Right Ventricular Apical Versus Non-Apical Implantable Cardioverter Defibrillator Lead: a Systematic Review and Meta-Analysis.

Jalaj Garg MD
Lehigh Valley Health Network, jalaj.garg@lvhn.org

Rahul Chaudhary MD

Neeraj Shah MD
Lehigh Valley Health Network, Neeraj_N.Shah@lvhn.org

Chandrasekar Palaniswamy MD

Babak Bozorgnia MD
Lehigh Valley Health Network, Babak.Bozorgnia@lvhn.org

See next page for additional authors

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Authors

Jalaj Garg MD; Rahul Chaudhary MD; Neeraj Shah MD; Chandrasekar Palaniswamy MD; Babak Bozorgnia MD; Talha Nazir MD; and Valentina Kutyifa MD, PhD

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Right ventricular apical versus non-apical implantable cardioverter defibrillator lead: A systematic review and meta-analysis

Jalaj Garg, MD, FESC, [a,*,1] Rahul Chaudhary, MD, [b,1] Neeraj Shah, MD, MPH, [a] Chandrasekar Palaniswamy, MD, [c] Babak Bozorgnia, MD, FACC, [a] Talha Nazir, MD, [a] Andrea Natale, MD, FACC, FHRS, FESC, [d,e,f,g,h,i,j,k] Valentina Kutyifa, MD, PhD [l]

[a] Division of Cardiology, Lehigh Valley Health Network, Allentown, PA
[b] Department of Medicine, Sinai Hospital of Baltimore, Johns Hopkins University, Baltimore, MD
[c] University of San Francisco, Fresno, CA
[d] Montefiore-Einstein Center for Heart and Vascular Care, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY
[e] Texas Cardiac Arrhythmia Institute at St. David's Medical Center, Austin, TX
[f] Department of Biomedical Engineering, University of Texas, Austin, TX, USA
[g] Division of Cardiology, Stanford University, Palo Alto, CA, USA
[h] Case Western Reserve University, Cleveland, OH, USA
[i] Scripps Clinic, San Diego, CA, USA
[j] Dell Medical School, Austin, TX, USA
[k] Department of Cardiology, University of Foggia, Foggia, Italy
[l] University of Rochester Medical Center School of Medicine, Rochester, NY

Abstract

Introduction: We aimed to study the effect of right ventricular implantable cardioverter defibrillator (ICD) lead positioning on clinical outcomes in patients undergoing ICD placement.

Methods: A systematic literature search was performed using PubMed, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials to identify clinical trials comparing outcomes in patients with ICD leads in apical and non-apical positions. The primary outcome of our study was death at 1-year follow-up. Secondary outcomes studied were "death at 3 years", "total number of shocks", "appropriate shocks", "inappropriate shocks" and "cut-to-suture time".

Results: We analyzed a total of 3731 patients (2852 in apical and 879 in non-apical ICD groups) enrolled in 4 clinical trials. No significant difference was observed between the apical and non-apical ICD groups in all-cause mortality at 1 year (OR 0.88; 95% CI 0.51–1.49, p = 0.63; I^2 = 5.32%). Similarly, no differences were seen between the two groups in death at 3 years (OR = 0.76; 95% CI 0.56–1.04, p = 0.08; I^2 = 0%), total number of shocks (OR 0.99; 95% CI 0.81–1.22, p = 0.95; I^2 = 0%), appropriate shocks (OR 1.00; 95% CI 0.79–1.27, p = 0.99; I^2 = 0%), inappropriate shocks (OR 0.98; 95% CI 0.70–1.37, p = 0.91; I^2 = 0%) and cut-to-suture time (Standard mean difference = −0.03; 95% CI −0.20 to 0.14, p = 0.73; I^2 = 0%). No publication bias was seen.

Conclusion: Non-apical RV ICD lead implantation is non-inferior to traditional RV apical position with no significant differences in mortality, total number of shocks, appropriate shocks, inappropriate shocks and procedural time.

