Efficacy of Implantable Cardioconverter Defibrillator or Cardiac Resynchronization Therapy Compared With Combined Therapy in Survival of Patients With Heart Failure

A Meta-Analysis

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Abstract: The aim of this meta-analysis was to compare the efficacy of implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT) monotherapies with CRT–ICD combined therapy.

Databases were searched to identify studies that compared CRT or ICD alone with CRT–ICD combined therapy in patients with heart failure. The primary outcome was rate of death for any cause, and secondary outcomes included rate of death or hospitalization due to heart failure or any cause.

Nine studies with 7679 patients were included. Combined data of ICD and CRT monotherapies found that there was a higher risk of all-cause death (odds ratio [OR] 1.348, $P < 0.001$) and death or hospitalization from heart failure (OR 1.368, $P < 0.001$) with monotherapy compared with CRT–ICD combined therapy. No significant difference was observed between mono and combined therapy groups for risk of death or hospitalization from any cause (OR 1.292, $P = 0.083$).

Compared with ICD or CRT monotherapy, CRT–ICD therapy had favorable outcomes regarding all-cause death and the risk of hospitalization or death due to heart failure.

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Abbreviations: CRT = cardiac resynchronization therapy, ICD = implantable cardioverter defibrillator, LBBB = left bundle branch block, NYHA = New York Heart Association, RBBB = right bundle branch block.

KEY MESSAGES

Compared with ICD or CRT monotherapy, CRT–ICD therapy had favorable outcomes regarding all-cause death and the risk of hospitalization or death due to heart failure.

The monotherapies and combined therapies were similar in regard to risk of death or hospitalization from any cause.

INTRODUCTION

Heart failure is a growing public health problem and a major cause of cardiovascular morbidity and mortality worldwide. It is also increasing in many countries owing to aging populations.[1,2] Despite recent advances in diagnostic and therapeutic options, mortality of patients with heart failure remains high, and is accompanied by a significant loss in quality of life.[3,4]

Important treatment options for patients with heart failure include not only pharmacologic therapies, but also device-based treatments such as implantable cardioverter defibrillators (ICDs) and biventricular cardiac pacing devices that can deliver cardiac resynchronization therapy (CRT).[5] Both ICDs and CRTs have shown benefit in patients with heart failure in a number of clinical trials, and have exhibited improvement in cardiac performance and a decrease in overall mortality compared with antiarrhythmic drugs.[6–13] A number of studies have compared ICD or CRT monotherapy with the combination of both therapies (CRT–ICD).[14–23] However, the findings from these studies have been inconsistent with only a few of the studies showing mortality benefits of the combined therapy compared with the monotherapy.[18,19,22–24]

The efficacy of ICD for preventing sudden cardiac death has been well studied. However, less is known regarding the efficacy of CRT either alone or in combination with ICD in regards to preventing heart failure-associated death. It is possible that the combined therapies may have synergistic effects in treating patients with heart failure. The aim of this meta-analysis was to compare the efficacy of ICD or CRT monotherapy with CRT–ICD combined therapy.

MATERIALS AND METHODS

Search Strategy

A comprehensive search of Medline, Cochrane, EMBASE, and Google Scholar (until September 2013) was carried out to identify randomized controlled or 2-arm prospective studies that compared CRT or ICD monotherapy with CRT–ICD therapy in patients with heart failure. The search was limited to English publications and performed using the following terms: heart failure, sudden cardiac death, sudden death, cardiac resynchronization therapy, CRT, implantable cardioconverter defibrillator, ICD, and Cardiac resynchronization therapy combined with implantable cardioverter defibrillator. Single-arm studies were excluded. An initial list of potential studies was screened by 2 independent reviewers. Any disagreement between the 2 reviewers was resolved by a third reviewer.

Data Extraction

The following data were extracted from the included studies using standardized forms: the name of the first author,

the title of the study, year of publication, study design, number of subjects in each treatment group, age and sex of patients, diagnostic criteria, results, and adverse events.

Included studies were assessed for risk of bias using the ''Risk of Bias'' assessment tool, Review Manager 5.1, ((RevMan) [Computer program]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and following Cochran recommendations.[25] An overall risk of bias was also determined.

Statistical Analysis

The primary outcome was rate of death for any cause, and secondary outcomes were rate of death or hospitalization due to any cause and rate of death or hospitalization due to heart failure. Heterogeneity among the studies was assessed by the Cochran Q and the I^2 statistics. If the Q statistic showed $P < 0.1$ or the I^2 statistic indicated $>50\%$, then heterogeneity existed among studies and a random effects model (DerSimonian–Laird method) was used. Otherwise, the fixed effects model was used (Mantel–Haenszel method). Sensitivity analysis was performed for all 3 outcomes based on the leave-one-out approach. Publication bias was assessed by funnel plot and Egger test when the number of studies included in a meta-analysis was >5.[26] A 2-sided P value <0.05 was considered statistically significant. All statistical analyses were performed using the software Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ).

Ethics

This study did not involve human subjects, so informed consent was not required. In addition, no approval was required from an institutional review board.

