Influence of diabetes on mortality and ICD therapies in ICD recipients: a systematic review and meta-analysis of 162,780 patients

Hualong Liu1†, Jinzhu Hu1†, Wen Zhuo1†, Rong Wan2 and Kui Hong1,2*

Abstract

Background: The influence of diabetes on the mortality and risk of implantable cardioverter defibrillator (ICD) therapies is still controversial, and a comprehensive assessment is lacking. We performed this systematic review and meta-analysis to address this controversy.

Methods: We systematically searched the PubMed, Embase, Web of Science and Cochrane Library databases to collect relevant literature. Fixed and random effects models were used to estimate the hazard ratio (HR) with 95% CIs.

Results: Thirty-six articles reporting on 162,780 ICD recipients were included in this analysis. Compared with nondiabetic ICD recipients, diabetic ICD recipients had higher all-cause mortality (HR = 1.45, 95% CI 1.36–1.55). The subgroup analysis showed that secondary prevention patients with diabetes may suffer a higher risk of all-cause mortality (HR = 1.89, 95% CI 1.56–2.28) (for subgroup analysis, P = 0.03). Cardiac mortality was also higher in ICD recipients with diabetes (HR = 1.68, 95% CI 1.35–2.08). However, diabetes had no significant effect on the risks of ICD therapies, including appropriate or inappropriate therapy, appropriate or inappropriate shock and appropriate anti-tachycardia pacing (ATP). Diabetes was associated with a decreased risk of inappropriate ATP (HR = 0.56, 95% CI 0.39–0.79).

Conclusion: Diabetes is associated with an increased risk of mortality in ICD recipients, especially in the secondary prevention patients, but does not significantly influence the risks of ICD therapies, indicating that the increased mortality of ICD recipients with diabetes may not be caused by arrhythmias. The survival benefits of ICD treatment in diabetes patients are limited.

Keywords: Diabetes, Influence, Mortality, ICD therapies, ICD recipients

Introduction

According to the latest data released by the International Diabetes Federation, the number of adult diabetic patients worldwide reached 537 million in 2021, and approximately 6.7 million people died of diabetes or diabetic complications, accounting for 12.2% of all-cause mortality [1]. Patients with diabetes have a higher risk of cardiovascular disease and mortality [2]. Heart failure (HF) is an end-stage clinical manifestation of organic heart disease and has become a major public health problem worldwide.

The prevalence of diabetes is 24% in chronic HF patients and up to 40% in hospitalized HF patients. Studies have shown that diabetes is an independent predictor of sudden cardiac death (SCD) in patients with HF and is associated with an increased risk of mortality [3, 4]. For example, in postinfarction patients, the mortality in the diabetic group was higher than that in the non-diabetic group [5]. It has been proven that implantable...
cardioverter defibrillator (ICD) can effectively prevent SCD and terminate malignant arrhythmias such as persistent ventricular tachycardia and ventricular fibrillation. Because of this unique property, ICD has been recommended as a class I recommendation to prevent SCD in patients with ischemic and nonischemic HF in current guideline [6]. Since diabetes generates a higher risk of SCD in HF patients, ICD implantation would be expected to have additional survival benefits.

To date, the influence of diabetes on the mortality and risk of ICD therapy is still controversial, and a comprehensive assessment is lacking. We performed this systematic review and meta-analysis to address this controversy.

Methods
This article was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7].

Search strategy
The meta-analysis was conducted according to the PRISMA guidelines. Two authors (H.-L.L and W.Z.) systematically searched the PubMed, Embase and Cochrane Library from through February 28, 2022 for relevant articles published in English. The search strategy was as follows: [(Diabetes Mellitus OR (Diabetes) AND (“Defibrillators, Implantable” OR “Implantable Defibrillators” OR “Implantable Defibrillator” OR “Cardioverter-Defibrillators, Implantable” OR “Implantable Cardioverter Defibrillators” OR “Defibrillator, Implantable”). Endnote X8 was used to manage the articles. The articles were independently selected by two authors (H.-L.L and J.-Z.H). After the title and abstract were reviewed and the off-topic articles were excluded, the full text of the remaining articles was screened against the inclusion criteria. Disagreements were resolved by discussion.

Selection criteria
The studies were included if (1) the articles were published in English with available full texts; (2) the studies reported the mortality or risk of ICD therapy and (3) the studies provided the hazard ratio (HR), odds ratio (OR) or risk ratio (RR) as well as their corresponding 95% confidence intervals (CIs).

