

# Atrial Fibrillation Is Associated With Higher Overall Mortality in Patients With Implantable Cardioverter-Defibrillator: A Systematic Review and Meta-Analysis

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**Background**—Implantable cardioverter-defibrillator (ICD) improves survival when used for primary or secondary prevention of sudden cardiac death. Whether the benefits of ICD in patients with atrial fibrillation (AF) are similar to those with normal sinus rhythm (NSR) is not well established. The aim of this study is to investigate whether ICD patients with AF are at higher risk of mortality and appropriate shock therapy compared with patients with NSR.

**Methods and Results**—Literature was searched and 25 observational studies with 63 283 patients were included in this meta-analysis. We compared the outcomes of (1) all-cause mortality and appropriate shock therapy among AF and NSR patients who received ICD for either primary or secondary prevention and (2) all-cause mortality among AF patients with ICD versus guideline directed medical therapy. All-cause mortality (odds ratio, 2.11; 95% confidence interval, 1.73–2.56;  $P<0.001$ ) and incidence of appropriate shock therapy (odds ratio, 1.77; 95% confidence interval, 1.47–2.13;  $P<0.001$ ) were significantly higher in ICD patients with AF as compared to NSR. There was no statistically significant mortality benefit from ICD compared with medical therapy in AF patients (odds ratio, 0.69; 95% confidence interval, 0.42–1.11;  $P=0.12$ ) based on a separate meta-analysis of 3 studies with 387 patients.

**Conclusions**—Overall mortality and appropriate shock therapy are higher in ICD patients with AF as compared with NSR. The impact of ICD on all-cause mortality in AF patients when compared to goal-directed medical therapy is unclear, and randomized controlled trials are needed comparing AF patients with ICD and those who have indications for ICD, but are only on medical therapy. (*J Am Heart Assoc.* 2018;7:e010156. DOI: 10.1161/JAHA.118.010156.)

**Key Words:** atrial fibrillation • ejection fraction • heart failure • implantable cardioverter defibrillator

Implantable cardioverter-defibrillator (ICD) therapy has been shown to reduce sudden cardiac death and improve survival when used as primary prevention in selected heart failure (HF) patients with left ventricular dysfunction and secondary prevention in patients who survive previous cardiac arrest or have sustained ventricular tachycardia.<sup>1</sup> ICD exerts

this benefit by successfully detecting and terminating life-threatening ventricular arrhythmias and thereby preventing sudden cardiac death. However, it is extremely important for the ICD device to precisely distinguish between atrial and ventricular arrhythmias before delivering a shock, given that inappropriate ICD shock therapy for atrial arrhythmias wrongly detected as ventricular arrhythmias is a common adverse event in patients with ICD.<sup>2</sup>

The rate of ICD implantation has increased in recent years; however, whether ICD is placed for primary or secondary prevention, atrial fibrillation (AF) is a frequently found supraventricular arrhythmia in these patients. Nonetheless, whether AF, which is an independent predictor of mortality in the general population,<sup>3</sup> heralds worse outcomes in patients with ICD is not fully established.

Previously published studies are contradictory and offer little insight.<sup>4–6</sup> Therefore, the aim of this meta-analysis is: (1) to determine whether mortality benefit of ICD is similar in patients with AF and normal sinus rhythm (NSR) and

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## Clinical Perspective

### What Is New?

- Implantable cardioverter-defibrillator patients with atrial fibrillation appear to have higher appropriate shocks and overall mortality risk.

### What Are the Clinical Implications?

- Atrial fibrillation may be a marker of worse outcome in patients with implantable cardioverter-defibrillator, and therefore implantable cardioverter-defibrillator patients with atrial fibrillation may need tailored programming and close monitoring.

(2) whether AF is an independent predictor of appropriate shock therapy.

## Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Search Strategy

We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to conduct and report this meta-analysis<sup>7</sup> as illustrated in Figure 1. We searched PubMed, Biological Abstracts, CINAHL Plus with Full Text, Web of Science, the Cochrane Library, and Google Scholar (inception through November 30, 2017). “Atrial fibrillation,” “implantable cardioverter-defibrillator,” and “shock” were the keywords used in this search. When available, filters/limiters were used to limit the search to clinical studies. Gray literature sources were not included. Titles and abstracts were independently reviewed by 2 authors (U.M., R.R.) and cross-verified by a third reviewer (J.D.) for inclusion.

## Inclusion Criteria

Observational studies (retrospective and prospective) reporting outcomes of all-cause mortality and appropriate shock therapy in ICD patients with persistent or paroxysmal AF or atrial arrhythmias were included. Studies (subgroup analysis of original randomized controlled trials testing outcomes of ICDs) comparing outcomes in AF patients who meet criteria for ICD therapy, but are only on guideline-directed medical therapy, and AF patients with ICD were also included in a separate meta-analysis in this article.

## Exclusion Criteria

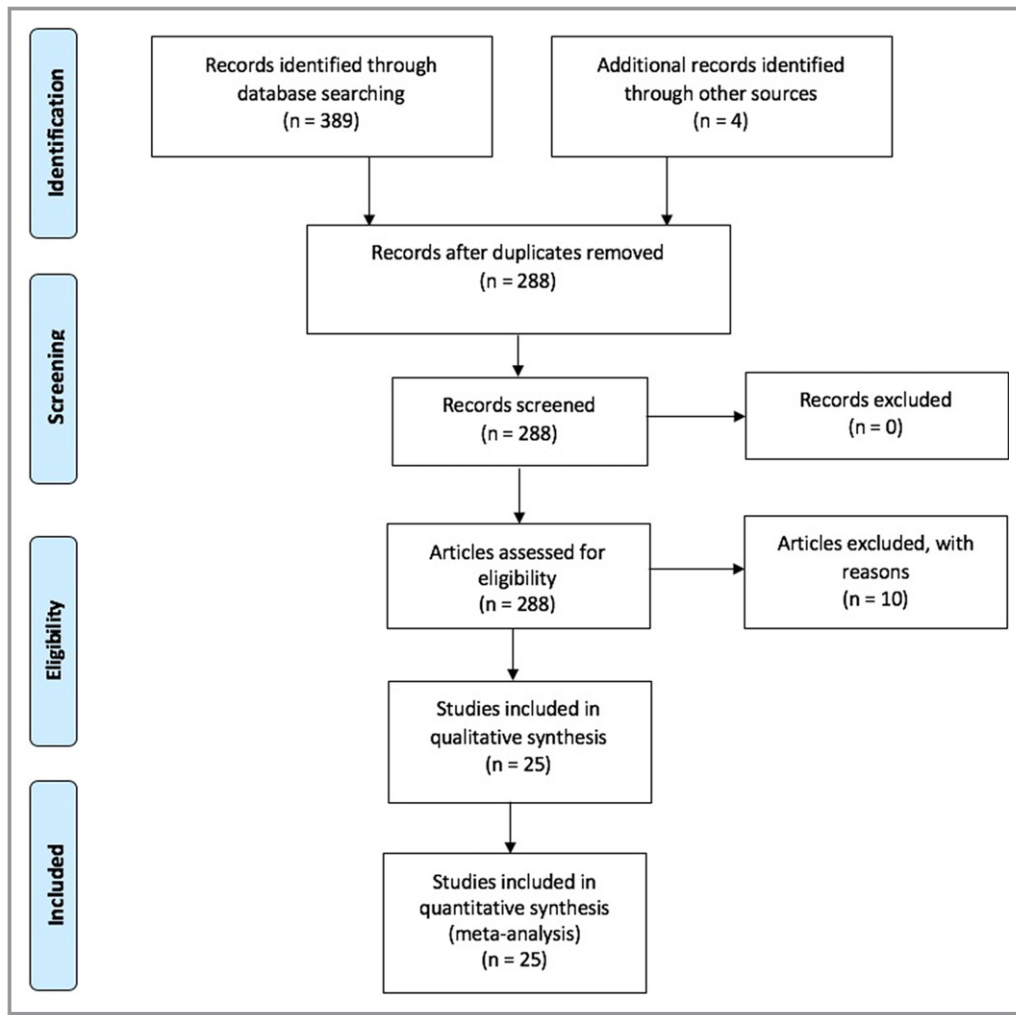
Studies were excluded if they lacked a control group, included patients with cardiac resynchronization therapy, had inadequate data on baseline characteristics, were non-English studies with no English translation, or only assessed inappropriate shock therapy.

