# Association between implantable cardioverter-defibrillator and survival in patients awaiting heart transplantation: A meta-analysis and systematic review

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**BACKGROUND** Patients with end-stage heart failure are at high risk for sudden cardiac death. However, implantable cardioverter-defibrillator (ICD) is not routinely implanted given the high competing risk of pump failure. A unique population worth separate consideration are patients with end-stage heart failure awaiting heart transplantation, as prolonged survival improves the chances of receiving transplant.

**OBJECTIVE** To compare clinical outcomes of heart failure patients with and without an ICD awaiting heart transplant.

**METHODS** We performed an extensive literature search and systematic review of studies that compared end-stage heart failure patients with and without an ICD awaiting heart transplantation. We separately assessed the rates of total mortality, sudden cardiac death, nonsudden cardiac death, and heart transplantation. Risk ratio (RR) and 95% confidence intervals were measured using the Mantel-Haenszel method. The random effects model was used owing to heterogeneity across study cohorts.

**RESULTS** Ten studies with a total of 36,112 patients were included. A total of 62.5% of patients had an ICD implanted. Patients with an ICD had decreased total mortality (RR 0.60, 95% CI 0.51–0.71, $P < .00001$) and sudden cardiac death (RR 0.27, 95% CI 0.11–0.66, $P = .004$) and increased rates of heart transplantation (RR 1.09, 95% CI 1.05–1.14, $P < .0001$). There was no difference in prevalence of nonsudden cardiac death (RR 0.68, 95% CI 0.44–1.04, $P = .07$).

**CONCLUSION** ICD implantation is associated with improved outcomes in patients awaiting heart transplant, characterized by decreased total mortality and sudden cardiac death as well as higher rates of heart transplantation.

**KEYWORDS** Advanced heart failure; Heart transplantation; Implantable cardioverter-defibrillator; Sudden cardiac death; Transplant waitlist

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## Introduction

Ventricular arrhythmias and sudden cardiac death (SCD) are significant causes of mortality in patients with heart failure.[1] Landmark trials have demonstrated a mortality benefit provided by an implantable cardioverter-defibrillator (ICD) in patients with heart failure and reduced ejection fraction.[2,3] As such, ICD therapy has become an important aspect of heart failure management. However, the increasing trend of ICD implantation is limited to patients with mild-to-moderate heart failure, as most prospective randomized studies excluded patients with advanced disease. Current guidelines do not recommend ICD therapy for patients with drug-refractory heart failure and New York Heart Association (NYHA) functional class IV symptoms who are not candidates for advanced therapies, given the high competing risk of mortality from pump failure.[1]

A unique population worth separate consideration are patients with end-stage heart failure awaiting heart transplantation (HT). According to the 2018 Organ Procurement and Transplantation Network (OPTN) report, the number of new listings for HT increased by 33.7% since 2008, which corresponded to a 39.7% increase in total number of patients actively awaiting HT, with nearly 37% of patients being on the waitlist for more than 1 year.[4] While progression of pump failure constitutes a significant proportion of mortality in patients with end-stage heart failure, those on the HT list are managed aggressively with inotropic agents and mechanical circulatory support (MCS) in the setting of hemodynamic instability, resulting in a higher listing status and increased chances of receiving HT. This could potentially lessen the effect of progressive pump failure on mortality, and therefore contribute to a sustained benefit of ICD implantation in this

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**KEY FINDINGS**

- A significant portion of patients with advanced heart failure awaiting heart transplant did not have an implantable cardioverter-defibrillator (ICD) implanted, even in the contemporary era.
- Patients with an ICD on the heart transplant list had lower rates of total mortality and sudden cardiac death compared to patients without an ICD.
- Patients with an ICD on the heart transplant list had higher rates of heart transplantation compared to patients without an ICD.

population. Previous studies have shown varying results on the presence of ICD on waitlist mortality in patients with heart failure.[5–14] The purpose of our current study was to perform a systematic review of literature and meta-analysis to assess the association between ICD therapy and survival in patients awaiting HT.

## Methods

### Literature search

We performed a systematic review of PubMed, Google Scholar, and the Cochrane Library. This was assessed up to July 2021. Restriction to humans was applied. Search terms included (*heart transplantation* or *transplant waitlist*) and (*implantable cardioverter defibrillator* or *heart failure* or *sudden cardiac death*). The reference lists of all included studies were also reviewed.

### Study selection

Studies were selected by 2 independent reviewers. The PRISMA statement for reporting systemic reviews and meta-analyses was applied to the methods for this study.[15] The studies had to fulfill the following criteria to be considered in the analysis: (1) All patients must be listed for HT. (2) Studies must have reported the mortality and transplant outcomes between patients with and without an ICD. (3) Studies were full manuscripts and published in peer-reviewed scientific journals. Studies were excluded if the following were met: (1) single-arm analysis; (2) included pediatric population, defined as age $\leq$16 years; (3) significant duplication of patients already included in a separate study.