We excluded studies if (1) the articles were of certain types, such as reviews, meta-analyses, notes, and case reports; (2) the studies contained overlapping study populations or (3) the full text could not be found.

Data extraction and quality assessment
Two reviewers (H.-L.L and W.Z.) independently extracted data from the included studies using a standard data extraction process. The following information was extracted from the articles: author’s name, publication year, study design, region of study, time frame, sample size, follow-up duration, age, sex ratio, region, time frame, left ventricular ejection fraction (LVEF), QRS duration, primary disease, prevention types, device implantation and outcomes.

The quality of the included studies was assessed independently by two reviewers (H.-L.L and J.-Z.H) using the Newcastle–Ottawa Scale (NOS). Each study was scored independently based on selection, comparability and outcome. We considered the article to be of high quality if it had a NOS score greater than 6. Disagreements were resolved by consensus.

Outcomes and subgroups
The primary outcome was mortality in diabetic and non-diabetic ICD recipients, which was divided into all-cause mortality and cardiac mortality. A subgroup analysis of all-cause mortality was further performed by separating patients into ICD recipients for primary prevention, ICD recipients for secondary prevention and ICD recipients for primary or secondary prevention. The secondary outcome was the risk of ICD therapies in diabetic and nondiabetic ICD recipients, which was divided into appropriate therapy, inappropriate therapy, appropriate shock, inappropriate shock, appropriate anti-tachycardia pacing (ATP) and inappropriate ATP.

Statistical analysis
Review Manager 5.3 (Cochrane Collaboration, Copenhagen, Denmark) was used to perform the meta-analysis. A sensitivity analysis was conducted to test the effect of individual studies using STATA version 12 (Stata Corporation, College Station, TX, USA). The natural logarithm of the hazard ratios (HRs) and its standard error (SElog HRs) were calculated. Heterogeneity was evaluated using chi-squared and I-squared tests. We considered there was substantial heterogeneity when $I^2 > 50\%$, and the random-effects model was used, otherwise, the fixed-effects model was used. Funnel plots as well as Begg and Egger test were drawn to evaluate the publication bias risk.

Results
Study selection and study characteristics
We identified 1100 articles through electronic retrieval strategies. Of these, 255 were duplicates, and 703 were excluded because the articles did not meet the inclusion criteria. Of 142 articles screened for eligibility, 57 studies were unwanted publication types, 41 articles were off-topic, 6 studies had overlapping study populations, and 2 studies were not published in English. Finally, 36 studies [8–43] of 162,780 ICD recipients were included in the
meta-analysis. The flow diagram of the literature inclusion process is shown in Fig. 1. Table 1 provides the main characteristics of the included studies, in addition to the regular index, including sample size, follow-up duration, region, time frame, age, sex ratio, LVEF, QRS duration, primary disease, device implantation, prevention types and outcomes. The quality of the included studies was assessed using the NOS, with an average NOS score of 7.55; the details of the quality assessment are shown in Table 2.

**Increased mortality in ICD recipients with diabetes**

In the included studies, 33 studies of 159,290 ICD recipients reported data for the association between diabetes and risk of all-cause mortality. A random effects model was used due to the existence of heterogeneity ($I^2 = 72\%$, $P = 0.001$), and the results showed that diabetes was associated with an increased risk of all-cause mortality in ICD recipients (HR = 1.45, 95% CI 1.36–1.55) (Fig. 2A). Data in 4 studies [10, 14, 29, 31] were available for cardiac mortality. The pooled data found an increased risk of cardiac mortality in ICD recipients with diabetes (HR = 1.68, 95% CI 1.35–2.08, $I^2 = 0\%$), shown in Fig. 2B. For the all-cause mortality outcome, funnel plots showed no significant publication bias (Additional file 1: Fig. S1). Furthermore, Begg and Egger tests also suggested no publication bias (all $P > 0.1$). Sensitivity analysis confirmed that the results did not change after removing individual studies (Additional file 1: Fig. S2).

**Subgroup analysis of prevention types**

We performed a subgroup analysis of prevention type by separating the ICD recipients into 3 groups: ICD recipients with primary prevention, with secondary prevention and with primary or secondary prevention. Figure 3 shows that diabetes was associated with an increased risk of all-cause mortality in all 3 groups. The increase of all-cause mortality varied between the above groups (for subgroup analysis, $P = 0.03$), and that secondary prevention patients with diabetes may suffer a higher risk of all-cause mortality (HR = 1.89, 95% CI 1.56–2.28).