RESULTS

The database search identified 362 possible references; of these, 342 were excluded because they were not relevant for this analysis (Figure 1). Of the 20 remaining studies, 11 were also excluded: 4 were secondary reports of an included study,[27–30] 4 did not use ICD, CRT, or CRT–ICD therapies,[31–34] 2 did not report the outcomes of interest,[35,36] and 1 did not report numerical data for the outcomes of interest.[24] A total of 9 studies were included (Figure 1).[15–23]
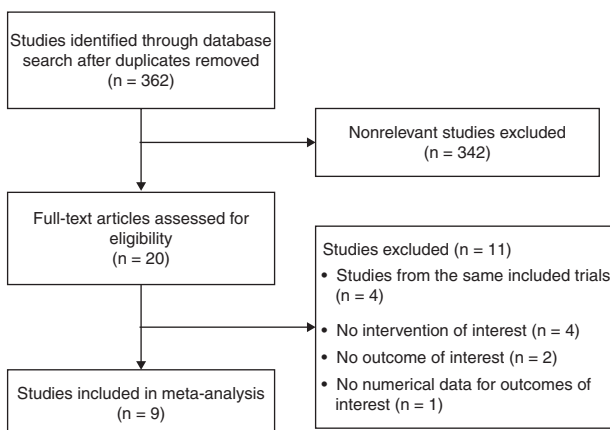

FIGURE 1. Flow chart for study selection.

Characteristics of the Included Studies

The clinical characteristics of patients in the included studies are summarized in Table 1. The 9 studies included 7679 patients (n = 3467 in the monotherapy groups and n = 4212 in the combined therapy group). Across the 9 studies, the number of patients who received CRT or ICD monotherapy ranged from 174 to 617 and 73 to 904, respectively, and 85 to 1089 for the combined therapy (Table 1). Age ranged from 61.8 to 68 years, and a lesser percentage of participants were women (range 9.9%–33.7%). Overall, 1436 patients were treated with CRT alone (and compared with the meta-analysis to 1848 patients treated with CRT–ICD), and 2031 patients were treated with ICD alone (and compared with 2364 patients treated with CRT–ICD). Among the 8 studies that reported the group-specific data on ischemic cardiomyopathy, the percentages were similar for 6 of the 8 but differed by 22% and 28% for the other 2 studies.[18,21] The studies enrolled patients of varying New York Heart Association (NYHA) functional class, with 3 studies enrolling class III/IV,[19,21,23] 2 each enrolling class II–IV[18,20] and I/II,[15,16] and 1 each enrolling class II/III[22] and class II[17] patients. The proportion of patients who were NYHA class I, II, III, and IV was 4.9%, 50.1%, 39.4%, and 5.6%, respectively. Subgroup analysis included studies of class II–IV patients. The mean left ventricular (LV) ejection fraction, reported by all studies, and the QRS duration, reported by all but 2 studies,[16,20] were similar (20–26.8 and 153–169 milliseconds, respectively); however, the LV end diastolic and systolic diameters varied between the studies (67–322 mm [reported by 6 studies[15–17,19,21,23]] and 57–248 mm [reported by 4 studies[15–17,23]], respectively). The proportion of patients with left bundle branch block (LBBB) and right bundle branch block (RBBB), reported by 4[16,18,19,22] and 5[16,17,19,22,23] studies, respectively, also varied between studies (LBBB range 11.9%–75%, RBBB range 7.6%–20.8%). For the comparison of ICD versus CRT–ICD, only 2 studies reported the proportion of patients with LBBB: 71.1% in Tang et al[22] and 71.3% in Moss et al.[16] Tang et al reported a substantial difference between the 2 treatment groups (71.1% vs 11.9%).

Table 2 summarizes the outcomes of interest for the included studies. Five of the studies reported higher rates of all-cause death in the monotherapy group (range 8.8%–26.1%) compared with the combined therapy group (range 4.6%–20.8%) (Table 2).[18–20,22,23] The rates of all-cause death were similar for 1 study,[17] whereas 3 had a higher rate for patients in the combined arm.[15,16,21] Of the 4 studies that reported death or hospitalization due to heart failure or any cause,[18,19,22,23] 3 found a higher proportion of patients died or were hospitalized due to any cause with monotherapy (range 26.2%–67.1%) compared with combined therapy (range 15.0%–65.5%). Death or hospitalization for any cause was slightly higher in the combined group for the other study. Of the 6 studies that reported death or hospitalization due to heart failure,[15,16,19,21–23] rates were similar between the mono (range 7.9%–38.4%) and combined (range 4.1%–35.6%) therapy groups for most studies; however, 2 studies reported a higher rate among patients in the monotherapy group.[19,22]

Quality Assessment

Risk bias analysis indicated that in general there was low risk of data bias across the 9 studies (Figure 2A and B). Four studies[15,16,18,21] showed a high risk of bias in several areas including randomization method, allocation concealment (both selection bias), blinding of subjects and/or personnel

TABLE 1. Summary of Basic Characteristics of Studies Included in the Meta-Analysis