## Data Extraction and Quality Assessment of Studies

Data were independently extracted by 2 reviewers (U.M., R.R.) and cross-verified by a third reviewer (J.D.). All disagreements between reviewers were resolved by consensus. We extracted data on study participants (sample size, age, sex, presence of hypertension, chronic kidney disease, diabetes mellitus, ischemic cardiomyopathy, dilated cardiomyopathy, and percent use of antiarrhythmics and beta-blockers), study design, and follow-up. Study characteristics are shown in Tables 1 and 2. The quality of each study and risk of bias was evaluated by the Newcastle–Ottawa quality assessment scale for nonrandomized studies. The following characteristics were assessed for sources of bias: (1) patient selection, including definitions of exposure and representation of the larger population; (2) comparability of study groups and controlling for confounding factors by design or analysis; and (3) assessment and documentation of outcome including duration and loss of follow-up. Studies were graded as “poor” if they met 4 of the 9 criteria, “fair” if they met 5 to 6 criteria, and “good” if they met more than 6 criteria (Tables 1 and 2).

## Statistical Analysis

Risk estimates were used to examine the outcomes of mortality and appropriate shocks and their association with AF. These were derived from reported relative risks, odds ratios (ORs), hazard ratios, incident rate ratios, or standardized incidence ratios, together with corresponding 95% confidence intervals (CIs) from the original studies. Where necessary and possible, all metrics were converted to ORs. If both uni- and multivariate analyses were available, data from multivariate analyses were taken. Pooled ORs and 95% CIs were calculated using the DerSimonian–Laird random-effects method.<sup>30</sup> All tests were 2-sided, and  $P < 0.05$  was deemed significant. Heterogeneity was assessed by the  $I^2$  statistic, which is the percentage of variation of study estimates beyond that which might be expected by chance alone.  $I^2 > 50\%$  was considered significant heterogeneity.<sup>31,32</sup> Potential publication bias was assessed by visual inspection of funnel plots, in which standard errors were plotted against log ORs, as well as Eggers’ regression intercept. All statistical analyses were performed using Comprehensive Meta-Analysis



**Figure 1.** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

(V3; Biostat Inc., Englewood, NJ). To remove publication and reporting bias, studies investigating AF specifically as a risk factor for appropriate shocks and mortality in patients with ICD were separated and analyzed for a prespecified sensitivity analysis, leaving out studies analyzing risk factors for mortality and appropriate shock with no a priori hypothesis.

## Results

### Search Results

The literature search yielded 389 articles. Hand-searching identified 4 additional publications. After removing duplicate titles (n=105) and excluding irrelevant papers (n=11), 288 articles were assessed for eligibility. Of these, 25 observational studies<sup>4-6,8-29</sup> with 63 283 patients (n=16 390 ICD with AF; n=46 684 ICD with NSR; n=209 AF on medical therapy only) met the inclusion criteria for this meta-analysis. Twenty-four studies were available as full text; however, 1<sup>18</sup>

was available only as an abstract. Follow-up averaged 28.6 months (range, 8–60).

Both AF and NSR patients were age-matched in studies (mean age, 64 years; range, 53–71); 93.4% of patients had ICD for primary prevention, and 6.6% patients had ICD as secondary prevention. Mean left ventricular (LV) ejection fraction was comparable between AF (31.2%) and NSR (31.8%). The relationship of AF and end points (all-cause mortality and appropriate shock therapy) was analyzed based on a priori hypothesis by 13 studies,<sup>4,9,11-19,21,28</sup> whereas the rest of the 12 studies investigated AF as 1 of the several risk factors for these outcomes in ICD patients.

### All-Cause Mortality

Twenty-two studies<sup>4-6,8,9,11-26,28</sup> with 61 154 patients reported all-cause mortality and were included for this meta-analysis. Risk of all-cause mortality was significantly higher in ICD patients with AF than ICD patients with NSR

**Table 1.** Study Characteristics of ICD Patients With and Without AF

Study	Year	Follow Up (m)	Total Patients	Patient With AF	Patients With NSR	Age (y)	Male (%)	ICD Indication	LVEF (%)	AA in AF (%)	AA in NSR (%)	NYHA in AF	NYHA in NSR	Quality Assessment*
Madhavan et al <sup>8</sup>	2016	40	253	115	138	68.3	NS	PP	32	...	...	<3: 85 <sup>†</sup> , ≥3: 15		Good
Grönefeld et al <sup>9</sup>	2000	20	229	38	191	64	82	Unspecified	37	21	13	NS	NS	Good
Rienstra et al <sup>10</sup>	2007	31	290	83	207	63	81	PP/SP	29	45	36	<3: 84, ≥3: 16	<3: 90, ≥3: 10	Good
Borleffs et al <sup>11</sup>	2010	28	913	250	663	67	79	PP/SP	32	24	10	<3: 55, ≥3: 45	<3: 66, ≥3: 34	Good
Deneke et al <sup>12</sup>	2004	9.5	359	68	291	62.8	81	PP/SP	39	37.3	24.8	<3: 81, ≥3: 29	<3: 83, ≥3: 17	Good
van Gelder et al <sup>4</sup>	2011	31	537	133	404	71	79	PP	28	20	11	NS	NS	Good
Köbe et al <sup>13</sup>	2013	14	3261	607	2654	70.9	82	PP/SP	31	17.2	14.7	<3: 78, ≥3: 22	<3: 84, ≥3: 16	Good
Smit et al <sup>14</sup>	2006	8	80	29	51	63	79	PP	24	24	18	<3: 55, ≥3: 45	<3: 51, ≥3: 39	Good
Zareba et al <sup>15</sup>	2006	20	655	61	594	65	NS	Unspecified	...	14	5	2 to 4: 73	2 to 4: 63	Good
van Rees et al <sup>16</sup>	2011	60	1544	355	1189	61	79	PP/SP	35	20 <sup>†</sup>	...	<3: 67 <sup>†</sup> , ≥3: 33		Good
Bunch et al <sup>17</sup>	2009	12	1530	174	1356	68.7	81	Unspecified	...	27	7.2	<3: 71, ≥3: 29	<3: 76, ≥3: 24	Good
Kraaier et al <sup>18</sup>	2013	41	647	183	464	64	81	Unspecified	...	...	...	NS	NS	...
Ryan et al <sup>19</sup>	2001	24	321	92	229	65	NS	Unspecified	...	...	...	NS	NS	...
Marijon et al <sup>20</sup>	2010	22	1030	277	753	63	89	PP/SP	36	54 <sup>†</sup>	...	NS	NS	Good
Schemthaler et al <sup>21</sup>	2007	24.5	77	32	45	66	NS	PP/SP	34	13 <sup>†</sup>	...	<3: 65 <sup>†</sup> , ≥3: 35		Good
Desai et al <sup>6</sup>	2010	40	549	70	479	74	NS	PP	29	32 <sup>†</sup>	...	2 to 3: 69 <sup>†</sup> , 4: 31		Good
Schefer et al <sup>22</sup>	2008	51	157	22	135	53	78	PP/SP	40	45 <sup>†</sup>	...	<3: 74 <sup>†</sup> , ≥3: 26		Good
Yang et al <sup>23</sup>	2012	29	148	20	128	53	86	PP/SP	51	...	...	NS	NS	Good
Stein et al <sup>5</sup>	2009	11.4	1655	433	1222	64.4	83	PP	...	46 <sup>†</sup>	...	<3: 69 <sup>†</sup> , ≥3: 31		Good
Smith et al <sup>24</sup>	2011	31	427	112	315	58	79	PP	27	46 <sup>†</sup>	...	<3: 82 <sup>†</sup> , ≥3: 18		Good
Kraaier et al <sup>25</sup>	2013	12	861	207	654	62.7	79	PP	25	...	...	NS	NS	Good
Hess et al <sup>26</sup>	2014	34.8	47 282	12 834	34 448	67	NS	PP	25	...	...	<3: 63 <sup>†</sup> , ≥3: 37		Good
Caputo et al <sup>27</sup>	2016	46	156	78	78	65	NS	SP	39	27 <sup>†</sup>	...	NS	NS	Good

AA indicates antiarrhythmic; AF, atrial fibrillation; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; Med, goal-directed medical therapy; NS, not specified; NSR, normal sinus rhythm; PP, primary prevention; SP, secondary prevention.