### Study outcomes

We evaluated the prevalence of ICD implantation in patients with end-stage heart failure awaiting HT. We compared the rates of total mortality, SCD, non-SCD, and HT between patients with and without ICD. Additionally, we separately assessed the total mortality and rates of HT in patients with ICD implanted for primary vs secondary prevention.

### Data extraction

Two authors (A.L. and J.D.) independently performed the literature search and extracted data from eligible studies. Outcomes were extracted from original manuscripts. Information was gathered using standardized protocol and reporting forms. Discrepancies were resolved by consensus. Two reviewers (A.L. and J.D.) independently assessed the quality items and differences were resolved by consensus.

### Individual study quality appraisal

Two authors (A.L. and J.D.) independently assessed the quality and reporting of the studies with the Newcastle-Ottawa scale.[16] Three categories were included in the analysis. Study quality was then classified into 1 of 3 categories: (1) high quality, 7–9 points; (2) satisfactory quality, 4–6 points; (3) unsatisfactory quality, 0–3 points.

### Statistical analysis

Statistical analysis was performed using Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Data were summarized across comparison groups using the Mantel-Haenszel risk ratio (RR). Heterogeneity was assessed using the $I^2$ statistics, and random effects models for analyses were used owing to heterogeneity across study cohorts. Funnel plot analysis was used to assess publication bias.[17] In addition, we assessed adjusted total mortality using the inverse variance approach to combine the log hazard ratios and corresponding standard errors. Categorical or dichotomous variables are presented as numbers with percentage (%); continuous variables are presented as means with standard deviations or median and interquartile range if otherwise specified.

## Results

### Patient characteristics and study selection

The initial search resulted in 1856 abstracts, of which 1827 were excluded owing to duplications or based on titles and abstracts (Figure 1). We included 10 studies in our final analysis with a total of 36,112 patients. Baseline characteristics are summarized in Table 1. Patients were mostly male, with multiple medical comorbidities. Mean duration on the HT waitlist ranged from 2 months to 18 months. A total of 22,450 out of 22,584 ICDs (99%) were implanted prior to transplant listing, although this was mainly driven by one study.[12] Indication for ICD implantation was available in 8 studies; 413 out of 1057 patients (39.1%) received an ICD for primary prevention. Presence of left ventricular assist device (LVAD) was available in 5 studies; 9685 out of 35,022 patients (27.6%) received an LVAD as bridge to transplant.

Study characteristics are shown in Table 2. All 10 studies were retrospective in nature and were conducted in 8 countries. Six were single-center studies, one was multicenter,