Study	Study Design (Trial Name)	Number of Patients		Age, y*		Female†		Ischemic cardiomyopathy†		NYHA I/II/III/IV†		LVEF (%)*		LV End-Diastolic Diameter, mm*		LV End-Systolic Diameter, mm*		QRS Duration, ms*		LBBB†		RBBB†	
		Mono	Combined	Mono	Combined	Mono	Combined	Mono	Combined	Mono	Combined	Mono	Combined	Mono	Combined	Mono	Combined	Mono	Combined	Mono	Combined	Mono	Combined
CRT vs CRT–ICD																							
Schuchert et al[21] (MASCOT)	RCT	174	228	68 (10)	68 (9)	30.5	13.6	38	60	0/0/83/17	0/0/87/13	25 (7)	25 (7)	69 (10)	71 (9)	na	na	169 (31)	159 (26)	na	na	na	na
Linde et al[15] (REVERSE)	RCT	191	419	61.8 (10.6)	62.9 (10.6)	20.4	22.0	51	56	17/83/0/0	18/82/0/0	26.4 (7.1)	26.8 (7.0)	70 (90)	69 (9)	58 (11)	57 (10)	154 (24)	153 (21)	na	na	na	na
Auricchio et al[18] Prospective		454	606	64 (10)	64 (9)	33.7	16.8	27	55	0/4/72/11	0/6/78/16	25 (7)	25 (7)	na	na	na	na	168 (28)	169 (30)		75	na	na
Bristow et al[19] (COMPANION)	RCT	617	595	67	66	32.7	32.6	54	55	0/0/87/13	0/0/86/14	22	20	68	67	na	na	160	160	69	73	12	10
ICD vs CRT-ICD																							
Tang et al[22] (RAFT)	RCT	904	894	66.2 (9.4)	66.1 (9.3)	19.0	15.2	64.9	68.7	0/81/19/0	0/79/21/0	22.6 (5.1)	22.6 (5.4)	na	na	na	na	Intrinsic: 158.3 (24.0) Paced: 210.3 (18.3), n=67 ≥150: 65.1%	Intrinsic: 157 (23.6), n=826 Paced: 206.5 (24.0), n=68 ≥150: 64.2%	71.1	11.9	10.3	7.6
Moss et al[16] (MADIT-CRT)	RCT	731	1089	64 (11)	65 (11)	24.4	25.3	54.9	54.9	15/85/0/0/	14/86/0/0/	24 (5)	24 (5)	251 (65)‡	245 (60)‡	179 (53)‡	175 (48)‡	165 (23)	166 (25)	71.3	69.9	12.6	12.5
Abraham et al[17] (MIRACLE ICD II)	RCT	101	85	63.1 (12.1)	63.0 (12.8)	9.9	11.8	58.4	55.3	0/100/0/0/	0/100/0/0/	24.6 (6.7)	24.4 (6.6)	75 (10)	76 (10)	65 (12)	65 (12)	165 (23)	166 (25)	na	na	20.8	11.8
Young et al[23] (MIRACLE ICD)	RCT	182	187	67.6 (9.2)	66.6 (11.3)	22.5	24.1	75.8	64.0	0/0/90/10	0/0/88/12	23.9 (6.0)	24.2 (6.5)	311 (96)‡	322 (100)‡	240 (87)‡	248 (93)‡	162 (22)	165 (22)	na	na	13	13
Lozano et al[20]	RCT	113	109	65 (10)			17		68		0/35/57/8		22 (7)	na	na	na	na	>120		na	na	na	na

COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial, CRT = cardiac resynchronization therapy, HF = heart failure, ICD = implantable cardioverter defibrillator, LBBB = left bundle branch block, LV = left ventricle, LVEF = left ventricular ejection fraction, MADIT = Multicenter Automatic Defibrillator Implantation Trial, MASCOT = Management of Atrial Fibrillation (AF) Suppression in AF-Heart Failure (HF) Comorbidity Therapy trial, MIRACLE = Multicenter InSync Randomized Clinical Evaluation trial, na = not available, NYHA = New York Heart Association, RAFT = Resynchronization–Defibrillation for Ambulatory Heart Failure Trial, REVERSE = Resynchronization Reverses Remodeling In Systolic Left Ventricular Dysfunction trial, RBBB = right bundle branch block, RCT = randomized clinical trial.
* Data presented as mean (standard deviation).
† Data presented as percentage.
‡ Volume (mL).

TABLE 2. Summary of Outcomes of Studies Included in the Meta-Analysis

Treatment Groups	Study	All-Cause Death		All-Cause Death or Hospitalization		Heart Failure-Related Death or Hospitalization	
		Mono	Combined	Mono	Combined	Mono	Combined
CRT vs CRT–ICD	Schuchert et al[21]	19 (10.9)	20 (8.8)	na	na	38 (21.8)	42 (18.4)
	Linde et al[15]	3 (1.6)	9 (2.2)	na	na	15 (7.9)	17 (4.1)
	Auricchio et al[18]	96 (21.1)	74 (12.2)	119 (26.2)	91 (15.0)	na	na
	Bristow et al[19]	131 (21.2)	105 (17.6)	414 (67.1)	390 (65.5)	237 (38.4)	212 (35.6)
ICD vs CRT–ICD	Tang et al[22]	236 (26.1)	186 (20.8)	364 (40.3)	297 (33.2)	236 (26.1)	174 (19.5)
	Moss et al[16]	53 (7.3)	74 (6.8)	na	na	185 (25.3)	187 (17.2)
	Abraham et al[17]	2 (2.0)	2 (2.4)	na	na	na	na
	Young et al[23]	15 (8.2)	14 (7.5)	78 (42.9)	85 (45.5)	47 (25.9)	48 (25.7)
	Lozano et al[20]	10 (8.8)	5 (4.6)	na	na	na	na