\* Newcastle-Ottawa Quality Assessment Scale: poor <4, fair 5 to 6, good >7.

<sup>†</sup>All patients.

**Table 2.** Study Characteristics of AF Patients With ICD and Goal-Directed Medical Therapy

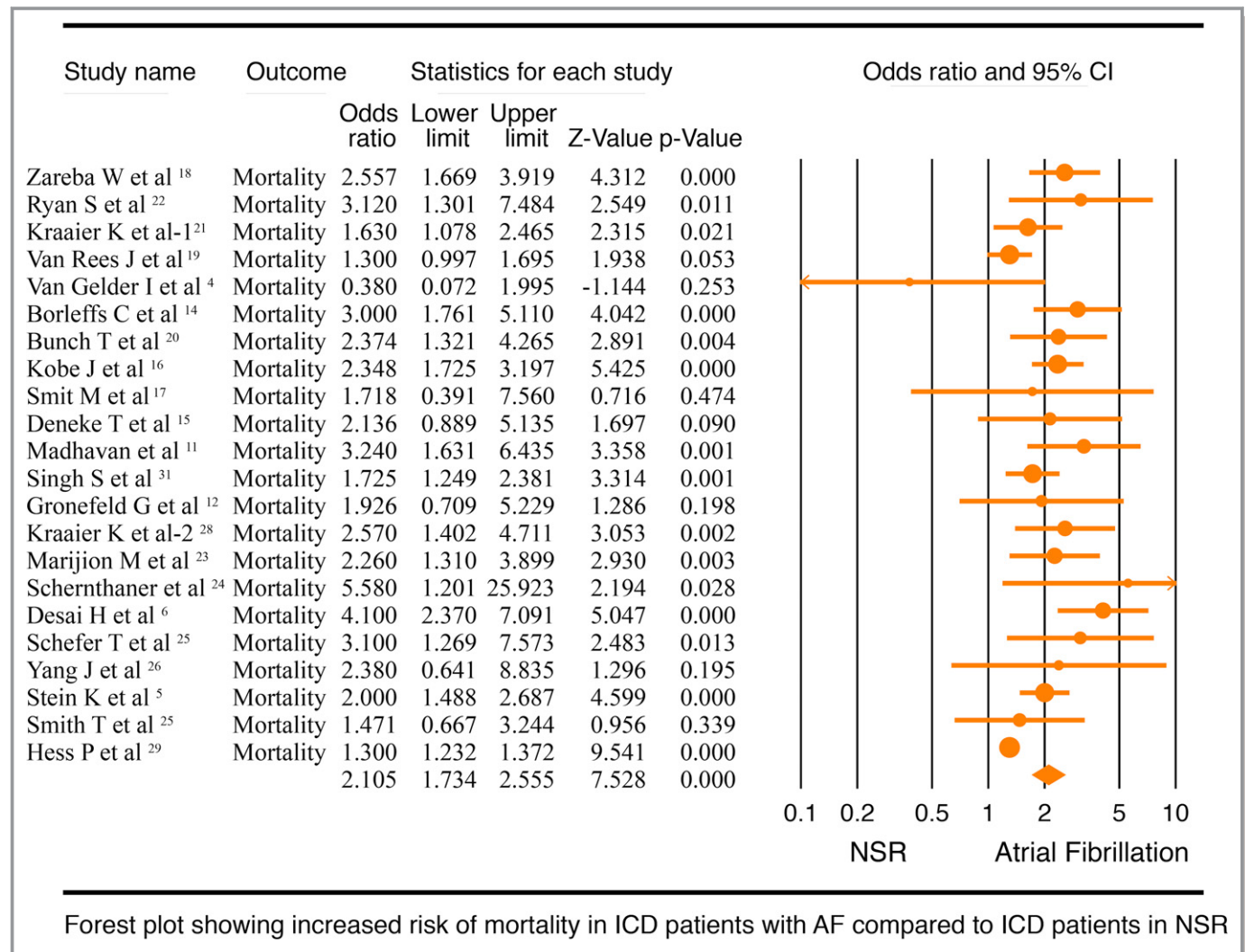
Study	Year	Follow Up (m)	Total AF Patients	AF Patient With ICD	AF Patients on Med Therapy	Age (y)	Male (%)	ICD Indication	LVEF (%)	Use of AA (%)	NYHA Class (%)	Quality Assessment*
Zareba et al <sup>15</sup>	2006	20	102	61	41	65	NA	Unspecified	...	14	2 to 4:73	Good
Singh et al <sup>28</sup>	2006	29	173	65	108	64	91	Unspecified	25	37	<3: 60, ≥3: 40	Good
Kadish et al <sup>29</sup>	2004	45.5	112	52	60	58	NA	SP	21	5.2	<3: 79, ≥3: 21	...

AA indicates antiarrhythmic; AF, atrial fibrillation; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; Med therapy, goal-directed medical therapy; SP, secondary prevention.

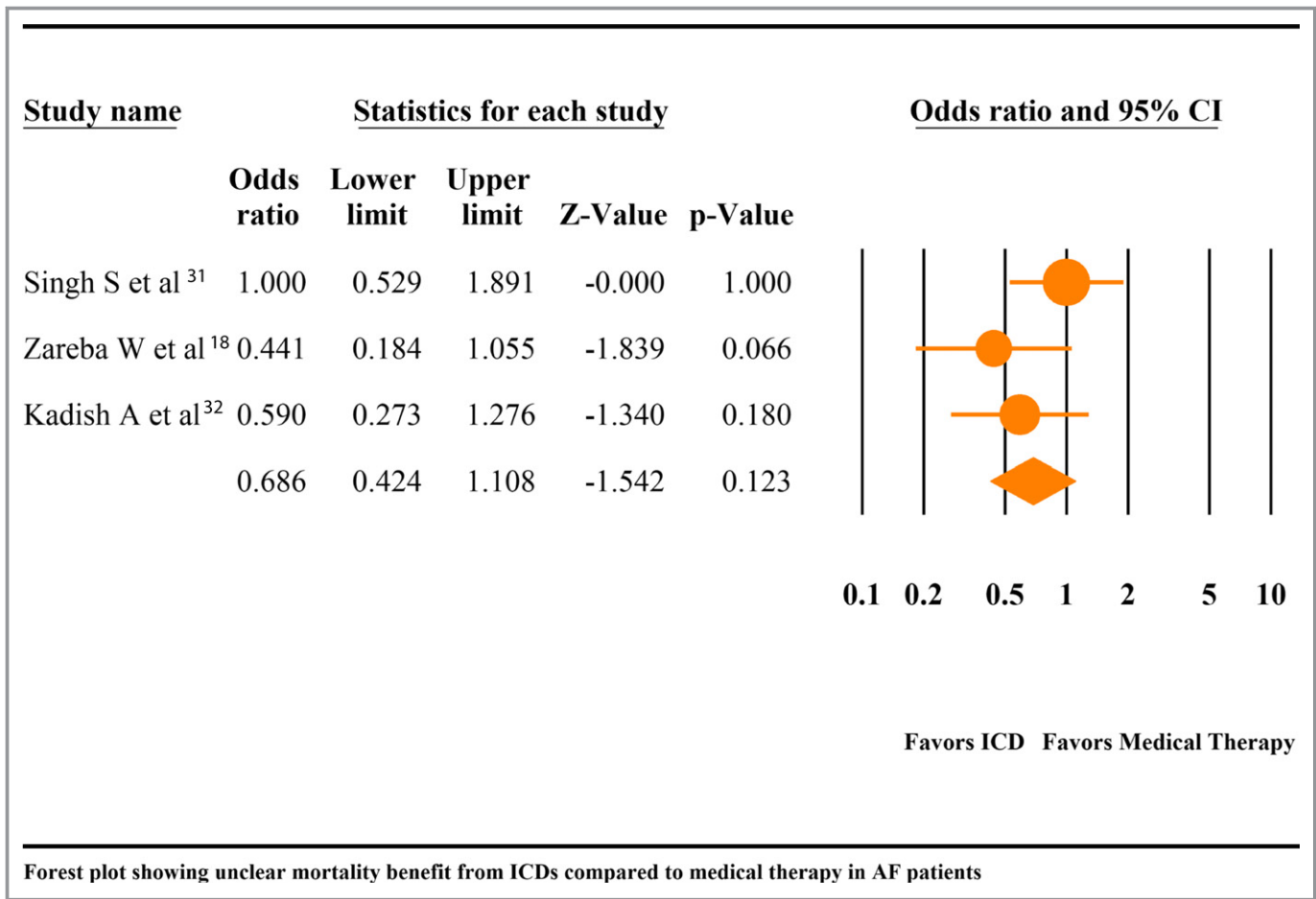
\*Newcastle–Ottawa Quality Assessment Scale: poor <4, fair 5 to 6, good >7.

