Implantable Cardioverter Defibrillator Use in Patients with Left Ventricular Assist Devices: A Systematic Review and Meta-Analysis

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IMPLANTABLE CARDIOVERTER DEFIBRILLATOR USE IN PATIENTS WITH LEFT VENTRICULAR ASSIST DEVICES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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*Both authors contributed equally to the work of this manuscript.

Short Title: ICDs in LVAD-supported patients

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ABSTRACT

Objective: To evaluate the impact of implantable cardioverter-defibrillators (ICDs) on mortality in patients with left ventricular assist device (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 PubMed and OVID databases. Weighted relative risks were estimated using random-effects meta-analysis techniques.

Results: Six observational studies (N=937) were included. Patients were 53±12 years old and 80% were male. Bridge-to-transplantation was the indication for LVAD use in 93% 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 (38%) patients. During a mean follow-up of 7 months, 241 (26%) patients died (16% in ICD group vs. 32% in no-ICD group). Presence of an ICD was associated with a 39% relative risk reduction in all-cause mortality (RR: 0.61, 95% CI: 0.46-0.82; p<0.01). Amongst sub-group of patients with CF-LVAD (n=361) ICD use was associated with a statistically non-significant trend towards improved survival (RR: 0.76; 95% CI: 0.51-1.12; p=0.17).

Conclusion: ICD use was associated with a significant reduction in mortality in LVAD patients, however, this effect was not significant in patients with CF-LVADs. While these data support the use of ICDs, larger-scale randomized trial data are strongly warranted to evaluate ICD effectiveness in patients with current generation LVADs.

KEY WORDS: Implantable cardioverter defibrillator; left ventricular assist device; mortality;
systematic review; meta-analysis

**ABBREVIATIONS**

**BIVAD:** biventricular assist device

**CI:** confidence interval

**ICD:** implantable cardioverter-defibrillator

**LVAD:** left ventricular assist device

**RR:** relative risk

**RVAD:** right ventricular assist device
INTRODUCTION

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%-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 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 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.

Although prior observational studies have reported a high burden of appropriate and inappropriate ICD therapies, the data on 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 previously published studies.

METHODS

Data sources and search strategy

We searched PubMed and OVID electronic databases for studies published from January 2000
through October 2015 using the following 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 include 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 utilized in this study has been previously used and validated (18-20).

**Study selection**

To be eligible, studies had to fulfill the following inclusion criteria: (1) randomized controlled trial or observational study; (2) compare LVAD-supported patients with and without ICDs; (3) report information on all-cause mortality for both ICD and no-ICD groups; and (4) report the estimate of relative risk (RR) with 95% confidence interval (CI), or different measures of RR such as hazard ratio or odds ratio, or 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 six studies (12-17). Our search strategy is displayed 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 resolved by consensus or consulting with a third reviewer (K.V).

**Quality of studies in analysis**
Assessment of bias was conducted as described by Downs and Black (21), with two 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 for publication bias.

**Patient groups and outcomes**

Patients that had an ICD at the time of LVAD implantation and those that received an ICD after LVAD implantation were included in the ‘ICD group’. Patients that did not have an ICD, and those that 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 Enriquez et al. (14)], was the incidence of blood stream or device related infections.

**Statistical analysis**

Continuous variables were expressed as mean ± SD and were cumulated using single arm continuous variable random-effects meta-analysis. Categorical variables were expressed as percentages and were cumulated 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 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 five studies after excluding the study by Cantillon et al.

Sub-group analysis was also performed to assess the impact of ICDs on mortality in patients with continuous flow (CF) LVADs. Four of the six studies included patients only with
CF-LVADs (12,14-16), study by Refaat et al. included patients only with pulsatile flow (PF) LVADs (17), whereas Cantillon et al. included patients with both CF- and PF-LVADs (13). To facilitate such sub-group analysis, the primary author for the study from the Cleveland Clinic Foundation (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 two tailed and a p-value <0.05 was considered significant. Analyses were performed by H.R. using STATA software version 10.1 (STATA Corporation, College Station, TX). This study was exempt from Institutional Review Board approval.