Data presented as number of events (rate). CRT = cardiac resynchronization therapy, ICD = implantable cardioverter defibrillator, na = not available.
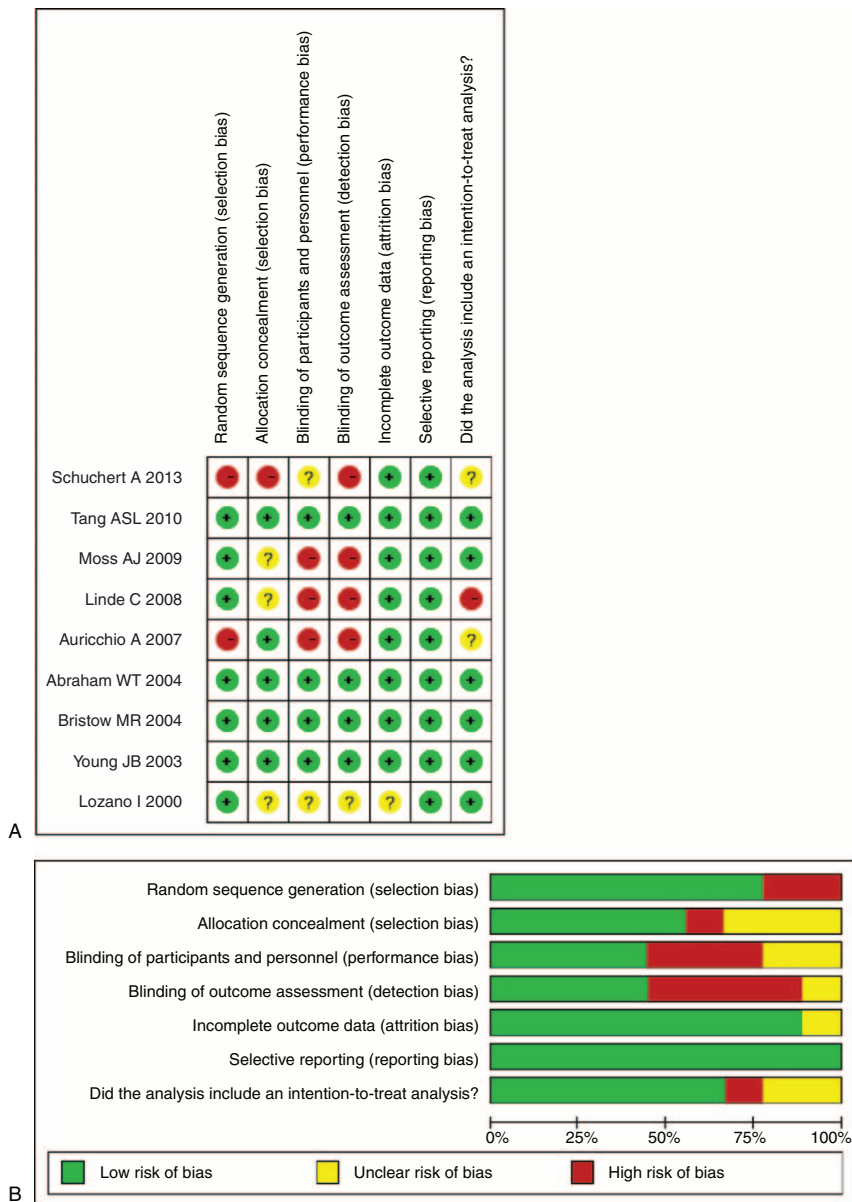

FIGURE 2. Quality assessment for each included study was summarized in (A) ''risk of bias summary'' or (B) presented as percentages across all included studies in ''risk of bias graph.''

A

Study name	Number of event/ total Mono	Number of event/ total Combined	Odds ratio	Lower limit	Upper limit	Z-value	P-value	Relative weight (subtotal)	Relative weight (total)
Schuchert (2013)*	19/174	20/228	1.268	0.654	2.456	0.703	0.482	5.038	4.21
Linde (2008)	3/191	9/419	0.723	0.196	2.666	−0.487	0.626	-	1.54
Tang (2010)*	236/904	186/894	1.345	1.080	1.675	2.647	0.008	44.986	37.55
Moss (2009)	53/731	74/1089	1.079	0.749	1.555	0.410	0.682	-	14.98
Auricchio (2007)*	96/454	74/606	1.925	1.381	2.682	3.869	<0.001	16.267	13.58
Bristow (2004)*	131/617	105/595	1.260	0.946	1.677	1.582	0.114	27.352	22.83
Abraham (2004)*	2/101	2/85	0.830	0.116	5.935	−0.186	0.853	0.707	0.59
Young (2003)*	15/182	14/187	1.102	0.516	2.354	0.250	0.803	4.135	3.45
Lozano (2000)*	10/113	5/109	2.001	0.661	6.057	1.222	0.220	1.515	1.27
Subtotal (fixed)*			1.408	1.218	1.629	4.615	<0.001		
Total (fixed)			1.348	1.179	1.542	4.373	<0.001		

Heterogeneity test:

Subtotal*: Q-value = 0 with P-value <0.001 I-square = 0%

Total*: Q-value = 5.32 with P-value = 0.503 I-square = 0%

B

Study name	Number of event/ total Mono	Number of event/ total Combined	Odds ratio	Lower limit	Upper limit	Z-value	P-value	Relative weight (subtotal)	Relative weight (total)
Tang (2010)*	364/904	297/894	1.358	1.120	1.646	3.118	0.002	28.900	-
Auricchio (2007)*	119/454	91/606	2.012	1.482	2.731	4.481	<0.001	24.188	-
Bristow (2004)*	414/617	390/595	1.074	0.846	1.363	0.589	0.556	27.057	-
Young (2003)*	78/182	85/187	0.900	0.597	1.358	−0.503	0.615	19.855	-
Subtotal (random)*			1.292	0.967	1.725	1.734	0.083		