**No significant effect on ICD therapy, shock and appropriate ATP, but a decreased risk of inappropriate ATP**

In the 36 included articles, 5 studies [31–34, 39] reported appropriate therapy, 3 studies [31, 33, 39] reported inappropriate therapy, 5 studies [15, 24, 33, 36, 39] reported appropriate shock, 2 studies [33, 39]
Table 1  Characteristic of included studies

| Study     | Study design | Region | Source | Time frame  | Number of participants (N) | Age (year) | Male (%) | LVEF (%) | QRS (ms) | Follow-up duration (m) | Primary disease prevention types | Device implantation | Outcomes |
|-----------|--------------|--------|--------|-------------|-----------------------------|------------|----------|----------|----------|------------------------|---------------------------------|---------------------|----------|
| Bilchick  | Retrospective study | USA     | Centers for Medicare and Medicaid Services | 2003-2007 | 45,884 | 72.5 (median) | 76.0  | NA      | NA      | NA | Development cohort: 52.8 (50.4–55.2); validation cohort: 43.2 (37.2–48) | HF | Primary | ICD | All-cause mortality |
| Borleffs | Prospective study | Netherlands | Leiden University Medical Center | 1996–2009 | 456 | 65.0±10.0 | 86.0 | 35.0±14.0 | 119.0±30.0 | 54.0±35.0 | Ischaemic heart disease | Secondary | ICD | All-cause mortality |
| Briongos  | Prospective study | Spain | UMBRELLA | 2006-2015 | 621 | 61.1±11.4 | 87.3 | 26.6±5.4 | 109.8±25.3 | 52.8±25.2 | HF | Primary | ICD | All-cause mortality |
| Chao      | Retrospective study | Taiwan | Three Taiwan medical centers | 1998–2009 | 238 | 63.0±15.3 | 76.5 | 40.3±13.3 | NA | 36.8±29.8 | NA | Secondary | ICD | All-cause mortality |
| Coleman   | Prospective study | USA | Hartford hospital | 1997–2007 | 1204 | Non statin: 64.5±13.3, stain: 67.5±10.8 | Non statin: 76.2±8.7 | Non statin: 229±9.1, stain: 244±8.3 | NA | 31.1±30.7 | HF | Primary or secondary | ICD | All-cause mortality |
| Cygankiewicz | Prospective study | USA | Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) | 1997–2001 | 655 | 64.0±10.0 | 84.0 | 28.0±5.0 | > 120 (40%) | 63.0 | MI and LVEF < 30% | Primary | ICD | All-cause mortality |
| Dendel    | Prospective study | Netherlands | Two Dutch referral hospitals | 2003–2009 | 589 | 62.6±10.1 | 81.0 | ≤ 35.0 (83%) | NA | 38.4 (9.6–78.0) | Distressed (type D) | Primary or secondary | ICD | All-cause mortality |
| Desai     | Prospective study | USA | NA | NA | 209 | Non statin: 72.0±10.0, stain: 720±11.0 | Non statin: 79.9 | Non statin: 290±7.0, stain: 270±7.0 | NA | Non statin: 35.0±20.0, stain: 32.0±19.0 | HF | NA | ICD/CRT-D | All-cause mortality |
| Echouffo  | Retrospective study | USA | NCDR-ICD Registry (CRT-D) + Centers for Medicare & Medicaid (ICD) | 2006–2009 | Non-diabetics: 74±6.2, diabetics: 74±0.58 | Non-diabetics: 66±4.6 | Non-diabetics: 24±6.3, diabetics: 24±6.2 | ≥ 120.0 | 36.0 | HF | Primary | CRT-D | All-cause mortality |
| Study          | Study design | Region | Source                          | Time frame | Number of participants (N) | Age (year) | Male (%) | LVEF (%) | QRS (ms) | Follow-up duration (m) | Primary disease types | Prevention types | Device implantation | Outcomes          |
|---------------|--------------|--------|---------------------------------|------------|---------------------------|------------|----------|----------|----------|-----------------------|----------------------|----------------|---------------------|-------------------|
| Eckart 2006   | Retrospective study | USA    | Military Health System Data Repository (MDR) | 2000–2004 | 741                        | 64.0±14.0 | 80.8     | NA       | NA       | 24.0±20.4             | Renal insufficiency | Primary or secondary | ICD                 | All-cause mortality |
| Exner 2001    | Retrospective study | Canada | Atrial fibrillation: reduced atrial fibrillation (AF) versus Implantable Defibrillators (AVID) Trial | 1993–1997 | 457                        | Survived electrical storm: 67.0±11.0; survived other VT/VF episode: 64.0±10.0; remaining patients: 65.0±11.0 | Survived electrical storm: 73.0±11.0; survived other VT/VF episode: 81.0; remaining patients: 76.0 | NA       | 31.0±13.0 | HF                  | Secondary | ICD                 | All-cause mortality |
| Fumagalli 2014 | Prospective study | Italy | 117 Italian cardiologists centers | 2004–2011 | 6311                       | NA         | 82.0     | 290±9.0  | NA       | 27.0 (14.0–44.0)     | HF                   | NA               | ICD/CRT-D           | All-cause mortality |
| Hager 2010    | Retrospective study | USA    | Two centers in USA               | 2000–2006 | 958                        | 67.0       | NA       | < 40.0   | NA       | 36.0                  | HF with CKD          | Primary | ICD                 | All-cause mortality |
| Hess 2004     | Retrospective study | USA    | National Cardiovascular Data Registry's (NCDR) ICD Registry | 2006–2007 | 47,282                     | 67.0 (57.0–75.0) | 74.8     | 249±6.1  | < 120 (69.2%); 120–140 (13.5%); > 140 (17.3%) | 34.8 (28.8–39.6)     | MI + HF (LVEF < 30%) + congestive HF (LVEF < 35%) | Primary | ICD                 | All-cause mortality |
| Ho 2005       | Retrospective study | USA    | Loma Linda University Medical Center (LLUMC) | NA         | 360                        | 62.0±13.0  | 80.0     | 33.0±17.0| NA       | 52.8±44.4             | Compromised left ventricular function | NA               | ICD                 | All-cause mortality |
| Jahangir 2017 | Retrospective study | USA    | Their tertiary care center       | 2010–2011 | 904                        | 66.7±13.0 | 69.0     | 24.7±7.0| NA       | 31.2±12.0            | HF                   | Primary or secondary | ICD                 | All-cause mortality |
Table 1 (continued)