RESULTS

Included studies

A total of 6 studies reporting data on 937 patients (range 23-478) were included in the analysis (Table 1). All studies were observational and were published between the years 2009 and 2015. One study was conducted in Europe (12), four in the United States (13-15,17), and one 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 old and majority (80%) were male (Table 2). All patients (except 39 patients with RVAD alone in Cantillon et al.) had an LVAD. Patients with RVAD alone comprised 4% of the entire cohort, while 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 (93%) patients. Mean left ventricular (LV) ejection fraction (EF) and LV end-diastolic dimension were 16±6% and 6.8±1.2 cm, respectively. A significant proportion of
patients were on 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 the supplemental table.

An ICD was present in 355 (38%) patients. Table 2 shows the pooled clinical characteristics of the patients with vs. 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. These patients were more likely to be on beta-blockers and aldosterone receptor antagonists.

ICD use and outcomes
A total of 241 (26%) patients died during a mean follow up of 7 months; 16% (57/355) in the ICD group and 32% (184/582) 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: 0.46-0.82; p<0.01) in all-cause mortality (Figure 4). Approximately 6 patients (95% CI 4.8-9.9) 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: 0.41-0.89; p=0.011) that contributed nearly half of the patients (n=478) in this systematic review.

Five studies (except that by Enriquez et al.) provided information on secondary outcome; i.e. data on infection was available on 839 out of the 937 patients. The incidence of infection was significantly lower in patients with ICDs (18/293 patients) as opposed to patients without an ICD (96/546 patients) – 6% vs. 18% (p<0.01).

Sub-group analysis of patients with CF-LVADs
Of the total 937 patients, 361 (39%) patients had a CF-LVAD. In this sub-group, an ICD was present in 245 (68%) patients, whereas 116 (32%) did not have an ICD. Mortality in the ICD group was 14% as 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: 0.51-1.12; 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

The 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 implantation was relatively low at 38%. This may be related to inclusion of larger number of patients from 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 towards improved survival with ICD use did not reach statistical significance. Lastly, the rate of bloodstream or device-related infections was significantly lower in the ICD group as compared to 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 at relatively higher risk for infections.

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. While 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 CF-LVAD patients only despite a 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 may have caused the RR to cross the line of identity in this sub-group. 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%-59% and depends on several factors such as the presence of ventricular arrhythmias prior to LVAD implant, LVAD type, and the presence of ischemic heart disease (25). Although the burden of ventricular arrhythmias is the highest in the first 30-days following LVAD implant (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 one study, Bedi et al reported a 15% higher absolute risk of mortality in patients with ventricular arrhythmias, with overall mortality being highest amongst those who developed arrhythmias within one week of LVAD implantation (7). In another study, Brenyo et al found a nearly 10-fold increase in mortality in LVAD patients that had ventricular arrhythmias as compared to those that did not (28). 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).

Further Garan et al (15) in their study of 94 patients reported that ICDs in CF-LVAD patients appear to be beneficial only in those who had ventricular arrhythmias prior to LVAD implantation. To that regard, they advocated that it might be reasonable to not implant ICDs in LVAD patients without a history of ventricular arrhythmias. However, Ziv et al in a retrospective study of 91 patients showed that 28 (31%) patients without pre-LVAD ventricular arrhythmias developed de novo ventricular arrhythmias after LVAD implantation (27). Unfortunately, the absence of patient-level data limits our ability to differentiate the utility of ICDs amongst those that had pre-implant ventricular arrhythmias versus 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 two decades (1991-2008), had a much lower prevalence of ICD use, and a significantly worse overall survival as compared to the other studies, perhaps due to the use of predominantly older generation PF-LVADs. When sensitivity analyses were performed after excluding this 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.

This study has a few 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%) that 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 relation 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%. Lastly, cause of death (sudden vs. non-sudden) could not be ascertained.

In conclusion, ICD use is associated with a significant reduction in all-cause mortality in LVAD patients, and has a non-significant trend towards 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.