Keywords: Implantable cardioverter defibrillator; ICD; Apical; Non-apical; Cardiac resynchronization therapy

Introduction

The implantable cardioverter–defibrillator (ICD) is highly effective for prevention of sudden cardiac death (SCD) [1,2], success of which depends upon timely arrhythmia recognition, delivery of anti-tachycardia pacing or an efficient high-voltage shock. Typically, right ventricular (RV) lead is implanted in the apex due to its easy accessibility, better lead stability, and adequate sensing, pacing and defibrillation thresholds. However, apical RV pacing is associated with a non-physiologic ventricular activation resulting in myocardial perfusion abnormalities [3,4], functional mitral regurgitation [5] and heart failure syndrome [6,7]. Additionally, studies have also shown that excessive RV pacing is associated with worse hemodynamics

* Corresponding author at: Division of Cardiology, Lehigh Valley Health Network, 1250 S Cedar Crest Blvd, Allentown, PA 18103.
E-mail address: garg.jalaj@yahoo.com
[1] Have contributed equally to the manuscript.

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and increased morbidity and mortality, and hence devices are usually programmed to avoid excess RV pacing [8,9].

With a paradigm shift from passive fixation leads (implanted mostly at the RV apex) to active fixation leads, alternate sites (mid septum or right ventricular outflow tract) can be selected due to various reasons. These could include unsatisfactory sensing or pacing thresholds, high defibrillation thresholds (although not performed any more), technically difficult implant, or physician preference [10]. A subset of ICD patients may require concurrent RV anti-bradycardic pacing, and hence alternate pacing sites should be considered. Studies have shown that non-apical RV anti-bradycardic pacing is associated with preserved left ventricular ejection fraction with no increase in the rate of lead dislodgments, and achieves a similar defibrillation threshold as compared to apically placed lead [11,12]. Although numerous leads have been already implanted in a non-apical position, the long-term safety and efficacy of this practice on the efficacy of ICD treatment are largely unknown. We analyzed all the available clinical trials to evaluate the clinical outcomes of this alternative electrode position in comparison to the traditional RV apical site.

Methods

The present review was performed according to Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [13].

Search strategy

We carried out a literature search using PubMed, MEDLINE, EMBASE, EBSCO, CINAHL, Web of Science and Cochrane databases, of all studies published from the inception through December 15, 2016 to identify trials evaluating clinical outcomes in apical and non-apical ICD lead positions. We combined the terms apical or non-apical or ICD or implantable cardiac defibrillator or cardiac resynchronization therapy-defibrillator or CRT-D as keywords or medical subject heading terms. The identified studies were systematically assessed using the inclusion and exclusion criteria described below.

The studies had to fulfill the following criteria to be included in the analysis: 1) age $\geq$ 18 years; 2) human subjects with indications for single or dual chamber ICD or cardiac resynchronization therapy (CRT-D) placement; 3) studies including mortality, and ICD shocks as their end point. Retrospective studies, abstracts, case reports, conference presentations, editorials, reviews, and expert opinions were excluded from our analysis. Longest available follow-up data from individual studies were used for our analysis.

Data extractions and quality appraisal

Two authors (JG and RC) searched the studies and extracted the data independently and in duplicate. Two reviewers (JG and RC) independently assessed the quality items, and any discrepancies were resolved by discussion and consensus. Final results were reviewed by senior investigator (VK) (Fig. 1).

Assessment of risk of bias for each selected study was performed according to PRISMA 2009 guidelines. Qualitative evaluation of bias using the following key parameters were performed for each study: 1) clear definition of study population; 2) clear definition of outcomes and outcome assessment; 3) independent assessment of outcome parameters; 4) sufficient duration of follow-up; 5) selective loss during follow-up; and 6) important confounders and prognostic factors identified.

Outcomes

The primary outcome of our study was “death at 1 year”. Secondary outcomes studied in our study were “death at 3 year follow-up”, “total number of shocks”, “appropriate shocks”, “inappropriate shocks” and “cut-to-suture time”.