Heterogeneity test:

Subtotal*: Q-value = 13.56 with P-value = 0.004, I-square = 77.88%

Total*: Not assessed

C

Study name	Number of event/ total Mono	Number of event/ total Combined	Odds ratio	Lower limit	Upper limit	Z-value	P-value	Relative weight (subtotal)	Relative weight (total)
Schuchert (2013)*	38/174	42/228	1.236	0.756	2.021	0.846	0398	8.74	6.06
Linde (2008)	15/191	17/419	2.006	0.983	4.097	1.912	0.056	-	2.87
Tang (2010)*	236/904	174/894	1.458	1.167	1.821	3.325	0.001	42.77	29.63
Bristow (2004)*	185/731	187/1089	1.128	0.893	1.424	1.009	0.313	-	26.87
Moss (2009)	237/617	212/595	1.630	1.296	2.051	4.179	<0.001	38.78	27.84
Young (2003)*	47/182	48/187	1.011	0.634	1.611	0.044	0.965	9.71	6.73
Subtotal (fixed)*			1.255	1.086	1.452	3.066	0.002		
Total (fixed)			1.368	1.212	1.544	5.081	<0.001		

Heterogeneity test:

Subtotal*: Q-value = 3.39 with P-value = 3.000, I-square = 11.43%

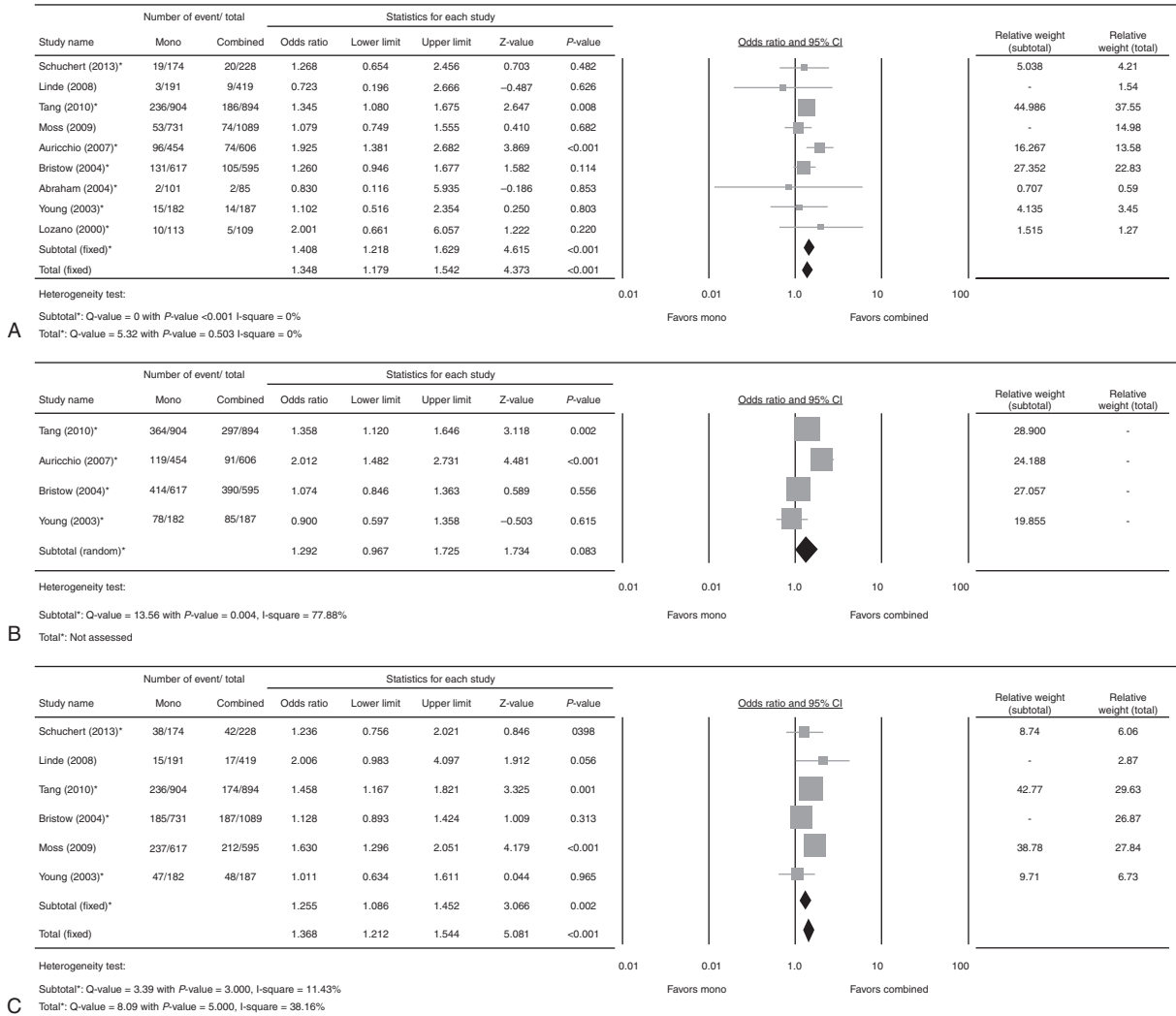Total*: Q-value = 8.09 with P-value = 5.000, I-square = 38.16%

FIGURE 3. Meta-analysis for treatment effects between monotherapy (ICD only or CRT only) versus combined therapy (CRT–ICD) on (A) the risk of all-cause death, n = 9; (B) the risk of death or hospitalization from any cause, n = 4; (C) the risk of death or hospitalization from heart failure, n = 6. *Studies with NYHA class II–IV patients were also analyzed as a subgroup. CRT = cardiac resynchronization therapy, ICD = implantable cardioverter defibrillator, NYHA = New York Heart Association.