**CLINICAL PERSPECTIVES**

Results from this meta-analysis are the largest till 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 mechanism of death in these patients. While 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 non-significant trend towards 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. While 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


13. Cantillon DJ, Tarakji KG, Kumbhani DJ, Smedira NG, Starling RC, Wilkoff BL. Improved survival among ventricular assist device recipients with a concomitant


FIGURE LEGENDS

**Figure 1:** Selection of clinical studies included in the systematic review and meta-analysis

**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

**Figure 3:** Funnel plot for assessment of publication bias

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

**Figure 4:** Forest plot and pooled analysis for all-cause mortality (N=937)

RR: relative risk; CI: confidence interval

**Figure 5:** Forest plot and pooled analysis for all-cause mortality in CF-LVAD patients (N=361)

*Data for mortality for CF-LVAD sub-group patients stratified by ICD use was obtained via personal communication with D.C (Cleveland Clinic Foundation).

RR: relative risk; CI: confidence interval
Table 1: Clinical studies of ICD vs. no-ICD in LVAD patients

<table>
<thead>
<tr>
<th>Study first author (Ref #)</th>
<th>Patient enrollment years</th>
<th>Publication year</th>
<th>N</th>
<th>Participants</th>
<th>Design</th>
<th>Mean follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen et al (12)</td>
<td>2006-2008</td>
<td>2009</td>
<td>23</td>
<td>CF-LVAD only</td>
<td>Retrospective observational</td>
<td>9 months</td>
</tr>
<tr>
<td>Refaat et al (17)</td>
<td>1996-2003</td>
<td>2012</td>
<td>144</td>
<td>PF-LVAD + BIVAD</td>
<td>Retrospective observational</td>
<td>12 months</td>
</tr>
<tr>
<td>Enriquez et al (14)</td>
<td>2008-2012</td>
<td>2013</td>
<td>98</td>
<td>CF-LVAD + BIVAD</td>
<td>Retrospective observational</td>
<td>7 months</td>
</tr>
<tr>
<td>Garan et al (15)</td>
<td>2012</td>
<td>2013</td>
<td>94</td>
<td>CF-LVAD only</td>
<td>Retrospective observational</td>
<td>13 months</td>
</tr>
<tr>
<td>Lee et al (16)</td>
<td>2004-2013</td>
<td>2015</td>
<td>100</td>
<td>CF-LVAD + BIVAD</td>
<td>Retrospective observational</td>
<td>12 months</td>
</tr>
<tr>
<td>Cantillon et al (13)</td>
<td>1991-2008</td>
<td>2009</td>
<td>478</td>
<td>CF-LVAD + PF-LVAD + BIVAD + RVAD</td>
<td>Retrospective observational</td>
<td>3 months</td>
</tr>
</tbody>
</table>

*CF: continuous flow; PF: pulsatile flow; LVAD: left ventricular assist device; BIVAD: biventricular assist device; RVAD: right ventricular assist device
Table 2: Clinical characteristics (pooled) of the entire cohort stratified by presence of an ICD^* 

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Data available (N=937 n [n studies*])</th>
<th>ICD group Weighted mean or frequency (n patients n=355)</th>
<th>No ICD group Weighted mean or frequency (n patients n=582)</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>914 [5]</td>
<td>56±11 (338)</td>
<td>53±12 (576)</td>
<td>0.12</td>
</tr>
<tr>
<td>Male sex</td>
<td>816 [4]</td>
<td>86% (238/276)</td>
<td>77% (416/540)</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>722 [3]</td>
<td>12% (24/199)</td>
<td>7% (39/523)</td>
<td>0.049</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>914 [5]</td>
<td>43% (144/338)</td>
<td>58% (336/576)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV EF, %</td>
<td>816 [4]</td>
<td>16.4±5.3 (276)</td>
<td>15.5±0.5 (540)</td>
<td>0.092</td>
</tr>
<tr>
<td>LVEDD, cm</td>
<td>436 [4]</td>
<td>7.1 ± 0.9 (248)</td>
<td>6.3±1.2 (188)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>816 [4]</td>
<td>67% (184/276)</td>
<td>54% (290/540)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>722 [3]</td>
<td>70% (139/199)</td>
<td>66% (344/523)</td>
<td>0.28</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>722 [3]</td>
<td>51% (102/199)</td>
<td>42% (222/523)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anti-arrhythmic therapy</td>
<td>816 [4]</td>
<td>40% (111/276)</td>
<td>37% (202/540)</td>
<td>0.64</td>
</tr>
<tr>
<td>CF-LVAD</td>
<td>937 [6]</td>
<td>69% (245/355)</td>
<td>20% (116/582)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BIVAD</td>
<td>816 [4]</td>
<td>9% (25/276)</td>
<td>13% (68/540)</td>
<td>0.14</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>244 [2]</td>
<td>1.4 ± 0.6 (109)</td>
<td>1.3±0.5 (135)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

*Number of studies providing the mentioned clinical variable.