| Study          | Study design | Region              | Source                                                                 | Time frame | Number of participants (N) | Age (year) | Male (%) | LVEF (%) | QRS (ms) | Follow-up duration (m) | Primary disease outcomes                  | Prevention types | Device implantation | Outcomes                        |
|----------------|--------------|---------------------|                                                                      |            |                            |            |          |          |          |                   |                                     |                 |                     |                                 |
| Junttila 2020  | Retrospective study | European                | European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators (EU-CERT-ICD) project | 2002–2014  | Non-diabetics: 2540; Diabetics: 995 | Non-diabetics: 62.9±11.7; diabetics: 65.7±9.4 | Non-diabetics: 81.5; diabetics: 83.9 | Non-diabetics: 25.3±6.1; diabetics: 25.7±6.0 | NA              | 38.4±27.6 | HF                             | Primary                  | ICD/CRT-D              | All-cause mortality/ appropriate shock |
| Lee 2007       | Retrospective study | Canada               | Canadian Institute for Health Information (CIHI)                     | 1997–2003  | 2467                        | 62.5±13.4 | 78.8     | NA       | NA       | 4551 (person-years)  | All-cause mortality                |                     | ICD                  |                                 |
| Lee 2015       | Prospective study | Canada               | Ontario ICD Database                                                 | 2007–2011  | 3445                        | 66.0 (58.0–73.0)^a | 79.7     | < 35.0   | 126.0 (104.0–158.0)^a | 2.0                       | HF                              | Primary                  | ICD/CRT-D              | All-cause mortality                    |
| Morani 2013    | Prospective study | Italy                | Contak Italian Registry                                              | 2004–2007  | 266                          | 67.0±9.0  | 85.0     | 165.0±32.0 | 55.0 (41.0–64.0)^a | HF                              | Primary or secondary              | CRT-D                | All-cause mortality                    |
| Morani 2018    | Retrospective study | Italy                | Eleven cardiology Italian centers                                  | 2004–2007  | 821                         | 67.0±11.0 | 80.4     | 32.3±11.2 | NA       | 44.3±26.5 | NA                             | Primary or secondary              | ICD/CRT-D              | All-cause mortality                    |
| Perkkimaki 2015| Prospective study | USA                  | The Multicenter Automatic Defibrillator Implantation TrialCardiac Resynchronization Therapy (MADIT-CRT) | 2015-2018  | 1798                        | Cardiac death: 65.9±10.9, non-cardiac death: 69.1±9.7, alive: 64.1±10.7 | Cardiac death: 89.0, non-cardiac death: 82.0, alive: 74.0 | Cardiac death: 220±5.4, non-cardiac death: 239±4.7, alive: 239±5.2 | Cardiac death: 156.2±21.7, non-cardiac death: 157.9±18.1, alive: 158.3±19.7 | 48.0                        | Ischaemic cardiomyopathy (NYHA I-II) or non-ischaemic cardiomyopathy (NYHA II) with LVEF <30, QRS >130 | Primary or secondary | CRT-D + ICD | Cardiac mortality                                  |