(OR, 2.11; 95% CI, 1.73–2.56;  $P<0.001$ ;  $I^2=75.46$ ; Figure 2). Pooled analysis with a fixed-effects model did not change the results (OR, 1.42; 95% CI, 1.35–1.49;  $P<0.001$ ;  $I^2=75.45$ ; Figure S1). Funnel plot of these 22 studies showed significant publication bias (Figure S2). Therefore, we performed a

preplanned sensitivity analysis by excluding studies that did not primarily look for all-cause mortality based on presence or absence of AF, but found AF as a risk factor for mortality among other predictors. This sensitivity meta-analysis of 13 studies showed a similar finding of significantly higher all-



**Figure 2.** Forest plot comparing mortality in implantable cardioverter defibrillator (ICD) patients with atrial fibrillation (AF) and normal sinus rhythm (NSR). CI indicates confidence interval.



**Figure 3.** Forest plot comparing mortality in atrial fibrillation (AF) patients with implantable cardioverter defibrillator (ICD) vs goal-directed medical therapy (GDMT). CI indicates confidence interval.

cause mortality in AF patients with ICD than in NSR patients with ICD (OR, 2.00; 95% CI, 1.62–2.47;  $P < 0.001$ ;  $I^2 = 46.91$ ; Figure S3). A fixed-effects model did not change the overall direction of the results (OR, 1.89; 95% CI, 1.65–2.15;

$P < 0.001$ ;  $I^2 = 46.91$ ; Figure S4). Funnel plot of these studies did not show any significant publication bias. We also performed another sensitivity analysis by excluding the only abstract,<sup>18</sup> and found that results were unchanged with the risk of mortality being higher in ICD patients with AF than ICD patients with NSR (OR, 2.15; 95% CI, 1.75–2.63;  $P < 0.001$ ).

**Table 3.** ICD Programming Protocol

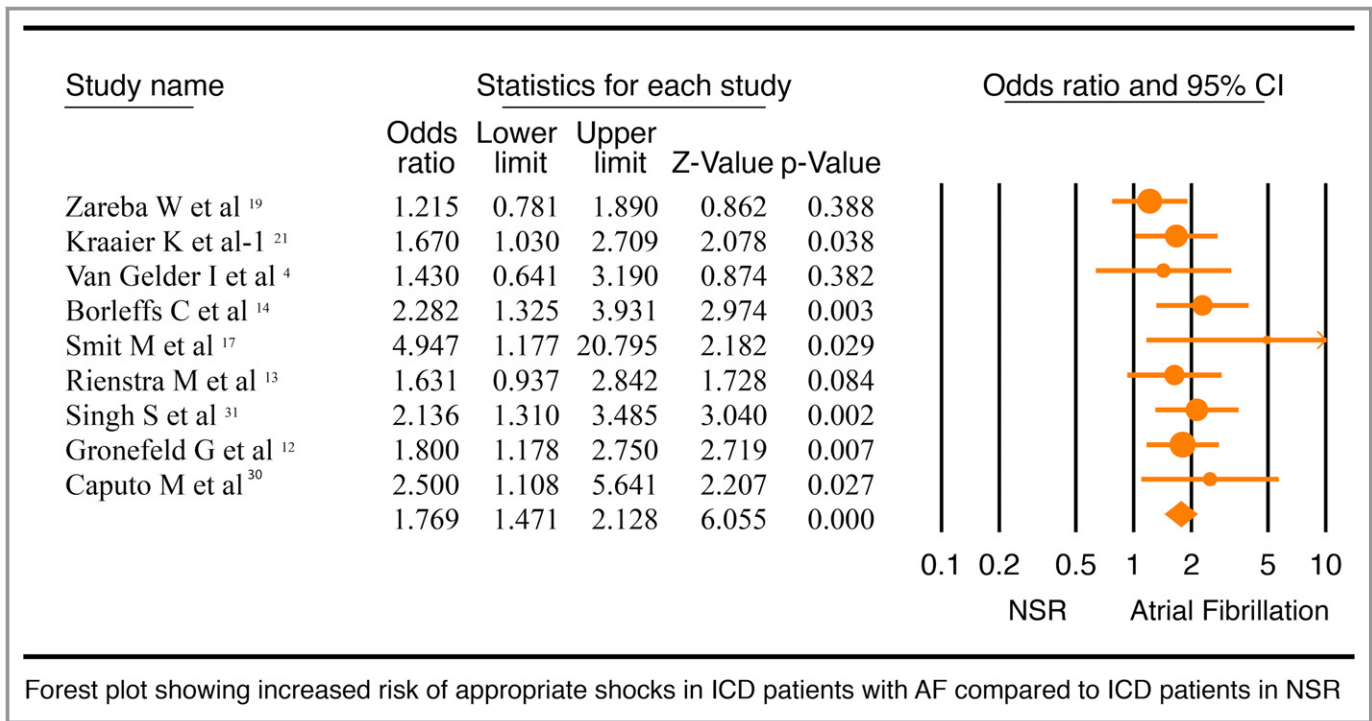
Study	ICD Programming
Borleffs et al <sup>11</sup>	Unspecified
Caputo et al <sup>27</sup>	Monitor Zone: >150 bpm. VT zone: 180 to 200 bpm. VF zone: >200 bpm
Grönefeld et al <sup>9</sup>	Varied based on patients' needs
Kraaier et al <sup>18</sup>	Unspecified
Rienstra et al <sup>10</sup>	VT zone: >150 bpm. VF zone: >200 bpm
Singh et al <sup>28</sup>	Unspecified
Smit et al <sup>14</sup>	VT zone: >150 bpm. VF zone: >200 bpm
van Gelder et al <sup>4</sup>	Unspecified
Zareba et al <sup>15</sup>	Unspecified

We then performed a meta-analysis of 3 studies<sup>15,28,29</sup> with 387 patients that compared all-cause mortality among AF patients with ICD to AF patients who met the criteria for ICD implantation, but were only on guideline-directed medical therapy. The all-cause mortality was comparable between AF patients with ICD and goal-directed medical therapy (OR, 0.69; 95% CI, 0.42–1.11;  $P = 0.12$ ;  $I^2 = 18.96$ ; Figure 3). A fixed-effects model did not change the outcome (OR, 0.70; 95% CI, 0.46–1.07;  $P = 0.10$ ;  $I^2 = 18.96$ ; Figure S5).

bpm indicates beats per minute; ICD, implantable cardioverter-defibrillator; VF, ventricular fibrillation; VT, ventricular tachycardia.