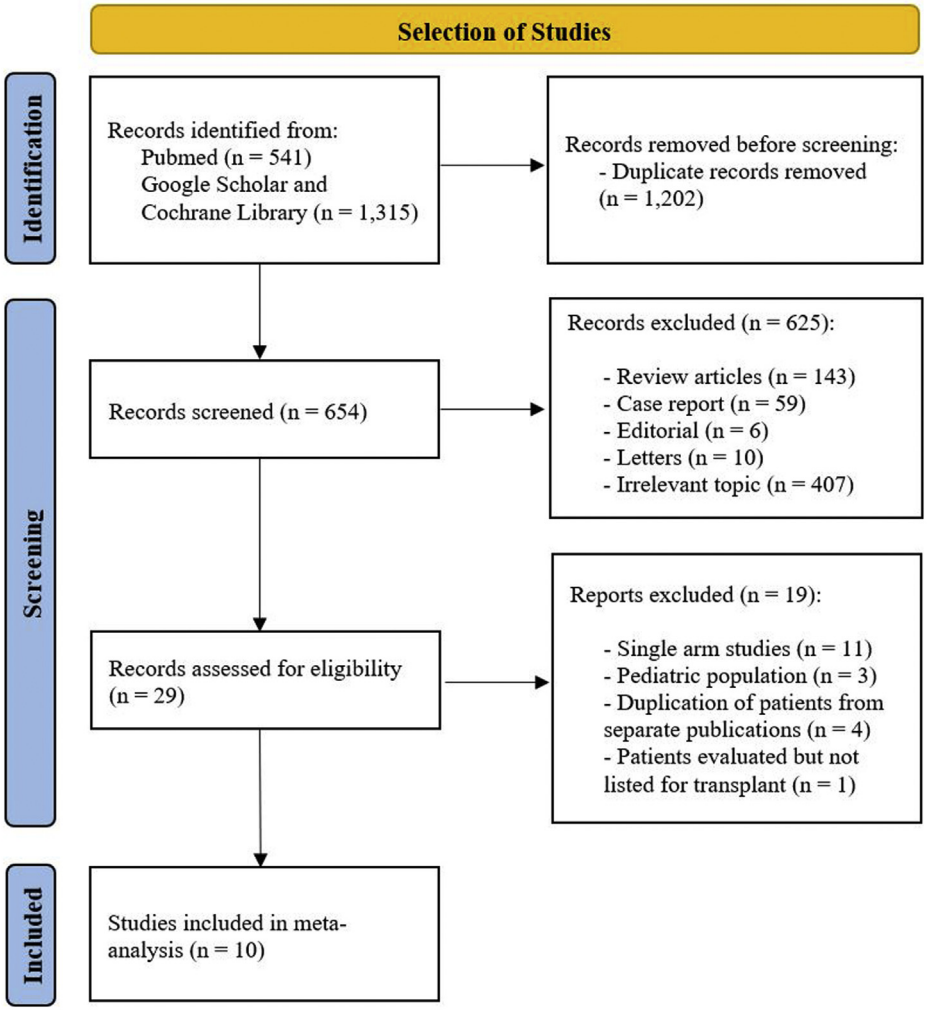


**Figure 1** Selection of studies: screening strategy for selection of 10 eligible studies.

and one utilized the United Network for Organ Sharing (UNOS) database. Follow-up duration ranged from 2.6 months to 40.9 months.

## Study endpoints

Overall, 62.5% of heart failure patients awaiting HT had an ICD implanted. Total mortality and SCD adjusted for duration of follow-up favored patients with an ICD (Table 3). In unadjusted analysis, patients with an ICD had decreased total mortality (9.7% vs 16.7%, RR 0.60, 95% confidence interval [CI] 0.51–0.71, $P < .00001$) and SCD (0.7% vs 8.9%, RR 0.27, 95% CI 0.11–0.66, $P = .004$) without a statistically significant difference in nonsudden cardiac death (16.1% vs 16.8%, RR 0.68, 95% CI 0.44–1.04, $P = .07$) compared to patients without an ICD (Figure 2). In pooled adjusted analysis, transplant candidates with an ICD is associated with lower total mortality (HR 0.54, 95% CI 0.31–0.94, $P = .03$) (Figure 3). The ICD group also had higher rates of HT (64.4% vs 59.1%, RR 1.09, 95% CI 1.05–1.14, $P < .0001$) (Figures 2 and 4). Subanalysis comparing patients who received ICD implantation for primary vs secondary prevention did not show difference in total mortality (15.5% vs 25.8%, RR 0.59, 95% CI 0.33–1.07, $P = .08$) or transplant (58.8% vs 54.9%, RR 0.98, 95% CI 0.77–1.24, $P = .85$).

Five studies included data on occurrence of ICD therapies while on the transplant list. The percentage of patients who received appropriate ICD therapy ranged from 15% to 65%, with an overall prevalence of 26%. Rates of inappropriate ICD therapy ranged from 5% to 7%. Four studies reported use of cardiac resynchronization therapy (CRT) defibrillator in patients who were in the ICD group, with rates between 19% and 44%. When including studies prior to the approval of CRT, ICD implantation was still associated with lower total mortality (14.3% vs 30.4%, RR 0.43, 95% CI 0.30–0.60, $P < .00001$) and SCD (1.0% vs 14.1%, RR 0.16, 95% CI 0.04–0.56, $P = .004$).

## Publication bias and quality assessment

Funnel plots did not reveal publication bias for any of the reported outcomes (Figure 2). Based on the Newcastle-Ottawa scale 3 of the 9 studies were of high quality, 6 were satisfactory quality, and none were unsatisfactory quality (Table 4).