Statistical analysis

Random effects model of DerSimonian and Laird were used [14] to estimate the odds ratio (OR) and respective 95% confidence intervals (CI). Measure of heterogeneity between the studies was assessed using Higgins I^2 statistic and was considered significant if $I^2 > 50\%$. All p-values were 2-sided, and p value of <0.05 was considered significant. To address publication bias we used funnel plots [15], Begg–Mazumdar test [16] and Egger test [17]. Sensitivity analyses were performed using the one-study-out method, addressing the influence of each study by testing whether deleting each individually would significantly change the pooled results of the meta-analysis on the final effect and its precision. Descriptive statistics are presented as means ± standard deviations (SDs) for continuous variables and as number of cases and percentages for dichotomous and categorical variables. The statistical analysis was performed using the Comprehensive Meta-Analysis 2.0 software (Biostat, Inc., Englewood, NJ).

Results

A total of 154 studies were identified after exclusion of duplicate or irrelevant references (Fig. 1). After a detailed evaluation of these studies, 4 relevant clinical trials were included that incorporated a total of 3731 patients, 2852 in apical and 879 in the non-apical ICD group [18–21]. The characteristics of these trials and mean follow-up periods are described in Tables 1 and 2. Of note, among the included trials, 2 trials were sub-analyses of randomized controlled trials [18,21]. The trial by Amit et al. was a sub-analysis of the Shockless IMPLant Evaluation (SIMPLE) trial and that by Kutyifa et al. was a sub-analysis of the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) trial. In both original trials, the randomization scheme did not involve ICD lead in an apical versus non-apical position.

Quality assessment and publication bias

Overall, there were clear definitions of the study population, outcomes, and assessment in most component studies, but blinded assessment of outcomes was not reported in all studies resulting in potential bias. Jadad score was calculated for all RCTs with a mean Jadad score of

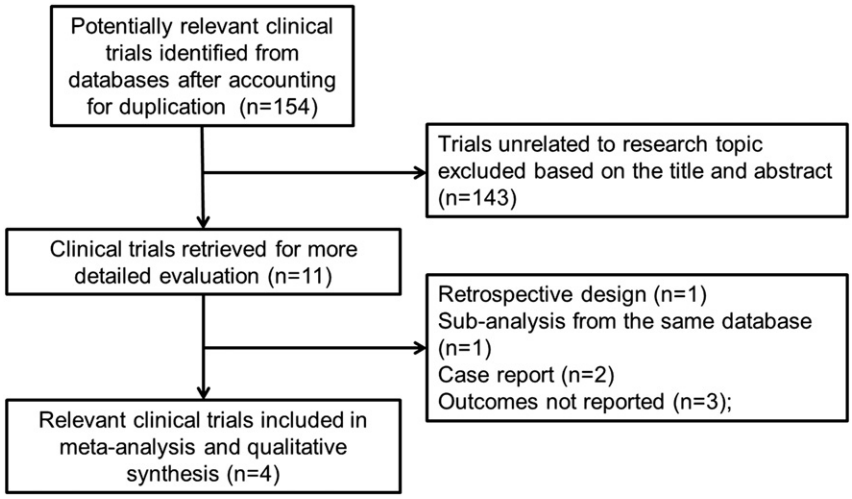

Fig. 1. Process of study selection for randomized and prospective trials (PRISMA Statement).

3 indicating that the studies involved were of high quality (Table 1). Funnel plots did not reveal publication bias for comparison of death at 1 year between non-apical and apical ICD group (Fig. 1). Funnel plot analysis was not conducted for secondary outcomes due to lack in number of trials.

Sensitivity analysis was performed using one-study out method, which did not demonstrate any difference or change in the overall outcomes (Table 3).

Baseline characteristics

In the participant studies, there were no significant differences between the two groups in terms of age, gender, heart failure (New York Heart Association class III–IV), left ventricular ejection fraction, ischemic cardiomyopathy, non-ischemic cardiomyopathy, primary prevention ICD, use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers or antiarrhythmic drugs, paced QRS duration, number of single chamber ICD, dual-chamber ICD, pacing threshold and presence of dual coil defibrillator leads. Non-apical ICD group had wider native QRS complex as compared to apical ICD group. Apical ICD group had higher lead impedance and R wave amplitude as compared to non-apical ICD group ($p < 0.05$). The mean duration of follow up was 24 months (±14 months). The mean age of our study population was 63 years (±2 years).