### Appropriate Shock Therapy

Nine studies<sup>4,9–11,14,15,18,27,28</sup> with 3680 patients assessed the association of AF and appropriate shock therapy among patients with ICD. Studies used an inconsistent protocol for



**Figure 4.** Forest plot comparing appropriate shock therapy in implantable cardioverter defibrillator (ICD) patients with atrial fibrillation (AF) and normal sinus rhythm (NSR). CI indicates confidence interval.

ICD programming, which have been summarized in Table 3. Our meta-analysis suggests that compared with NSR patients, AF patients with ICD are at higher risk of appropriate shock therapy (OR, 1.77; 95% CI, 1.47–2.13;  $P < 0.001$ ;  $I^2 = 0.00$ ; Figure 4). A separate fixed-effects model did not change the outcome (OR, 1.77; 95% CI, 1.47–2.13;  $P < 0.001$ ;  $I^2 = 0.00$ ; Figure S6). No significant publication bias was noted on a funnel plot of these studies (Figure S7). A separate sensitivity analysis, where we excluded the only abstract,<sup>18</sup> showed the same results (OR, 1.79; 95% CI, 1.46–2.19;  $P < 0.001$ ).

### Discussion

To our knowledge, this is the first meta-analysis comparing survival benefit of ICD in AF and NSR patients. The principal finding of this meta-analysis is that mortality ( $P < 0.001$ ) and appropriate shock therapy ( $P < 0.001$ ) are relatively higher in AF patients with ICD than NSR patients with ICD. In addition, the mortality benefit from ICD in AF patients, as compared with medical therapy alone, is currently unclear ( $P = 0.12$ ).

AF in the general population has been found to have an adverse prognosis and is independently associated with 1.5- to 1.9-fold increased risk of mortality, as reported in the Framingham study.<sup>3</sup> Similarly, the AVID (Antiarrhythmics Versus Implantable Defibrillators) registry analysis and the SOLVD (Studies of Left Ventricular Dysfunction) trial showed

that AF is associated with an increased mortality risk in patients presenting with ventricular arrhythmias (relative risk, 1.2; CI=1.03–1.04;  $P = 0.02$ )<sup>33</sup> and in patients with LV dysfunction (relative risk, 1.34; CI=1.12–1.62;  $P = 0.002$ ),<sup>34</sup> respectively. The reasons for adverse outcome in patients with AF is likely multifactorial and may include development and progression of HF, thromboembolic events, and use of antiarrhythmic drugs. Whether the presence of AF in patients with ICD with LV dysfunction and other comorbidities compounds the problem would be interesting to know. AF and HF are known to coexist, and their combination renders a poor prognosis.<sup>35</sup> Thus, patients who are candidates for ICD placement with a combination of AF and HF are at a higher risk of mortality compared to those with HF alone. When indicated, ICD improves survival; however, our meta-analysis on AF patients with ICD and goal-directed medical therapy shows no difference in mortality. Based on available data from 3 studies and 387 patients, our pooled analysis suggests that there is no difference in mortality when comparing AF patients with ICD to those AF patients who otherwise meet criteria for ICD, but are only on goal-directed medical therapy. It is important to note that the interpretation of the results of this particular analysis (with 3 studies and 387 patients) is limited because the lack of statistical significance may stem from a low statistical power. On the other hand, the comparison of similar-sized trials that tested the benefit of ICD in the general population shows only 1 of 3 trials that showed a significant

mortality benefit. The MADIT (Multicenter Automatic Defibrillator Implantation Trial)<sup>36</sup> included 196 high-risk patients (with unsustained ventricular tachycardias and other ventricular tachycardias not suppressed with Procainamide) than the typical primary prevention population and showed that overall mortality improved by 54% in the ICD arm, whereas the CASH (Cancer and Steroid Hormone) Study,<sup>37</sup> a secondary prevention trial with 288 patients, showed a 23% (nonsignificant) reduction in mortality rates with ICD as compared with medical therapy alone. On the other hand, the CAT (Cardiomyopathy Trial),<sup>38</sup> another primary prevention trial with 104 patients, showed no mortality benefit from ICD. In the CAT trial, there was only a 6% difference between groups (86% in ICD arm, 80% in control at 4 years), and the investigators attribute this lack of survival benefit to low event rate in the study. Perhaps a well-powered, randomized trial comparing patients with high AF burden with ICD with those who need ICD, but are being managed medically, will shed more light.

It is well established that ICD prolongs survival by delivering shock to terminate life-threatening arrhythmias; however, these shock therapies are not completely benign. Existing evidence shows that patients who receive defibrillator shock therapy have a higher mortality than those who do not.<sup>39–43</sup> Direct myocardial damage from defibrillator shock therapy impairs cardiac function, leading to hemodynamic compromise and poor prognosis.<sup>44–46</sup> Several studies have shown that AF independently increases the risk of inappropriate, as well as appropriate, shocks in patients with ICD.<sup>4,16,23,47</sup> AF was found to be the most common cause of inappropriate shock therapy in the MADIT-II trial.<sup>48</sup> Our study focuses on appropriate shocks and validates these findings, partially explaining the finding of increased mortality in ICD patients with AF compared to those without AF. It is, however, important to note that the MADIT RIT (Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy) trial,<sup>49</sup> that excluded permanent AF patients, showed reduction in inappropriate shocks and all-cause mortality by programming ICD shocks only for tachyarrhythmias of 200 beats per minute or higher. However, studies included in our meta-analysis were either published before the MADIT RIT, or ICD programming was based on specific needs of patients and did not specifically follow the MADIT RIT protocol. Although MADIT RIT programming decreased inappropriate shocks, mortality, and appropriate antitachycardia pacing therapy, it did not affect the incidence of appropriate shocks, which is shown to be increased in patients with AF in our analysis. Furthermore, in a substudy of the the MADIT RIT,<sup>50</sup> although confirming a decrease in inappropriate ICD therapy with high-rate programming even in patients with atrial arrhythmias, the inappropriate therapies were still significantly higher in patients with atrial arrhythmias compared to patients with NSR. It is notable, from MADIT RIT findings, that

not all the appropriate shocks are required to terminate ventricular tachycardia/ventricular fibrillation; therefore, one can speculate that appropriate shocks in pre-MADIT RIT studies are likely overestimating the necessary appropriate shock therapy. Nonetheless, it is currently unclear whether MADIT RIT settings would have changed the results of this meta-analysis. Therefore, this should be addressed in future randomized trials comparing high-rate therapy to conventional therapy, specifically in patients with AF.

Furthermore, Klein et al, in the PROFIT (Prospective Analysis of Risk Factor for Appropriate ICD Therapy) study, investigated the predictors of ventricular arrhythmias in 250 ICD patients and reported a 1.8-fold increased risk of ventricular arrhythmias at 2 years' follow-up in patients with AF.<sup>51</sup> Similarly, an association of ventricular arrhythmias with AF was also reported in 2 different studies in patients with ICD.<sup>9,52</sup> One explanation for this could be the higher incidence of ventricular arrhythmias in AF patients attributed to shared risk factors, like ischemia, increased sympathetic tone, or increased LV filling pressures, and hemodynamic changes, like decreased cardiac output, which may lead to altered electrophysiological property of the ventricle causing appropriate shock delivery.<sup>14</sup> Second, concomitant use of antiarrhythmic drugs for atrial arrhythmia can provoke ventricular arrhythmias because of their proarrhythmic potential and thereby further increasing the risk of mortality<sup>53,54</sup> and appropriate shocks with an ICD in place. A third possibility could be the development and progression of HF in AF patients given that lower ejection fraction has been associated with higher ICD-unresponsive sudden cardiac death.<sup>20</sup> It is important to note that several recent trials have shown that catheter ablation decreases AF burden and improves overall mortality, LV systolic function, and quality of life in AF patients with HF.<sup>55–57</sup> The effect of catheter ablation and atrioventricular nodal ablation plus right ventricular pacing on outcomes of AF patients with ICD could not be ascertained from the included studies and will provide the basis for future randomized controlled trials.