**Table 1** Patient demographic and baseline characteristics

| | Sandner | | Forni | | Ermis | | Saba | | Da Rosa | | Cantero-Perez | | Fröhlich | | Gandjbakhch | | Vakil | | Vandenberk | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ICD | N-ICD | ICD | N-ICD | ICD | N-ICD | ICD | N-ICD | ICD | N-ICD | ICD | N-ICD | ICD | N-ICD | ICD | N-ICD | ICD | N-ICD | ICD | N-ICD |
| Patients | 102 | 752 | 21 | 176 | 59 | 251 | 35 | 159 | 29 | 95 | 28 | 51 | 550 | 539 | 122 | 258 | 21,498 | 11,101 | 140 | 146 |
| Age | 53.0 ± 9.0 | 53.8 ± 9.8 | 55 ± 8 | 54 ± 12 | 51.1 ± 9.9 | 48.9 ± 12.3 | 51.0 ± 11.8 | 51.3 ± 11.6 | 52 ± 13 | 56 ± 15 | 53.8 ± 11.8 | 50.0 ± 12.7 | 53† | 52† | 51.2 ± 11.9 | 48.7 ± 14.5 | 54.0 ± 11.0 | 50.8 ± 12.3 | 51.3 ± 12.7 | 49.9 ± 14.7 |
| Male | 92 (90) | 639 (85) | 22 (90) | 152 (86) | 40 (68) | 191 (76) | 29 (83) | 114 (72) | 24 (83) | 76 (80) | 22 (79) | 41 (80) | 477 (87) | 432 (80) | 99 (81) | 201 (78) | 16,958 (79) | 8151 (73) | 107 (76) | 115 (79) |
| Primary prevention | 0 (0) | – | 0 (0) | – | 0 (0) | – | 16 (46) | – | NR | – | 28 (100) | – | 216 (39) | – | 56 (46) | – | NR | – | 97 (69) | – |
| ICD implant before listing | 100 (100) | – | 21 (100) | – | 48 (81) | – | 0 (0) | – | 21 (72) | – | 28 (100) | – | 478 (87) | – | 114 (93) | – | 21498 (100) | – | 140 (100) | – |
| CRT-D | NR | – | NR | – | NR | – | NR | – | 10 (34) | – | NR | – | 104 (19) | – | 37/84 (44) | – | NR | – | 51 (36) | – |
| Time to HT, mo | 9.6† | 7.8† | NR | NR | 18.5 ±21.1 | 13.4 ± 14 | NR | NR | 4.7 | 2.7 | 4.8† | 1.9† | 9.4† [2.7–22.1] | | 2.9 ± 4.8 | 2.8 ± 6.3 | 5.1† | 5.2† | 6.7 ± 5.0 | 5.5 ± 5.0 |
| EF, % | 18.9 ± 9.2 | 17.5 ± 7.7 | NR | NR | 18.7 ± 6.8 | 20.8 ± 9.8 | 21.9 ± 6.8 | 22.1 ± 9.7 | 16 | 26 | 20† | 20† | 20† | 20† | 22.0 ± 8.4 | 22.1 ± 9.7 | NR | NR | 23.6 ± 7.4 | 23.9 ± 10.8 |
| CAD | 48 (47) | 263 (35) | 10 (48) | 73 (41) | 26 (44) | 114 (45) | 20 (57) | 73 (46) | 12 (41) | 47 (49) | 14 (50) | 25 (49) | 185 (34) | 167 (31) | 41 (34) | 90 (35) | 9280 (43) | 4776 (43) | 60 (43) | 85 (58) |
| AF | 28 (27) | 197 (26) | NR | NR | NR | NR | 6 (17) | 41 (26) | NR | NR | NR | NR | 102 (19) | 100 (20) | NR | NR | NR | NR | 49 (35) | 48 (33) |
| VT | 79 (78) | 252 (34) | NR | NR | NR | NR | 31 (89) | 24 (15) | 21 (72) | 24 (25) | NR | NR | NR | NR | NR | NR | NR | NR | 76 (54) | 48 (43) |
| LVAD implanted | 7 (7) | 20 (3) | NR | NR | NR | NR | 9 (26) | 42 (26) | NR | NR | NR | NR | 0 (0) | 0 (0) | 12 (10) | 75 (29) | 6529 (30) | 2949 (27) | 48 (34) | 81 (56) |
| Temporary MCS | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | | | 720 (3) | 715 (6) | NR | NR |
| Inotrope | 23 (23) | 182 (24) | NR | NR | NR | NR | 6 (17) | 3 (2) | 2 (8) | 19 (20) | NR | NR | NR | NR | NR | NR | 7269 (34) | 3597 (32) | 2 (1) | 9 (6) |
| ACEI/ARB | 96 (94) | 725 (96) | NR | NR | 47 (80) | 180 (72) | 27 (77) | 130 (82) | 20 (68) | 48 (51) | NR | NR | 467 (85) | 417 (87) | NR | NR | NR | NR | 128 (91) | 117 80) |
| Beta blocker | 34 (33) | 173 (23) | NR | NR | 32 (54) | 50 (20) | 19 (54) | 62 (39) | 24 (84) | 52 (55) | NR | NR | 409 (74) | 271 (57) | NR | NR | NR | NR | 133 (95) | 109 (75) |
| AAD | 42 (41) | 156 (21) | NR | NR | 46 (78) | 57 (23) | 8 (22) | 28 (17) | 10 (36) | 14 (15) | 2 (7) | 3 (6) | 177 (32) | 102 (22) | NR | NR | NR | NR | 77 (55) | 45 (31) |

AAD = antiarrhythmic drug; ACE = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CAD = coronary artery disease; EF = ejection fraction; HT = heart transplant; ICD = implantable cardioverter-defibrillator; LVAD = left ventricular assist device; MCS = mechanical circulatory support; N-ICD = non-ICD; NR = not reported; VT = ventricular arrhythmia.
†Median [interquartile range].