Primary outcome

Death occurred in 2.1% patients (n = 60) in the apical ICD group as compared to 3.1% patients (n = 27) in the non-apical ICD group at the end of 1-year follow-up period with no significant difference between apical and non-apical ICD groups (OR 0.88; 95% CI 0.51–1.49, p = 0.63; I^2 = 5.32%) (Fig. 2).

Secondary outcomes

The death at 3-year follow-up was not significantly different between apical and non-apical ICD lead groups (12.4% versus 11% respectively, OR 0.76; 95% CI 0.56–1.04, p = 0.08; I^2 = 0%) (Fig. 3).

No significant difference was observed between total number of ICD shocks (24.5% vs. 25.1% respectively, OR 0.99, 95% CI 0.81–1.22, p = 0.95; I^2 = 0%), appropriate shocks (16.7% vs. 17.3% respectively, OR 1.00; 95% CI 0.79–1.27, p = 0.99; I^2 = 0%), inappropriate shocks (7.8% vs. 7.9% respectively, OR 0.98; 95% CI 0.70–1.37, p = 0.91; I^2 = 0%) and cut-to-suture time (75 min vs. 76 min respectively; standard mean difference −0.03; 95% CI −0.20 to 0.14, p = 0.73; I^2 = 0%) between the two groups (Fig. 4). No significant heterogeneity was observed.

Discussion

To our knowledge, this is the first meta-analysis evaluating safety and efficacy non-apical versus apical RV ICD lead. The major findings in our study were 1) non-inferiority of non-apical ICD lead versus traditional RV apex ICD lead, 2) no difference in total ICD shocks, and appropriate and inappropriate shocks between the two groups, and 3) no differences in procedural time between the two groups.

The right ventricular apex has always been the traditional pacing/ICD lead implantation site mainly due to technical aspects such as the electrode design and the ease of the apical approach. However, studies have shown that RV apical pacing may have detrimental effects on hemodynamics and left ventricular ejection fraction. In the first RCT comparing right ventricular apical pacing to RV outflow tract pacing, there was no significant difference in pacing and sensing parameters between apical and non-apical pacing. Numerous RCT's and meta-analysis have been conducted since then evaluating non-apical sites to achieve more physiologic pacing pattern and thereby prevent LV dysfunction. This observation led to several small studies and RCT studies evaluating safety and feasibility of non-apical ICD versus apical ICD lead. These studies demonstrated non-inferior outcomes with similar defibrillation threshold in comparison to apical ICD. However, data from these individual studies were inconclusive due to small sample sizes and the long-term effect efficacy of this practice in non-apical ICD

Table 1
Study characteristics of included trials.

Name of the Study	Study design	CRT-D or ICD only	No. of patients (apical/non-apical)	Outcomes and position of non-apical leads	Follow-up (yrs)	Conclusion	Jadad score
Kutyifa et al., 2013 [18]	Sub-analysis of RCT	CRT-D	656/86	Primary: Heart failure or death Secondary: VT, VF, or death Position of non-apical leads: NS	3	No benefit of non-apical position compared to apical. Non-apical position associated with increased risk of ventricular tachyarrhythmias	–
Mabo et al., 2014 [19]	RCT	ICD	108/107	Primary: Success rate of ICD lead implantation in mid-septal versus apical region Secondary: Electrical lead characteristics; appropriate/inappropriate shocks; all-cause mortality. Position of non-apical leads: Mid-septal for all.	1	Non-inferior performance of ICD lead implanted in RV mid-septum compared to apex	3
Kolb et al., 2014 [20]	RCT	ICD (2/3rd) + CRT-D (1/3rd)	154/145	Primary: Survival free of lead revision, suboptimal right ventricular electrode performance or non-randomized lead position (3 months) Secondary: Accuracy of lead positioning; Safety margin defibrillation threshold testing; survival free of primary endpoint event within 12-month follow-up; All-cause mortality. Position of non-apical leads: Mid-septal for all.	1	ICD recipients had slightly different rates concerning the survival free of lead revision, suboptimal right ventricular electrode performance or non-randomized lead position. Non-inferiority of the mid-septal lead location cannot be concluded.	3
Amit et al., 2016 [21]	Sub-analysis of RCT	ICD	1934/541	Clinical outcomes included the ICD shocks and death. Position of non-apical leads: 29 leads in RVOT and rest in basal and mid-septum	3	No reduction in the ICD efficacy at the time of implant or during follow-up in patients receiving a non-apical RV lead	–

ICD = Implantable cardioverter defibrillator; CRT-D = Cardiac resynchronization therapy-defibrillator; RCT = Randomized Controlled trial; VT = Ventricular tachycardia; VF = Ventricular fibrillation; NS = Not specified; RVOT = Right ventricular outflow tract.