Although ICD is an effective strategy to reduce sudden cardiac death, poor outcomes in AF patients raises a question regarding the benefit of ICD in AF patients and further extends the discussion of carefully reviewing the need for ICD placement on a case-by-case basis. This also warrants multicenter, randomized controlled trials of ICD versus medical management in, specifically, HF patients with AF and NSR for head-to-head comparison.

## Limitations

Studies exploring predictors of mortality and appropriate shocks in patients with ICDs without an a priori hypothesis regarding AF offer a significant challenge attributed to the



possibility of nonreporting of negative studies. To combat that, we performed a sensitivity analysis excluding these studies from the meta-analysis and found similar results.

The included studies were observational or post-hoc analyses of prospective, randomized trials, and studies not reporting adjusted outcome measurements were included in the study with unadjusted event rates introducing unknown confounders.

For appropriate shocks, device settings were variable across studies, and therefore it is unclear whether MADIT RIT high-rate setting would have any impact on overall results.

Studies did not uniformly report AF type and whether AF was present at baseline or was new onset and detected by a device during the study, thereby limiting the interpretation of the results attributable to type of AF.

## Conclusions

In conclusion, our meta-analysis suggests that appropriate shock therapy and mortality are higher in AF patients with ICD as compared to NSR. With available data, the impact of ICD on all-cause mortality in AF patients when compared with goal-directed medical therapy is unclear. Randomized controlled trials comparing AF patients with ICD and those who have indications for ICD, but are only on medical therapy, are needed in this regard.

## Disclosures

None.

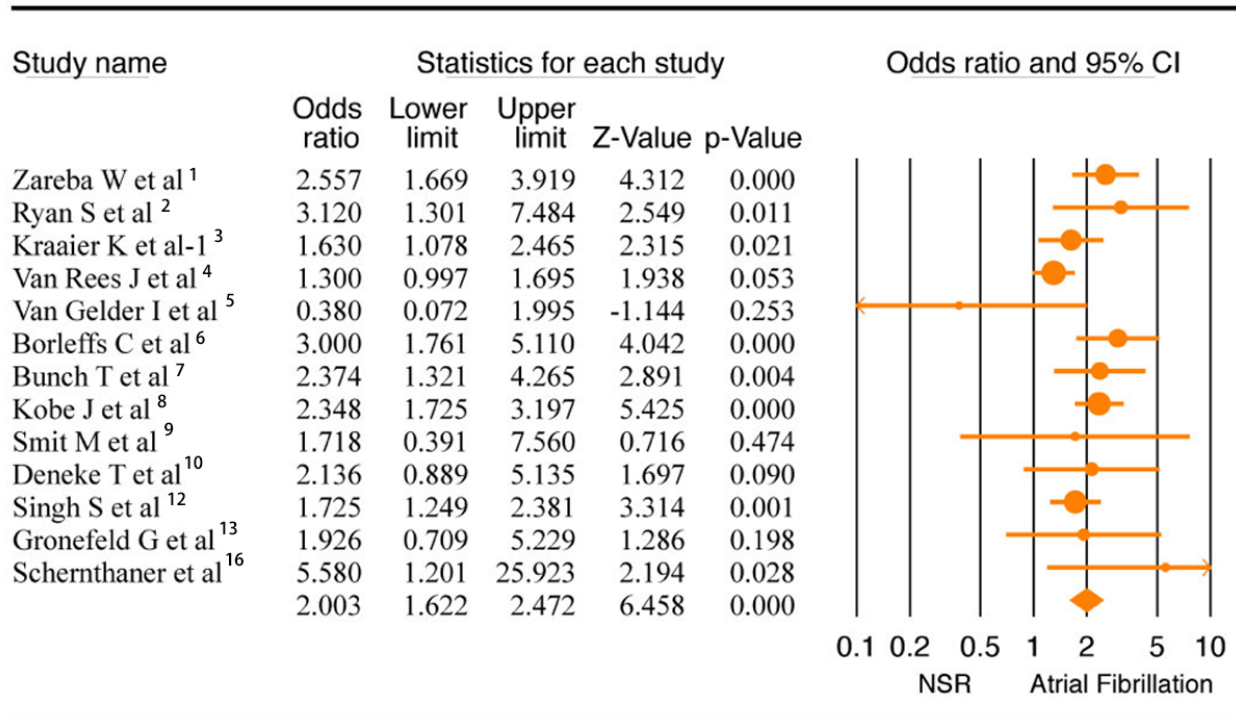
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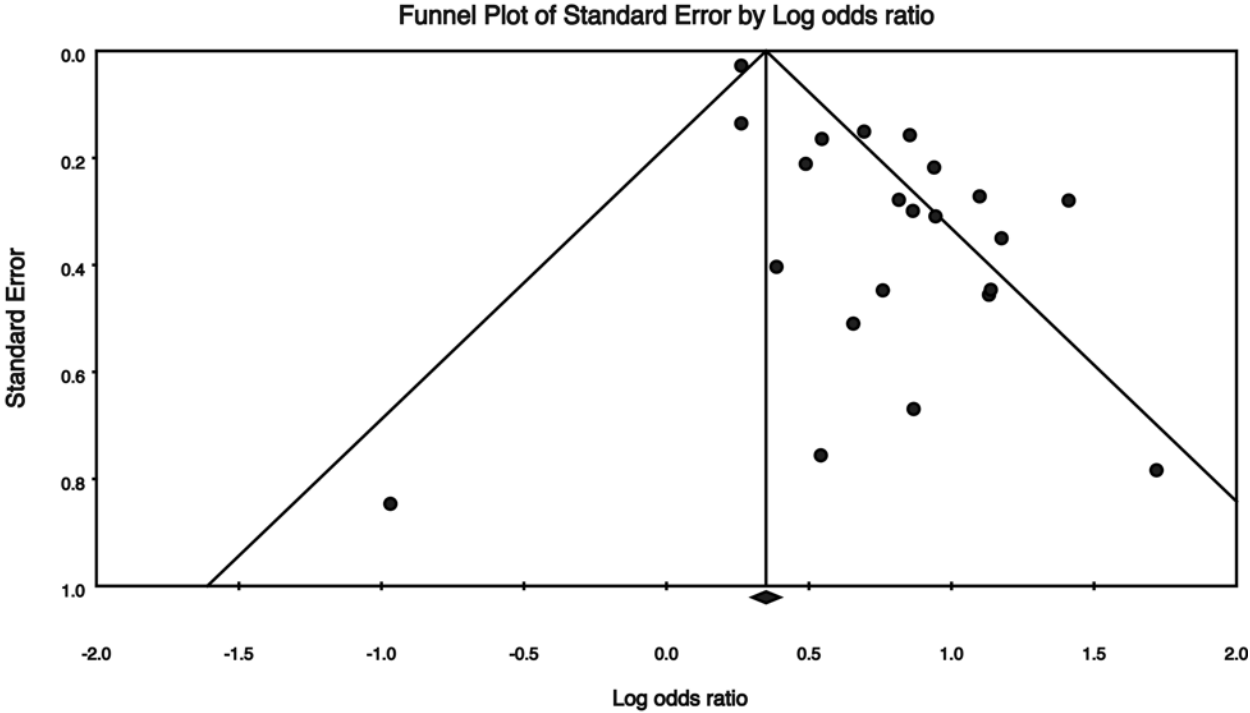
# **Supplemental Material**