^a Mean ± standard deviation.
| Study        | Study design  | Region     | Source                                                                 | Time frame          | Number of participants (N) | Age (year) | Male (%) | LVEF (%) | QRS (ms) | Follow-up duration (m) | Primary disease prevention types | Prevention types | Device implantation | Outcomes                                                                 |
|-------------|---------------|------------|------------------------------------------------------------------------|---------------------|---------------------------|------------|----------|-----------|----------|------------------------|-----------------------------|----------------|---------------------|--------------------------------------------------------------------------|
| Rogstad     | Retrospective study | USA       | Medicare Advantage                                                    | 2014–2015           | 8450                       | 70.9±8.92  | 72.0     | NA        | NA       | 12.0                   | All-cause mortality                                                     | NA             | ICD                 | All-cause mortality                                                      |
| Rorth       | Retrospective study | Danish    | Danish Study to Assess the Efficacy of ICDs in Patients with Nonischaemic Systolic Heart Failure on Mortality (DANISH) trial | 2008–2014           | Non-diabetics: 905; diabetics: 211 | Non-diabetics: 620±10.0; diabetics: 630±9.0 | Non-diabetics: 720; diabetics: 75.0 | Non-diabetics: 24.2±6.2; diabetics: 23.4±6.3 | NA       | 68.0                  | Non-ischaemic systolic HF                                               | Primary         | ICD                 | All-cause mortality/cardiac mortality/appropriate therapy/inappropriate therapy |
| Ruwald      | Retrospective study | USA       | Multicenter Automatic Defibrillator Implantation Trial—Reduce Inappropriate Therapy (MADIT-RIT) | 2009–2011           | Non-diabetics: 99; diabetics: 485 | Non-diabetics: 630±12.0; diabetics: 640±11.0 | Non-diabetics: 71.0; diabetics: 71.0 | ≤25.0 non-diabetics (50%); diabetics (46%) | NA       | 17.4                  | All-cause mortality                                                     | Primary         | ICD                 | Appropriate therapy/inappropriate therapy/appropriate shock/inappropriate shock/appropriate ATP/inappropriate ATP |
| Ruwald      | Retrospective study | Danish    | Danish nationwide clinical registers                                   | 2007–2012           | Primary: 1873; secondary: 2461 | Primary: 62.2±12.2; secondary: 62.3±13.2 | Primary: 81.0; secondary: 79.0 | Primary: 29.4±12.4; secondary: 40.4±14.5 | Primary: 103.4±23.7; secondary: 102.2±28.8 | 30.2±19.8 | NA                    | All-cause mortality                                                     | Primary or secondary | ICD                 | All-cause mortality                                                      |
| Santangeli  | Retrospective study | Italy     | San Paolo Hospital                                                      | NA                  | 193                        | 66.3±10.9  | 81.3     | 28.2±5.2  | NA       | 48.0                  | Chronic HF and reduced LVEF                                             | Primary         | ICD/CRT-D            | All-cause mortality                                                      |
| Seegers     | Retrospective study | Germany   | University Medical Center Gottingen                                   | 1998–2010           | 1151                       | Male: 65.0±12.0; female: 620±15.0 | Male: 29.0±11.0; female: 340±13.0 | Male: 123.0±32.0; female: 112.0±30.0 | 58.8±32.4 | HF                    | All-cause mortality                                                     | Primary or secondary | ICD/CRT-D            | All-cause mortality                                                      |
| Sjöblom     | Retrospective study | Sweden    | Swedish Pacemaker Registry                                             | 2006–2011           | 789                        | 65.0±11.0  | 83.0     | 25.0±10.0 | 39.0±18.0 | Congestive HF | All-cause mortality                                                      | Primary         | ICD/CRT-D            | All-cause mortality                                                      |
| Study | Study design | Region | Source | Time frame | Number of participants (N) | Age (year) | Male (%) | LVEF (%) | QRS (ms) | Follow-up duration (m) | Primary disease | Prevention types | Device implantation | Outcomes |
|-------|--------------|--------|--------|------------|--------------------------|------------|----------|----------|-----------|----------------------|-----------------|-----------------|-----------------|---------|
| Stein 2009 | Prospective study | USA | Synergistic Effects of Risk Factors for Sudden Cardiac Death (SERF) Study | 2001–2004 | 1655 | 66.8±11.7 | 82.0 | 31.7±12.4 | NA | 12.5 (median) | NA | Primary or secondary | ICD | All-cause mortality |
| Steiner 2016 | Prospective study | Israeli | Israeli ICD Database | 2010–2011 | Non-diabetics: 1346; diabetics: 764 | Non-diabetics: 62.2±14.0; diabetics: 66.3±9.4 | Non-diabetics: 82.0; diabetics: 85.0 | Non-diabetics: 30.5±11.6; diabetics: 28.0±8.3 | Non-diabetics: 115.8±29.8; diabetics: 124.6±30.9 | 21.0±10.2 | HF | Primary or secondary | ICD/CRT-D | All-cause mortality |
| Vandenberk 2016 | Retrospective study | Belgium | University Hospitals of Leuven | 1996–2014 | 727 | 62.5±11.7 | 84.9 | 32.4±12.4 | 131.0±34.0 | 62.4±49.2 | Ischemic and dilated cardiomyopathy | Primary or secondary | ICD/CRT-D | All-cause mortality |
| Wasiak 2020 | Retrospective study | Poland | Contemporary Modalities in Treatment of Heart Failure (COMMIT-HF) | 2009–2013 | 368 | Ischemic: 70.5; nonischemic: 52.8±12.9 | Ischemic: 64.0±10.2; nonischemic: 52.8±12.9 | Ischemic: 260±57; nonischemic: 240±56 | NA | 60.5 | Systolic HF | Primary | ICD/CRT-D | All-cause mortality |
| Wilson 2017 | Retrospective study | UK | Multicenter in Southampton and Bristol Heart Institute | 2006–2014 | 424 | > 60.0 | 86.3 | 60.0–69.9 years: 31.7±15.2; 70.0–79.9 years: 26.2±10.3; > 80.0 years: 31.9±11.4 | NA | 32.6 | HF | Primary | ICD/CRT-D | All-cause mortality |
| Winkler 2019 | Retrospective study | Poland | Military Institute of Medicine in Warsaw | 2011–2017 | 457 | 66.0±11.0 | 80.6 | 29.0 (25.0–33.0)* | NA | 31.0 (17.0–52.0) | HF | Primary or secondary | ICD/CRT-D | All-cause mortality/ appropriate therapy |
**Table 1** (continued)