(performance bias), and blinding of outcome assessments (Figure 2A). For all of the studies combined, the greatest biases were how patients were randomized and blinding of outcome assessments, followed by selection bias and lack of an intent-to-treat analysis (Figure 2B).

Meta-Analysis Comparing Treatments

Monotherapy Versus Combined Therapy

For all studies overall, there was a higher risk of all-cause death in patients receiving monotherapy compared with those treated with combined therapy (pooled odds ratio [OR] 1.348, $P < 0.001$). The results were similar for those studies that enrolled only patients who were NYHA class II–IV (pooled OR 1.408, $P < 0.001$) (Figure 3A). The data was not affected by publication bias, because the funnel plot analysis showed no obvious asymmetry (P value of 0.386) (Figure 4).
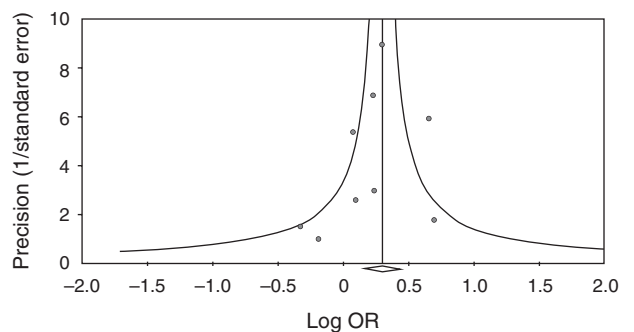

FIGURE 4. Funnel plot of standard error by log OR for monotherapy versus combined therapy for the risk of all-cause death for all 9 studies. The absence of publication bias is indicated by the data points forming a symmetric funnel-shaped distribution and 1-tailed $P > 0.05$ by Egger test. OR = odds ratio.

For the risk of death or hospitalization from any cause, no significant difference was observed between mono and combined therapy groups (pooled OR 1.292, $P = 0.083$) (Figure 3B). However, there was a higher risk of death or hospitalization from heart failure with monotherapy compared with combined therapy for studies that enrolled patients of all NYHA classes (pooled OR 1.368, $P < 0.001$) as well as for those that enrolled only NYHA class II–IV patients (pooled OR 1.255, $P = 0.002$) (Figure 3C).

CRT Versus CRT–ICD

There was a significant higher risk of all-cause death in patients treated with CRT monotherapy compared with those who received CRT–ICD therapy (pooled OR 1.455, $P < 0.001$) (Figure 5A). However, the 2 therapies were similar in respect to the rate of death or hospitalization due to any cause (pooled OR 1.459, $P = 0.228$) (Figure 5B) and for the rate of death or hospitalization from heart failure (pooled OR 1.197, $P = 0.082$) (Figure 5C).

ICD Versus CRT–ICD

The meta-analysis showed a significant higher risk of all-cause death in patients treated with ICD alone compared with those receiving CRT–ICD therapy (pooled OR 1.271, $P = 0.009$) (Figure 5A). There was no significant difference in the risk of death or hospitalization from any cause between treatments (pooled OR 1.153, $P = 0.481$) (Figure 5B). However, there was a significantly higher risk of death or hospitalization from heart failure with ICD therapy compared with CRT–ICD therapy (pooled OR 1.471, $P < 0.001$, Figure 5C).

Sensitivity Analysis

Sensitivity analysis using a leave-one-out approach did not affect the direction or magnitude of any of the pooled estimates, and there was not a large amount of variation among the different studies (Table 3), indicating no one study overly influenced the findings.