**Figure S1. Forest plot of studies comparing all-cause mortality in Implantable Cardioverter Defibrillator (ICD) patients with atrial fibrillation (AF) and normal sinus rhythm (NSR). A Fixed-Effects model.**



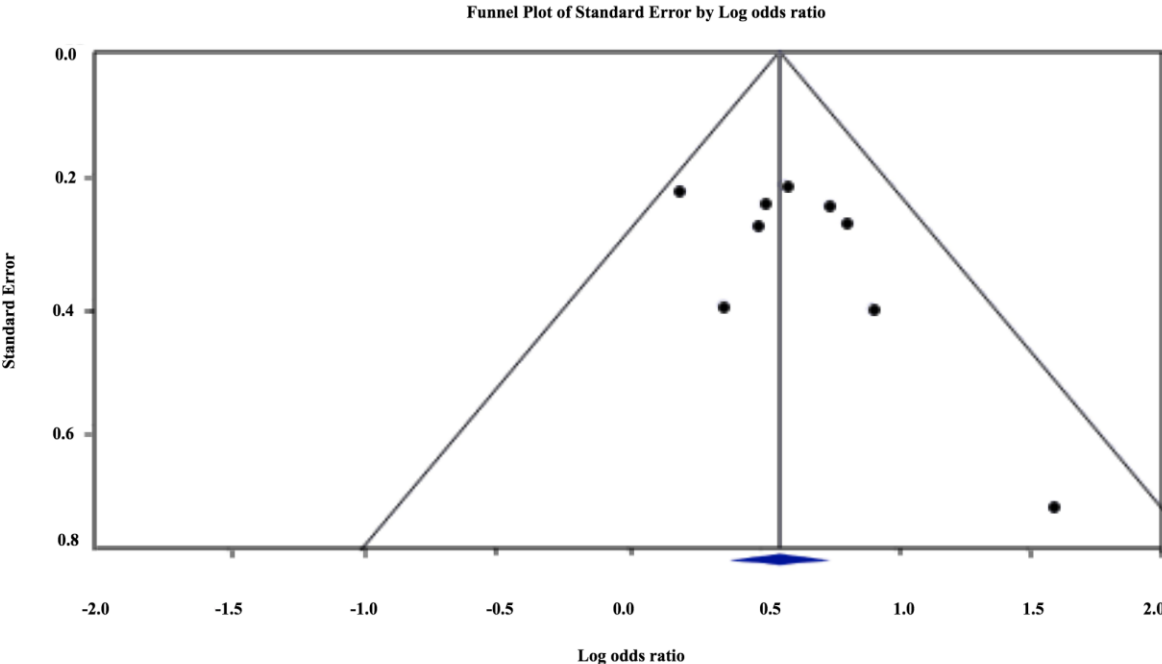
Forest plot showing increased risk of mortality in ICD patients with AF compared to ICD patients in NSR

Figure S2. Funnel plot for all-cause mortality.

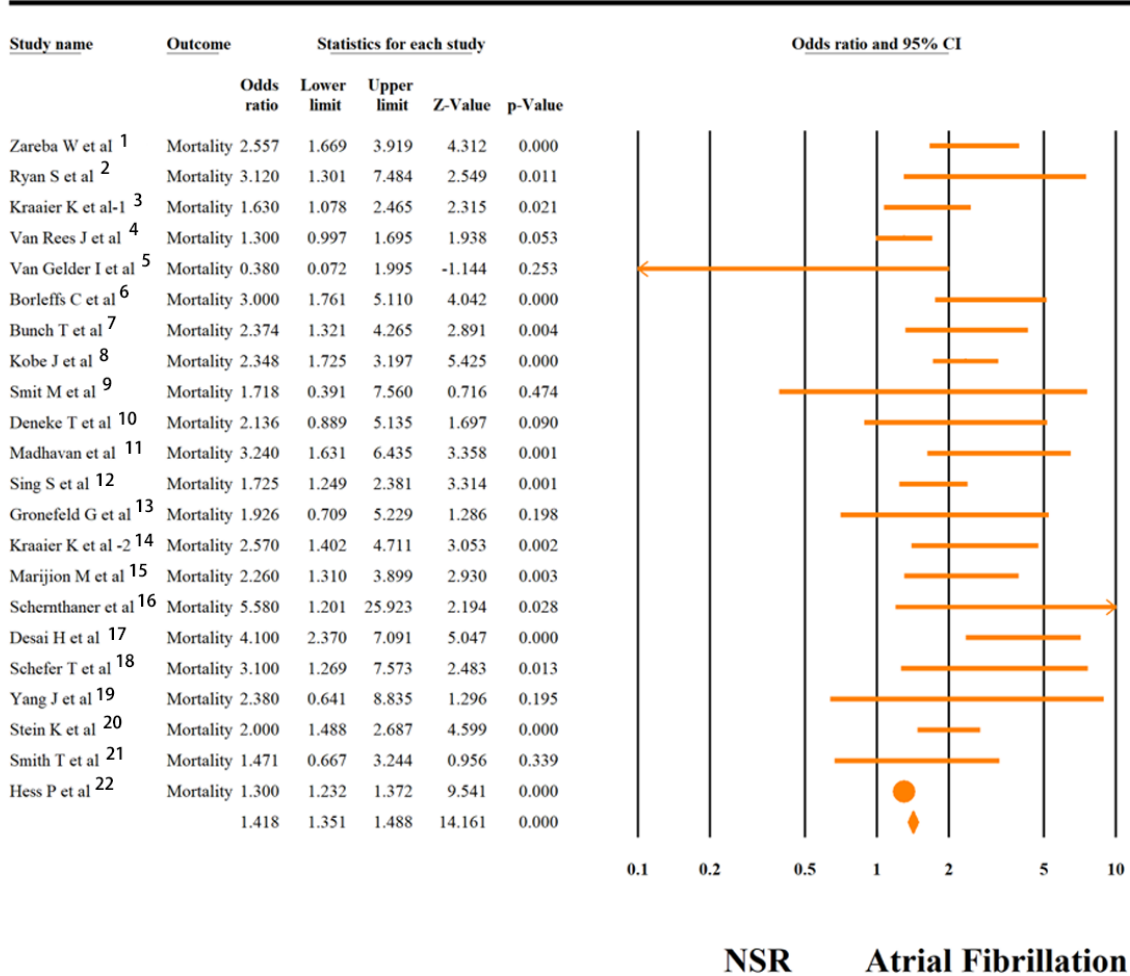


There appears to be paucity of studies published to the left of the final odds ratio of this meta-analysis, indicating a significant publication bias among studies comparing all-cause mortality between Implantable Cardioverter Defibrillator (ICD) patients with and without atrial fibrillation (AF)

Figure S3. Forest plot of studies with a priori hypothesis, comparing all-cause mortality in Implantable Cardioverter Defibrillator (ICD) patients with atrial fibrillation (AF) and normal sinus rhythm (NSR).