Table 2
Baseline demographics of study population.

Baseline Characteristic	Apical ICD	Non-apical ICD	N	Studies (n)	P for overall effect
Age, years (mean)	63 yrs	62 yrs	3731	4	0.56
Males, %	79%	79%	3731	4	0.95
Heart failure NYHA III–IV, %	53%	50%	2989	3	0.31
LVEF, %	30%	30%	3516	3	0.15
Ischemic cardiomyopathy, %	62%	62%	3731	4	0.62
Dilated cardiomyopathy, %	35%	35%	3731	4	0.18
ICD for primary prevention, %	79%	74%	2774	2	0.11
ACEI/ARBs, %	90%	92%	3217	2	0.07
Beta-blockers, %	91%	91%	3217	2	0.96
Anti-arrhythmic therapy, %	12%	14%	3217	2	0.81
Native QRS, ms	130.7	135.0	3516	3	**0.003**
Paced QRS, ms	159.4	157.6	2774	2	0.79
R wave, mV	12.3 mV	11.5 mV	2989	3	**<0.001**
Single-chambered ICD, %	44%	46%	2774	2	0.94
Dual-chambered ICD, %	24%	22%	2774	2	0.72
Lead impedance (ohms)	791 Ω	720 Ω	2989	3	**0.003**
Threshold (V), mean	0.71 V	0.68 V	2989	3	0.67
Type of RV lead (Dual coil), %	50%	39%	2774	2	0.43

ICD = Implantable cardioverter–defibrillator; NYHA = New York Heart Association; LVEF = Left Ventricular Ejection Fraction; ACEI = Angiotensin converting enzyme inhibitor; ARBs = Angiotensin II receptor blockers; RV = Right Ventricle.

Table 3
Sensitivity analysis for death at 1 year after excluding 1 trial at a time.

Analysis excluding trial	Overall Odds ratio (95% CI)	Odds ratio excluding the trial (95% CI)	Change in overall result
Amit et al.	0.88 (0.51 to 1.49)	0.93 (0.35 to 2.49)	No
Kolb et al.	0.88 (0.51 to 1.49)	0.74 (0.40 to 1.40)	No
Mabo et al.	0.88 (0.51 to 1.49)	1.01 (0.59 to 1.75)	No
Kutyifa et al.	0.88 (0.51 to 1.49)	0.82 (0.44 to 1.51)	No

treatment population was largely unknown. Our systematic review and meta-analysis has helped to reduce this limitation, lessening the amount of uncertainty surrounding treatment effects.

Prior studies have reported no difference in the RV ICD lead position on defibrillation safety margin and defibrillation threshold [11,12,19]. This reflects in our study with no difference in mortality, appropriate and inappropriate shocks between the two ICD lead positions. Non-apical lead position has been reported to cause T wave double counting due to lower sensed R waves resulting in inappropriate shocks [22]. In our analysis, although non-apical position had significantly lower sensed R-waves compared to apical position, no differences were found in the rate of inappropriate shocks with the two lead positions, a finding that echoes the results of prior studies [19,21,23].

Several factors play an important role in determining the position of the ICD lead during device implantation: physician's experience, adequate sensing and pacing parameters at the chosen site, and consideration for need of RV pacing in future. Additionally, apical RV pacing has been reported to be associated with increased morbidity and mortality in ICD recipients [8,9]. Shimony et al. demonstrated higher left ventricular function with non-apical RV pacing compared to apical pacing [24]. Hence, in patients with left ventricular dysfunction, who could require a significant percentage of ventricular pacing, avoidance of apical pacing might be advisable. With currently available evidence, our meta-analysis suggests that RV ICD lead position does not impact mortality, appropriate or inappropriate shocks and procedure time allowing the implanters to choose a non-apical site according to the patient's needs.