DISCUSSION

CRT is designed to eliminate the desynchronization of cardiac contraction in patients with heart failure, and ICD is designed to detect and correct high-risk arrhythmias. Whether the combination of CRT and ICD would have greater benefit than either treatment alone is not clear. The aim of this meta-analysis was to assess the efficacy of CRT and ICD
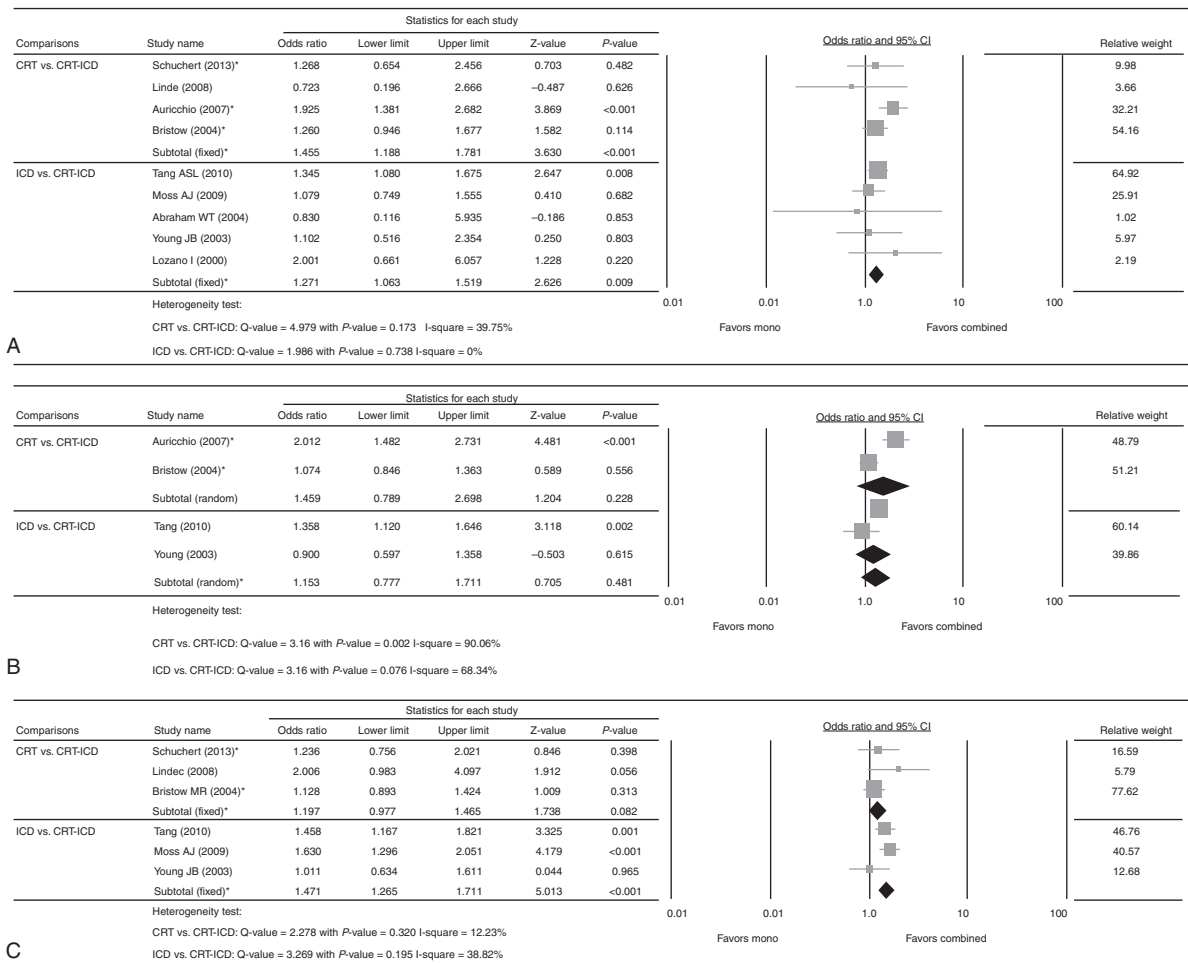

FIGURE 5. Meta-analysis for treatment effects of CRT only versus CRT–ICD and ICD only versus CRT–ICD on (A) the risk of all-cause death, (B) the risk of death or hospitalization from any cause, (C) the risk of death or hospitalization from heart failure. CRT = cardiac resynchronization therapy, ICD = implantable cardioverter defibrillator.

TABLE 3. Sensitivity Analyses for Meta-Analysis Using Leave-One-Out Approach

Outcomes (Comparison)	Study Name	Statistics With Study Removed				
		OR	Lower Limit	Upper Limit	Z Value	P Value
Risk of all-cause death (mono vs combined)	Schuchert et al[21]	1.352	1.179	1.550	4.320	<0.001
	Linde et al[15]	1.358	1.187	1.554	4.451	<0.001
	Tang et al[22]	1.350	1.140	1.599	3.481	<0.001
	Moss et al[16]	1.396	1.208	1.612	4.529	<0.001
	Auricchio et al[18]	1.258	1.086	1.456	3.065	0.002
	Bristow et al[19]	1.375	1.181	1.600	4.114	<0.001
	Abraham et al[17]	1.351	1.182	1.546	4.396	<0.001
	Young et al[23]	1.357	1.184	1.555	4.398	<0.001
	Lozano et al[20]	1.340	1.171	1.534	4.249	<0.001
Risk of all-cause death or hospitalization (mono vs combined)	Tang et al[22]	1.259	0.792	2.002	0.973	0.331
	Auricchio et al[18]	1.147	0.918	1.434	1.205	0.228
	Bristow et al[19]	1.378	0.943	2.012	1.657	0.097
	Young et al[23]	1.412	1.032	1.931	2.156	0.031
Risk of heart failure-related death or hospitalization (mono vs combined)	Schuchert et al[21]	1.375	1.214	1.558	5.004	<0.001
	Linde et al[15]	1.352	1.196	1.528	4.817	<0.001
	Tang et al[22]	1.329	1.151	1.535	3.867	<0.001
	Bristow et al[19]	1.467	1.273	1.690	5.309	<0.001
	Moss et al[16]	1.278	1.108	1.473	3.379	0.001
	Young et al[23]	1.397	1.232	1.583	5.227	<0.001
Risk of all-cause death (CRT vs CRT−ICD)	Schuchert et al[21]	1.480	1.195	1.832	3.594	<0.001
	Linde et al[15]	1.484	1.208	1.823	3.758	<0.001
	Auricchio et al[18]	1.234	0.954	1.596	1.601	0.109
	Bristow et al[19]	1.694	1.268	2.261	3.572	<0.001
Risk of all-cause death (ICD vs CRT−ICD)	Tang et al[22]	1.130	0.827	1.543	0.768	0.443
	Moss et al[16]	1.336	1.088	1.642	2.761	0.006
	Abraham et al[17]	1.274	1.064	1.525	2.634	0.008
	Young et al[23]	1.280	1.064	1.539	2.621	0.009
	Lozano et al[20]	1.254	1.045	1.504	2.440	0.015