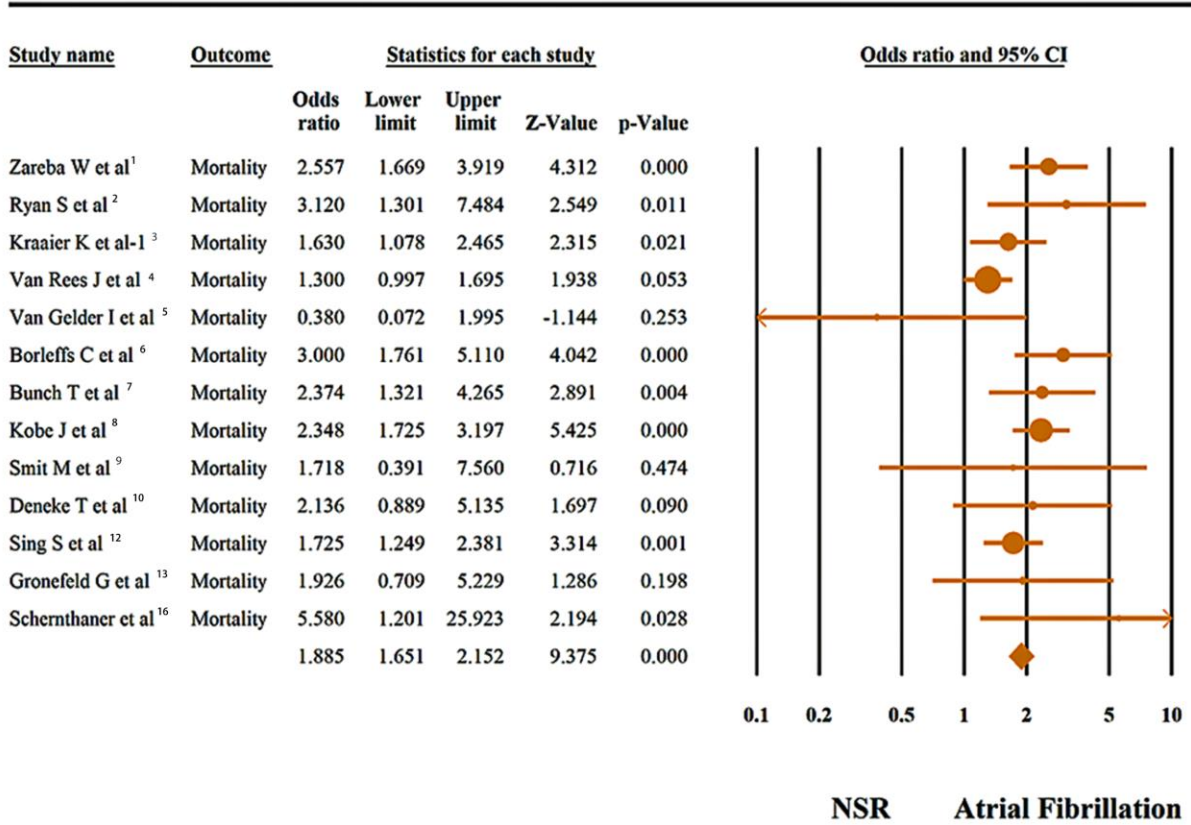


**Figure S4. Forest plot of studies with a priori hypothesis, comparing all-cause mortality in Implantable Cardioverter Defibrillator (ICD) patients with atrial fibrillation (AF) and normal sinus rhythm (NSR). A Fixed-Effects model.**



**Forest plot showing increased risk of mortality in ICD patients with AF compared to ICD patients in NSR**

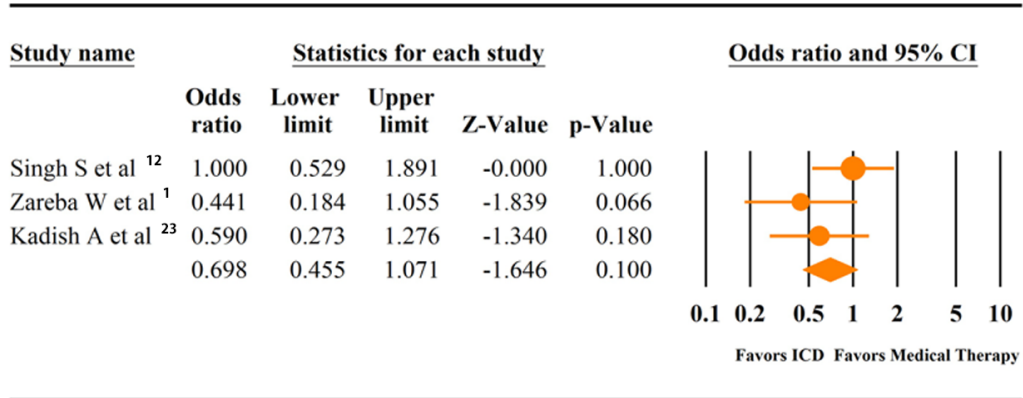
**Figure S5. Forest Plot comparing mortality in AF patients with Implantable Cardioverter Defibrillator (ICD) vs goal directed medical therapy (GDMT). A Fixed-Effects model.**



**Forest plot showing increased risk of mortality in ICD patients with AF compared to ICD patients in NSR**

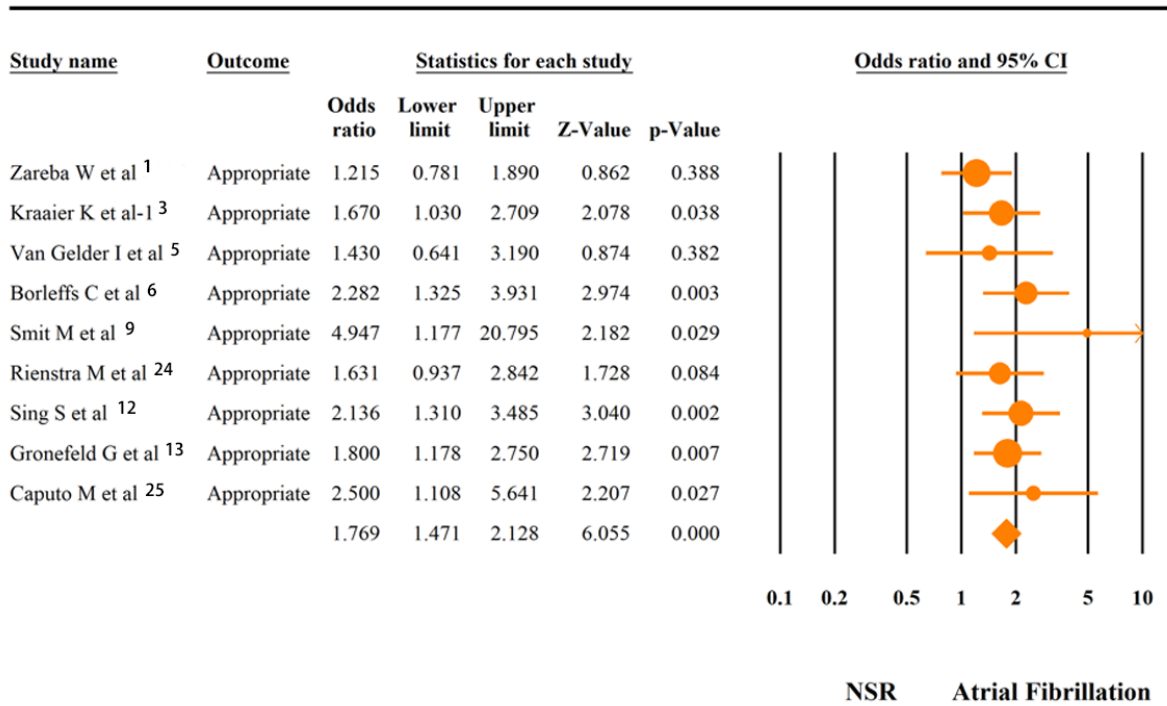


**Figure S6. Forest Plot comparing appropriate shock therapy in Implantable Cardioverter Defibrillator (ICD) patients with atrial fibrillation (AF) and normal sinus rhythm (NSR). A Fixed-Effects model.**



Forest plot showing no mortality benefit from ICD compared to medical therapy in AF patients

**Figure S7. Funnel plot for appropriate shock therapy.**



**Forest plot showing increased risk of appropriate shocks in ICD patients with AF compared to ICD patients in NSR**

The published studies are equally distributed on both sides of the final Odds Ratio of this meta-analysis, indicating no publication bias among studies comparing risk of appropriate shock therapy in Implantable Cardioverter Defibrillator (ICD) patients with and without atrial fibrillation (AF)

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