**Table 2** Study design and characteristics

| Study | Study design | Enrollment years | Patient source | Country | Mean follow-up, mo |
|---|---|---|---|---|---|
| Sandner 2001 | Retrospective | 1992–2000 | Single center | Austria | 4.7† |
| Forni 2001 | Retrospective | 1994–2000 | Single center | Italy | 31.0 ± 12.0 |
| Ermis 2003 | Retrospective | 1992–2001 | Single center | United States | 15.0 ± 16.4 |
| Saba 2003 | Retrospective | 1997–2001 | Single center | United States | 12.0 ± 13.4 |
| Da Rosa 2007 | Retrospective | 1995–2006 | Single center | Canada | NR |
| Cantero-Perez 2013 | Retrospective | 2006–2012 | Single center | Spain | 2.6† |
| Fröhlich 2013 | Retrospective | 1996–2010 | Multi-center | Germany | NR |
| Gandjbakhch 2016 | Retrospective | 2005–2009 | Single center | France | 40.9 ± 38.8 |
| Vakil 2017 | Retrospective | 1999–2014 | UNOS | United States | 5.1† |
| Vandenberk 2018 | Retrospective | 2002–2014 | Single center | Belgium | NR |

NR = not reported; UNOS = United Network for Organ Sharing.
†Median.

## Discussion

The survival benefit of ICD therapy in patients with heart failure and reduced ejection fraction is well validated in multiple large, prospective randomized controlled trials. However, the subgroup of patients with advanced heart failure and NYHA class IV symptoms awaiting HT were mostly excluded from these studies, and the data supporting ICD implantation in this patient population is limited to retrospective and mostly single-center studies. To the best of our knowledge, this is the first meta-analysis and systematic review comparing the survival benefits of ICD in patients with end-stage heart failure awaiting HT. Our results showed an association between ICD implantation and lower total mortality and SCD, with an increase in HT.

### Prevalence of ICD implantation in heart failure patients awaiting HT

The decision to pursue HT is due to progression of heart failure symptoms despite optimal medical therapy, usually over the course of months to years. Given the mortality benefit demonstrated by ICD therapy in primary and secondary prevention trials and the class I indication of ICD implantation in heart failure patients with reduced ejection fraction, it is surprising that fewer than two-thirds of patients eligible for HT had an ICD at time of listing. This finding is comparable to a prior report from the Get With the Guidelines – Heart Failure database, where only 42% of 11,880 ICD-eligible patients had an ICD implanted.[18] In light of the low prevalence of ICD in patients listed for HT, it is important to note that several studies enrolled patients prior to the publication of landmark ICD prevention trials such as MADIT-II in 2002 and SCD-HeFT in 2005. However, an analysis of the UNOS registry on temporal trends of ICD therapy among patients listed for HT between 1999 and 2014 showed that prevalence of ICD implantation in this patient population has plateaued at around 80% since 2007.[12] Furthermore, a European study showed only a 65% prevalence of ICD implantation in patients listed for HT between 2010 and 2014.[13]

**Table 3** Rates of total mortality and sudden cardiac death in patients with and without an implantable cardioverter-defibrillator adjusted for duration of follow-up

| | Total mortality | | Sudden cardiac death | |
|---|---|---|---|---|
| | ICD | Non-ICD | ICD | Non-ICD |
| Sandner 2001 | 30.0% | 55.0% | 0% | 39.4% |
| Forni 2001 | 2% | 4% | 2% | 3% |
| Ermis 2003 | 17.6% | 48.1% | 2.7% | 13.1% |
| Saba 2003 | 8.6% | 25.2% | 0% | 3.8% |
| Da Rosa 2007 | NR | NR | NR | NR |
| Cantero-Perez 2013 | 32.9% | 81.4% | 21.7% | 45.2% |
| Fröhlich 2013 | NR | NR | NR | NR |
| Gandjbakhch 2016 | 2.4% | 5.6% | 0.4% | 0.1% |
| Vakil 2017 | 21.9% | 34.7% | NR | NR |
| Vandenberk 2018 | NR | NR | NR | NR |

Values presented as annual percentage.
ICD = implantable cardioverter-defibrillator; NR = not reported owing to lack of data on mean duration of follow-up.

The majority of patients with an ICD in this study underwent ICD implantation prior to HT evaluation and listing. The decision for ICD implantation is dependent on shared decision-making of risks vs benefits between the medical provider and the patient. From the patient's perspective, common reasons to decline ICD implantation include lack of insight and concerns about procedural risks and device complications.[19] Additionally, receiving ICD shocks can be associated with significant detrimental psychological effects.[20] From the provider's perspective, ICD implantation may be deferred, as patients are critically ill or the estimated time to transplantation is too short to derive mortality benefit offered by an ICD. Given our findings that ICD implantation is associated with decreased mortality and higher rates of transplant in patients on the HT list, further efforts are needed to assess the reasons for deferring ICD implantation in this high-risk population.