Study limitations

This systematic review and meta-analysis has several important limitations that should be acknowledged. First, potential sources of bias in our study include pooling data from patients receiving ICD and CRT-D into one group and trials including sub-analysis of other randomized controlled trials. Second, although no publication bias was noticed based on Egger's and Begg's bias assessment, large studies are needed to assess safety of non-apical ICD lead position. Third limitation includes a short follow up duration. Hence, trials with longer follow-up periods are needed to determine a mortality benefit between the two ICD lead sites. Forth, we combined all non-apical RV ICD lead sites (as limited data availability) into one group which limits the interpretation of the results of the meta-analysis for a specific pacing site [25]. Additionally, an imbalance in percentage of pacing between the apical and non-apical groups could have affected our primary outcome of all-cause mortality, which could not be assessed due to lack of data.

Conclusions

Our analysis suggests that non-apical RV ICD lead implantation is non-inferior to traditional RV apical position with no significant differences in mortality, total number of shocks, appropriate shocks, inappropriate shocks and procedural time.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding source

None.

Ethics approval

Not applicable.

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None.

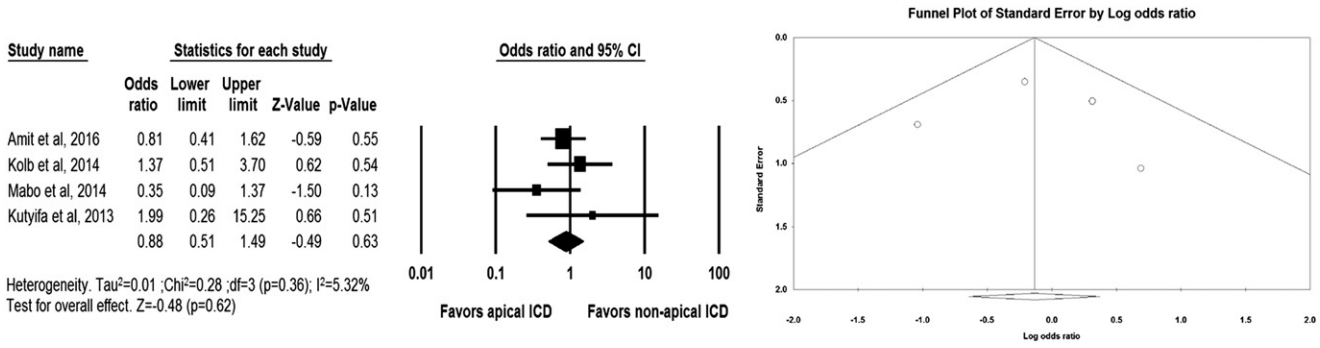


Fig. 2. Forest plot demonstrating deaths at 1-year follow up between apical and non-apical ICD lead position. Also, funnel-plot publication bias assessment for death at 1 year between apical and non-apical ICD lead position (Begg's p-value = 1.00; Egger's p-value = 0.88; publication bias is indicated when $p < 0.05$).