CRT = cardiac resynchronization therapy, ICD = implantable cardioverter defibrillator, OR = odds ratio.

monotherapies compared with CRT−ICD combined therapy in reducing all-cause death or death or hospitalization due to any cause or heart failure. To date, only 1 meta-analysis, published almost 8 years ago, has compared the efficacy of CRT monotherapy with CRT−ICD combined therapy in patients with heart failure.[37] Therefore, our results provide a crucial update to the field.

Our meta-analysis included 9 studies with a total of 7679 patients. Combined data of ICD and CRT monotherapies found that there was a higher risk of all-cause death and death or hospitalization from heart failure with monotherapy compared with CRT−ICD combined therapy. No significant difference was observed between mono and combined therapy groups for risk of death or hospitalization from any cause. There was a higher risk of all-cause death with CRT and ICD monotherapies compared with CRT−ICD therapy, and a higher risk of death or hospitalization due to heart failure for ICD compared with CRT−ICD. CRT and CRT−ICD had similar risk for death or hospitalization due to heart failure. CRT−ICD did not show benefit compared with the monotherapies for the risk of death or hospitalization from any cause. In addition, our subgroup analysis of NYHA classes revealed that risk was similar for patients of all classes and those who are class II–IV. These findings are consistent with CRT−ICD generally having greater benefit for reducing all-cause death in patients compared with ICD or CRT monotherapy, and for reducing death or hospitalization due to heart failure compared with ICD monotherapy.

This latter finding may indicate an advantage of CRT over ICD in reducing the risk of death or hospitalization due to heart failure, and is consistent with a prior meta-analysis that found that hospitalization due to heart failure was reduced significantly greater in patients receiving CRT compared with ICD therapy (11.6% vs 18.2%, $P < 0.001$).[38] The previous study also

found that CRT resulted in a greater reduction in all-cause mortality compared with ICD (8% vs 11.5%, $P = 0.04$).

Our findings are consistent with previous meta-analyses that evaluated the efficacy of ICD compared with CRT−ICD in patients with heart failure.[39–41] A meta-analysis by Rossi et al[39] compared ICD with CRT−ICD in reducing all-cause mortality and hospitalization due to heart failure. Their analysis included 6 studies. They found that ICDs alone and CRT−ICD significantly reduced hospitalization rates due to heart failure compared with no ICD or no CRT therapy. They also found that CRT−ICD reduced all-cause mortality, but had no clear impact on heart failure-associated hospitalization compared with ICD monotherapy.

Similarly, Bertoldi et al[40] performed a meta-analysis that included 6 studies with a total of 5364 patients with heart failure that compared CRT−ICD combined therapy with ICD alone. They found that CRT−ICD therapy was associated with a significant reduction in all-cause mortality (relative risk 0.83, 95% CI 0.72–0.96). Chen et al[41] performed a meta-analysis that pooled 8 randomized controlled trials characterizing 5674 patients with heart failure. Their meta-analysis found that the CRT−ICD therapy was associated with significant improvement in clinical conditions (OR 1.66, 95% CI 1.33–2.07), reduction in all-cause mortality (OR 0.8, 95% CI 0.67–0.95), and hospitalization (OR 0.7, 95% CI 0.6–0.81) compared with ICD alone.

Like our analysis, a meta-analysis by Lam and Owen[37] compared combined therapy to both CRT and ICD monotherapies. Lam and Owen analyzed all-cause death, whereas we further analyzed all-cause death or hospitalization and heart failure-related death or hospitalization. Although both meta-analyses found higher risk of all-cause death in CRT alone or ICD alone than CRT−ICD, results by Lam and Owen did not

reach statistical significance (combined therapy vs CRT 0.85 [0.60–.22], combined therapy vs ICD 0.82 [0.57–1.18]). Our meta-analysis included more studies, and we suspect that the larger number of patients contributed to our statistically significant results.

Our analysis indicated a benefit of combined CRT–ICD therapy compared with either ICD or CRT monotherapy. However, the patient population of the studies used in this analysis had a higher proportion of men compared with women, making it difficult to generalize our findings to women. In addition, the number of studies included in the analyses that evaluated CRT and ICD monotherapies individually with CRT–ICD were small (range 2–4). The present analysis also did not stratify patients by NYHA class as we combined all classes for the primary analysis. The included studies differed in baseline demographics, which may have affected the results. We only evaluated all-cause death or death due to heart failure. It is possible that CRT–ICD also reduces other forms of death such as sudden cardiac death or death from cardiovascular causes. It is of interest to perform other analyses to investigate whether CRT–ICD combined therapy can influence these other causes of death as well as other disease outcomes compared with CRT or ICD monotherapy.

CONCLUSION

Compared with ICD or CRT monotherapy, CRT–ICD therapy had favorable outcomes regarding all-cause death and the risk of hospitalization or death due to heart failure. The monotherapies and combined therapies were similar in regard to risk of death or hospitalization from any cause. Future studies are needed to further investigate the clinical application of CRT–ICD.

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