### Survival benefit of ICD implantation in patients awaiting HT

Ventricular arrhythmias and SCD are common in patients with advanced heart failure.[21] A remote study by the DEFIBRILAT group involving over 300 patients with ischemic cardiomyopathy across 11 transplant centers in the United States reported 41% of waitlist mortality was due to SCD.[22] In more

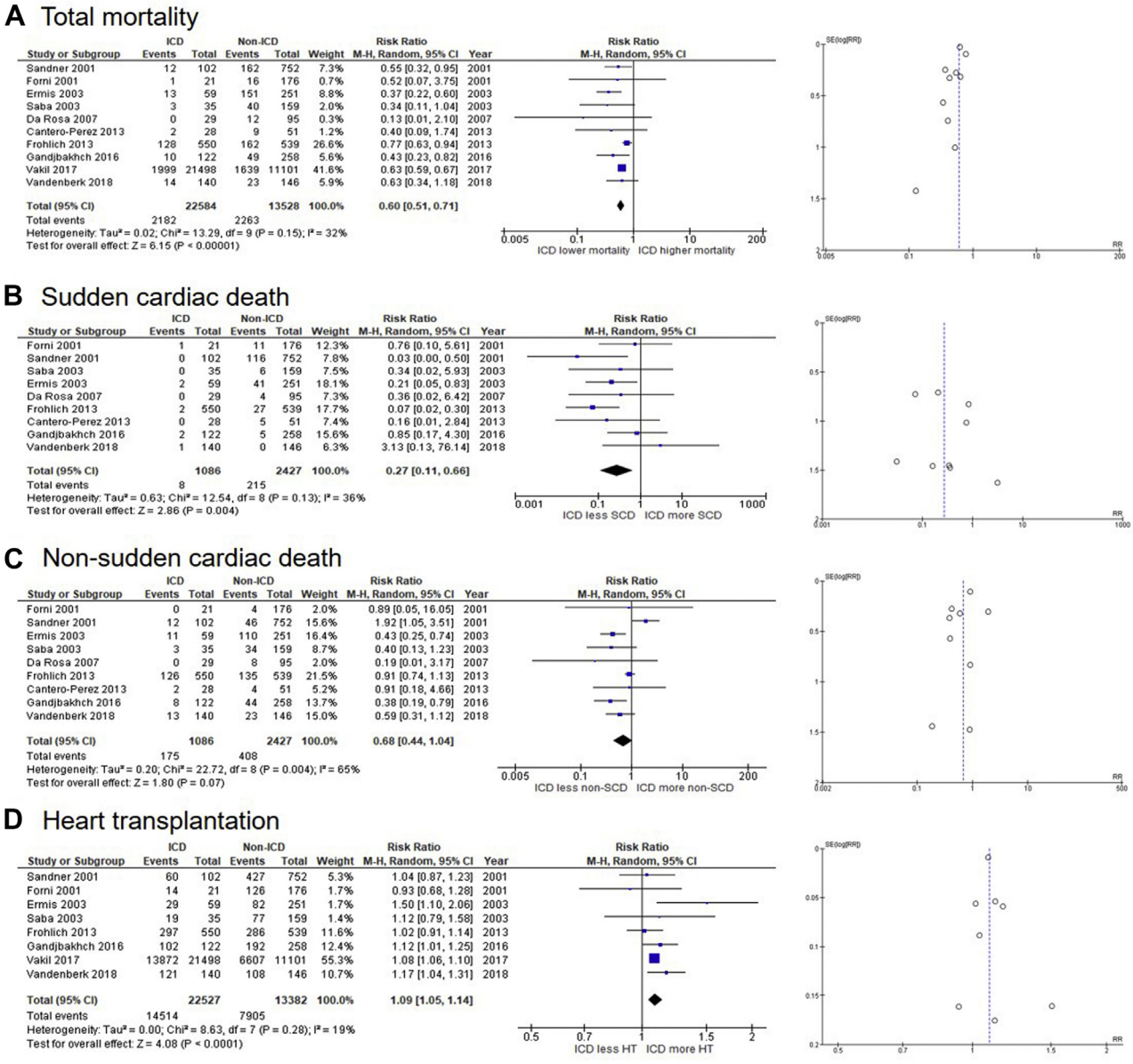


**Figure 2** Comparative analysis of outcomes in patients with and without an implantable cardioverter-defibrillator (ICD) on the heart transplant waitlist. Forest plot demonstrating end-stage heart failure patients with an ICD had lower rates of total mortality (**A**) and sudden cardiac death (**B**) and higher rates of transplantation (**C**) without a difference in nonsudden cardiac death (**D**), compared to patients without an ICD. Risk ratios are unadjusted.

recent studies, the incidence of SCD in patients without an ICD progressively increased with longer time spent on the waitlist, with 1 study reporting 20.2% at 1 year and 33.1% at 2 years,[23] and another study reporting 20.1% at 1 year and 31.7% at 2 years.[5] Early observational studies reported survival benefit of ICD implantation in HT candidates with history of SCD or malignant ventricular arrhythmias observed on Holter monitor (absence of ICD RR 5.2, 95% CI 1.8–14.5, $P = .022$) but prophylactic ICD implantation in all patients awaiting transplant did not translate to a