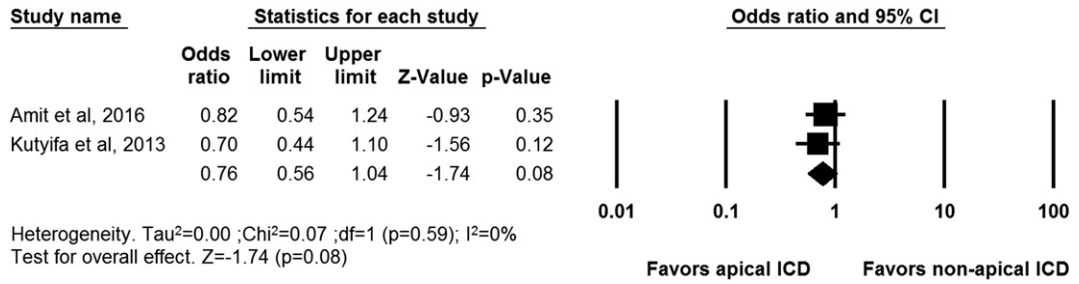
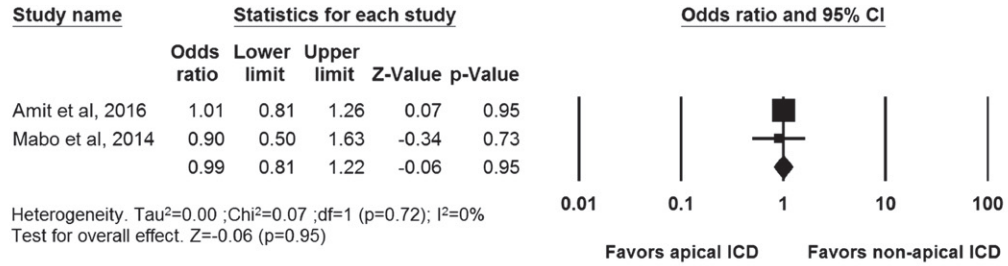
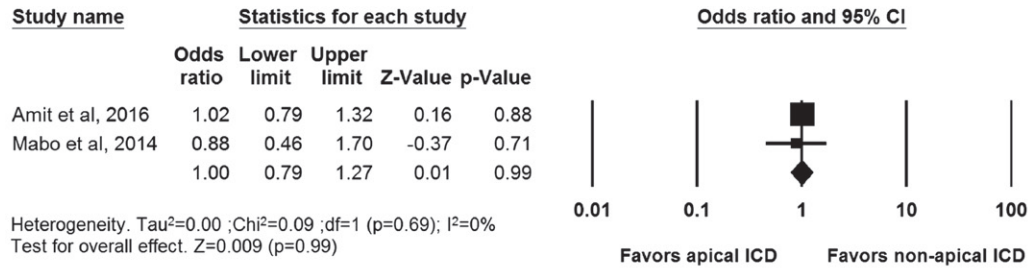


Fig. 3. Forest plot demonstrating secondary outcomes of death at 3-year follow up in apical and non-apical ICD lead positions.

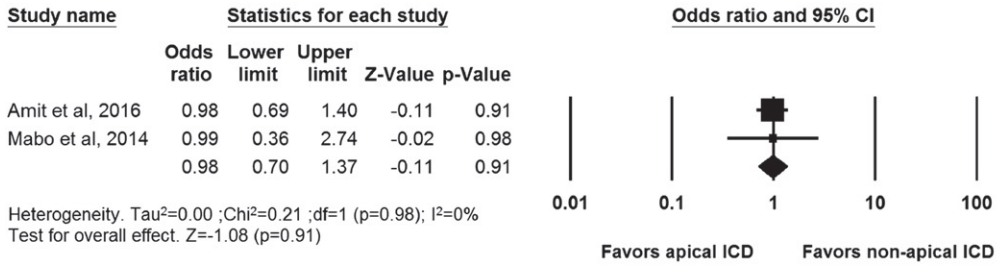
a) Total ICD shocks



b) Appropriate ICD shocks



c) Inappropriate ICD shocks



d) Cut-to-suture time

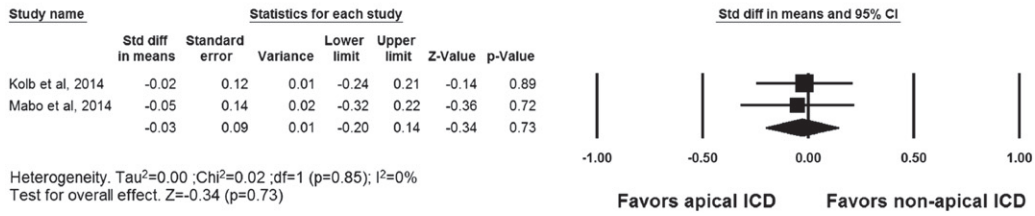


Fig. 4. Forest plot demonstrating secondary outcomes of total ICD shocks, appropriate ICD shocks, inappropriate ICD shocks and cut-to-suture time during longest available follow-up in apical and non-apical ICD lead positions.

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