**P-value of t-test or z-test, as appropriate, comparing the ICD vs. no ICD patient groups
Study by Andersen et al. (12) (n=23) did not stratify clinical characteristics of patients based on the presence of an ICD.

ACE: angiotensin converting enzyme; BIVAD: biventricular assist device; LV EF: left ventricular ejection fraction; LVEDD: Left ventricular end diastolic dimension; ICD: implantable cardioverter defibrillator
PubMed & OVID databases January 2000-October 2015

- 110 non-duplicate citations screened
  - 83 articles excluded after title or abstract review
  - 27 potentially relevant articles screened for full-text review
    - Excluded articles not meeting inclusion criteria
      - Mortality not reported (n=6)
      - Not stratified by presence of ICD (n=15)
  - 6 articles included in systematic review (N=938)
<table>
<thead>
<tr>
<th></th>
<th>Reporting</th>
<th>External Validity</th>
<th>Internal Validity - Bias</th>
<th>Internal Validity - Confounding</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen 2009</td>
<td>Green</td>
<td>Yellow</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
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<tr>
<td>Refaat 2012</td>
<td>Green</td>
<td>Yellow</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>Enriquez 2013</td>
<td>Green</td>
<td>Yellow</td>
<td>Red</td>
<td>Red</td>
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</tr>
<tr>
<td>Garan 2013</td>
<td>Green</td>
<td>Yellow</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>Lee 2015</td>
<td>Green</td>
<td>Yellow</td>
<td>Red</td>
<td>Red</td>
<td>Red</td>
</tr>
<tr>
<td>Cantillon 2015</td>
<td>Green</td>
<td>Yellow</td>
<td>Red</td>
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<td>Red</td>
</tr>
</tbody>
</table>
All-cause Mortality

<table>
<thead>
<tr>
<th>Study Name</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen et al 2009</td>
<td>0.13 (0.01, 2.82)</td>
<td>0.88</td>
</tr>
<tr>
<td>Refaat et al 2012</td>
<td>0.45 (0.22, 0.94)</td>
<td>15.47</td>
</tr>
<tr>
<td>Enriquez et al 2013</td>
<td>0.87 (0.34, 2.25)</td>
<td>9.26</td>
</tr>
<tr>
<td>Garan et al 2013</td>
<td>0.55 (0.12, 2.61)</td>
<td>3.45</td>
</tr>
<tr>
<td>Lee et al 2015</td>
<td>0.68 (0.39, 1.17)</td>
<td>27.47</td>
</tr>
<tr>
<td>Cantillon et al 2009</td>
<td>0.62 (0.40, 0.96)</td>
<td>43.47</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p=0.80)</td>
<td>0.61 (0.46, 0.82)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis
All-cause Mortality CF-LVAD Subgroup

<table>
<thead>
<tr>
<th>Study Name</th>
<th>RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen et al 2009</td>
<td>0.13 (0.01, 2.82)</td>
<td>1.62</td>
</tr>
<tr>
<td>Enriquez et al 2013</td>
<td>0.87 (0.34, 2.25)</td>
<td>17.12</td>
</tr>
<tr>
<td>Garan et al 2013</td>
<td>0.55 (0.12, 2.61)</td>
<td>6.37</td>
</tr>
<tr>
<td>Lee et al 2015</td>
<td>0.68 (0.39, 1.17)</td>
<td>50.81</td>
</tr>
<tr>
<td>Cantillon et al 2009 CF-only</td>
<td>1.08 (0.49, 2.40)</td>
<td>24.07</td>
</tr>
<tr>
<td><strong>Overall (I-squared = 0.0%, p=0.66)</strong></td>
<td><strong>0.76 (0.51, 1.12)</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Risk Ratio