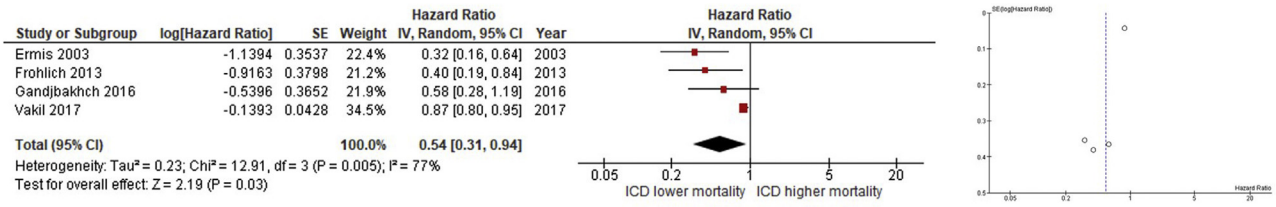


**Figure 3** Adjusted total mortality in patients on the transplant list with and without an implantable cardioverter-defibrillator (ICD).

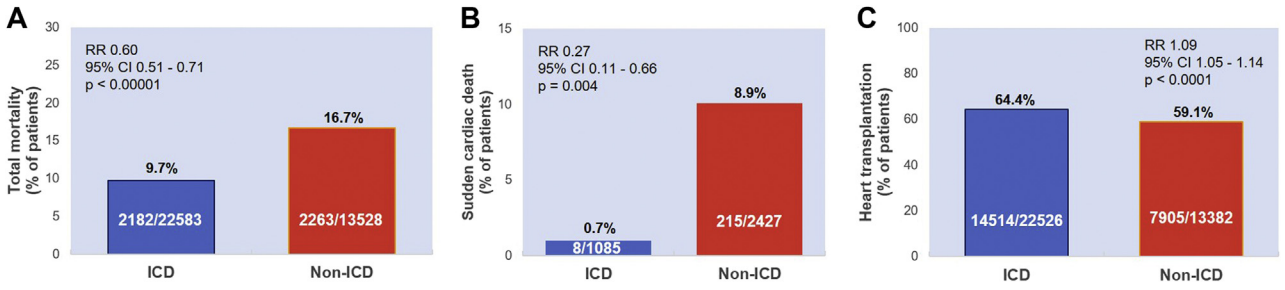


**Figure 4** Outcomes of heart failure patients with and without an implantable cardioverter-defibrillator (ICD) awaiting heart transplantation. Patients with end-stage heart failure who had an ICD experienced lower rates of (**A**) total mortality and (**B**) sudden cardiac death and higher rates of (**C**) heart transplantation compared to patients without an ICD. CI = confidence interval; RR = relative risk.

statistically significant survival benefit.[24] This contradicts more recent studies demonstrating improved outcomes for ICDs implanted for both primary and secondary prevention. In a multicenter study with 1089 patients, the survival benefit was actually more pronounced in patients who received an ICD for primary prevention vs the non-ICD group (88% vs 67%, $P < .0001$) as compared to secondary prevention vs the non-ICD group (77% vs 67%, $P = .01$). This finding persisted after adjusting for covariates (primary prevention HR 0.40, 95% CI 0.19–0.85, $P = .016$ and secondary prevention HR 0.48, 95% CI 0.26–0.89, $P = .019$).[10] Similarly, Gandjbakhch and colleagues[11] also reported no difference in survival between patients with an ICD implanted for primary vs secondary prevention (87.5% vs 96.0%, $P = .13$). Regardless of implant strategy, both primary and secondary prevention patients experience high rates of appropriate ICD therapy while on the transplant list, with reported incidence mostly ranging between 20% and 50%.[6,8–11,13] Patients on inotropic agents may be at particularly high risk, as one small study reported 67% of patients on dobutamine or milrinone received appropriate ICD therapy while on the transplant list.[7] This may be influenced by the severity of their cardiomyopathy and the arrhythmogenic property of inotropic medications.

The studies included in this analysis enrolled patients over the course of approximately 2 decades. During this time, there was a significant increase in 1-year survival on the HT waiting list from 34.1% in 1987–1990 to 67.8% in 2011–2017.[25] While this finding correlates with a definite increase in ICD implantation over this time period, the decrease in waitlist mortality is likely also contributed by improvement in heart failure management with the introduction of temporary MCS and the evolution of LVADs.[26,27] As mentioned previously, early studies of ICD use in HT candidates only showed a survival benefit in patients implanted for secondary prevention. This may be due to high risk of mortality from pump failure and circulatory collapse in an era that lacked well-developed temporary or durable MCS. While it is difficult to ascertain the incremental value provided by ICD implantation on mortality in patients awaiting transplant given the observational nature of our study, the use of MCS directly results in a higher listing status and higher chances of receiving HT. This could potentially lessen the effect of progressive pump failure on mortality, and therefore contribute to a sustained benefit of ICD implantation in this population.

