant or LVAD exchange, which is associated with approximately 30% one-year mortality, and increased health care cost and burden. Despite no significant difference in the adverse effects between the two groups, it still remains unclear at this time if there is an added advantage of de novo implantation of ICD after cf-LVAD. However, it seems reasonable to pursue generator exchange in secondary prevention patients or those with any pacing indications (although our study was not designed to assess this outcome in particular).

Limitations

Our study has several important limitations. First patient selection bias due to the retrospective nature of the included studies could not be excluded. Second, the decision and timing for ICD implantation/ICD

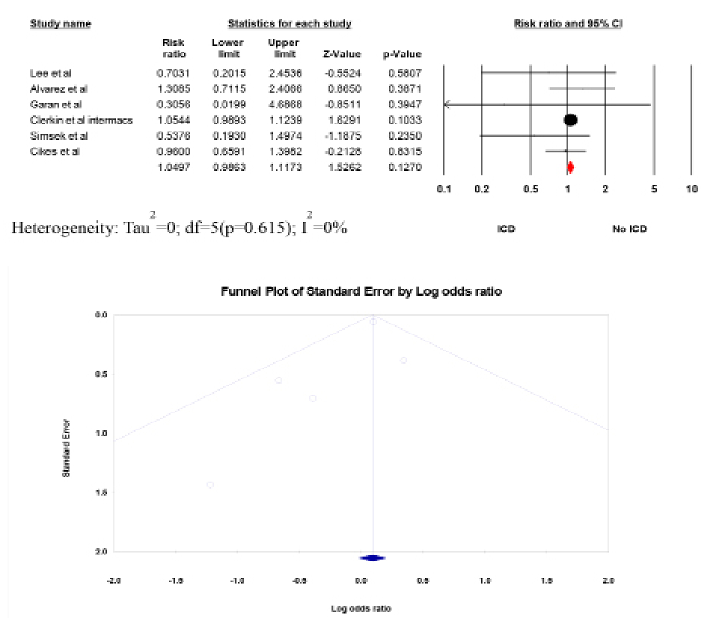


Figure 8: Infectious complications (sepsis or bacteremia or driveline infection). The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favor active ICD. Funnels plot demonstrates no publication bias.

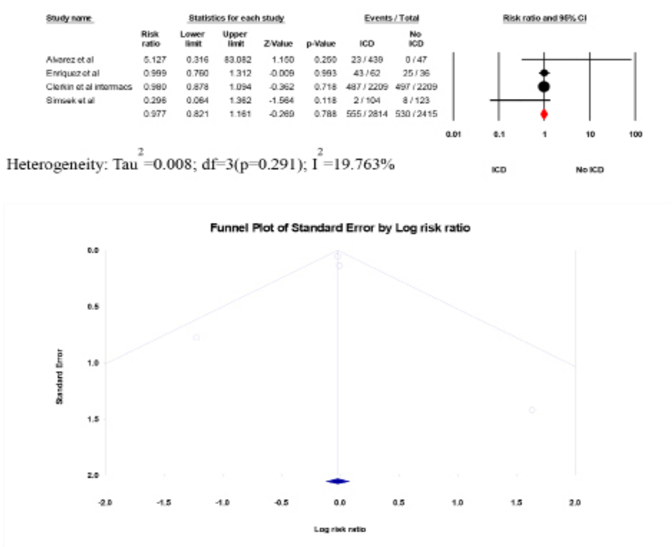


Figure 9: LVAD related complications (pump thrombosis or driveline malfunction or device malfunction). The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favor active ICD. The funnel plot demonstrates no publication bias

programming parameters in cf-LVAD patients were not well defined. Third, information on arrhythmia burden/morphology and its timing in relation to LVAD implantation were inaccessible. Forth patient-level data or right heart catheterization hemodynamics or arrhythmia details/ICD therapies stratified by LVAD typewere not available. Fifth, the etiology of death (cardiac, or non-cardiac) could not be ascertained in all trials. Our meta-analysis results wereprimarily driven by the two largest included studies (UNOS and INTERMACS), accounting together for more than two-thirdsof the total study population.

Conclusion

All-cause mortality, the likelihood of survival to transplant, and worsening RV failure were not significantly different between active ICD and inactive/no ICD in cf-LVAD recipients. However, there was an increased burden of ventricular arrhythmias in our pooled analysis, as evident by a 27.5% appropriate ICD shockrate, suggesting active ICD might bea practical decision in selected patients with cf-LVAD. Future research should be directed to study the safety and efficacy of active ICD's in end-stage heart failure patients with cLVAD in a dedicated randomized controlled study.

Table 4: Proposedprogramming setting across different device vendors in patients with cf-LVAD and ICD

	Biotronik	Boston Scientific	Medtronic	St. Jude Medical
VT detection	190 bpm 80 intervals to detect 20 intervals to redetect	190 bpm 60 seconds to detect	188 bpm 100 intervals to detect (33 seconds) 52 intervals to redetect	190 bpm 100 intervals to detect (33 seconds) 6 intervals to redetect
VF detection	250 bpm 30/40 intervals 12/16 intervals to redetect	≥250 bpm 15 seconds to detect	250 bpm 30/40 intervals 12/16 intervals to redetect 120/160 beats to detect (32.4 seconds) 30/40 beats to redetect	≥250 bpm 100 intervals to detect (25 seconds) 6 intervals to redetect

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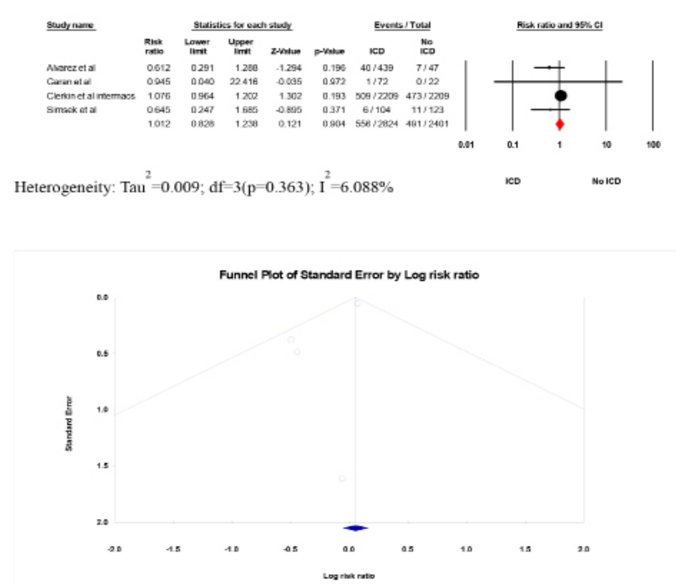

Figure 10: Neurological complications (ischemic or hemorrhagic stroke). The Forest plot shows the outcomes of the individual trials as well as the aggregate. Point estimates to the left favor active ICD. The funnel plot demonstrates no publication bias

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