Another important advancement in heart failure management during the study period is the use of CRT. CRT implantation increased significantly in the United States during the early 2000s, with more than 40,000 newly implanted devices annually between 2004 and 2010.[28] While large clinical trials have shown the benefits of CRT in reducing mortality in patients with heart failure, as many as one-third of real-world CRT recipients fail to respond.[29] Furthermore, data on CRT in patients with end-stage heart failure awaiting HT are limited to small retrospective studies.[30] Although information on the outcomes of CRT defibrillator implantation in the current study is lacking, the need for transplant listing suggests these patients were likely nonresponders, and the additive benefit of CRT to ICD on decreasing waitlist mortality and prevention of SCD may not be significant.

**Table 4** Newcastle-Ottawa scale of the included studies

| Study | Selection† | Comparability‡ | Outcome§ |
|---|---|---|---|
| Sandner et al | 3 | 1 | 2 |
| Saba et al | 2 | 1 | 2 |
| Ermis et al | 3 | 1 | 3 |
| Da Rosa et al | 2 | 1 | 2 |
| Cantero-Perez et al | 2 | 1 | 2 |
| Fröhlich et al | 4 | 2 | 3 |
| Gandjbakhch et al | 3 | 1 | 2 |
| Vakil et al | 4 | 1 | 2 |
| Vandenberk et al | 3 | 1 | 2 |

†Maximum 4 stars.
‡Maximum 2 stars.
§Maximum 3 stars.

## Timing of ICD implantation and the impact of time on waitlist

As evident in this study, a significant portion of patients were referred to transplant centers for transplant evaluation without a pre-existing ICD. This is likely contributed by guideline recommendations against ICD implantation in patients with advanced heart failure who are not necessarily candidates for advanced therapies. While the majority of patients with an ICD included in this study underwent ICD implantation prior to transplant listing, Fröhlich and colleagues[10] reported 72 patients had an ICD implanted for either primary or secondary prevention after listing. These

patients had a significantly lower 1-year freedom from all-cause mortality in comparison to patients without an ICD.

It is important to take into consideration a patient's estimated wait time on the transplant list in the decision to pursue ICD implantation. The average time from listing to HT in the majority of included studies ranged from 5 months to 8 months. In a study by Gandjbakhch and colleagues[11] where the average wait time was only 86 days, the presence of ICD was not an independent predictor for survival after multivariate analysis, despite crude analysis showing more than two-fold decrease in all-cause mortality. Since the time from listing to first appropriate ICD therapy in patients awaiting transplant have been reported in a few small studies to be between 2 and 6 months,[7,31,32] it is understandable that the benefit of ICD may be more significant if a patient is expected to have a longer wait time on the transplant list, such as those with higher UNOS waitlist status.

Given the lack of randomized controlled trials in this area, current ACC/AHA/HRS guidelines recommend consideration of ICD implantation in nonhospitalized patients awaiting HT (class IIa).[33] Similarly, the ESC guideline for the management of patients with ventricular arrhythmias and the prevention of SCD states ICD implantation should be considered for primary and secondary prevention in patients who are listed for HT.[34] With increasingly more patients listed for HT worldwide, our study provides the largest analysis of the association between presence of ICD and survival in patients awaiting HT, and provides insight into the role of ICD implantation in this high-risk population.

## Limitations

We acknowledge several limitations to our study. First, there was notable heterogeneity in the patients included, with some requiring home inotropes or living with an LVAD. These patients may have different SCD risk profiles, and application of our findings to the clinical setting still requires individual assessment of risks vs benefit for ICD implantation. Secondly, data on ICD programming were unavailable and may have contributed to the occurrence of appropriate and inappropriate therapies. Third, variables that may affect outcomes on waitlist mortality were not addressed in this study, as the lack of data precludes sensitivity analysis. However, multiple studies included in our analysis separately performed multivariate analysis adjusting for confounders and identified the presence of ICD to be associated with improved survival. Next, all included studies were retrospective analyses and are limited by the nature of retrospective designs. Finally, this study showed an association between ICD implantation and improved outcomes in patients awaiting HT but does not represent causation. Further studies are needed to assess the direct impact of ICD use on survival in HT candidates.

## Conclusion

ICD implantation was associated with improved outcomes in advanced heart failure patients awaiting HT, characterized by decreased total mortality and SCD as well as higher rates of HT. This underscores the potential need for a prospective evaluation on the impact of ICD on survival in HT candidates.

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## Authorship

All authors attest they meet the current ICMJE criteria for authorship.

## Ethics Statement

The PRISMA statement for reporting systemic reviews and meta-analyses was applied to the methods for this study.

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