| Study   | Study design  | Region | Source                                               | Time frame | Number of participants (N) | Age (year) | Male (%) | LVEF (%) | QRS (ms) | Follow-up duration (m) | Primary disease | Prevention types | Device implantation | Outcomes               |
|---------|---------------|--------|------------------------------------------------------|------------|-----------------------------|------------|----------|-----------|-----------|-----------------------|------------------|------------------|---------------------|------------------------|
| Zhang 2014 | Prospective study | USA    | Prospective Observational Study of Implantable Cardioverter-Defibrillators (PROSICD) | NA         | 1189                        | 60.6±12.7  | 72.9     | 22.3±7.4  | 118.7±30.7 | 12.0                  | HF               | Primary          | ICD                 | All-cause mortality |

ICD implantable cardioverter-defibrillators, CRT-D cardiac resynchronization therapy defibrillators, HF heart failure, LVEF left ventricular ejection fraction, CKD chronic kidney disease, MI myocardial infarction, NYHA New York Heart Association, ATP antitachycardia pacing, NA not available

a Medians with interquartile range

b Mean±SEM
Table 2  NOS items scores

| Study            | Selection | Comparability | Outcome | Scores |
|------------------|-----------|---------------|---------|--------|
| Bilchick 2012    | 3         | 2             | 3       | 8      |
| Borleffs 2009    | 4         | 2             | 3       | 9      |
| Briongos 2019    | 4         | 1             | 3       | 8      |
| Chao 2014        | 3         | 1             | 3       | 7      |
| Coleman 2008     | 3         | 2             | 3       | 8      |
| Cygankiewicz 2009| 3         | 2             | 3       | 8      |
| Denollet 2012    | 3         | 1             | 2       | 6      |
| Desai 2009       | 4         | 1             | 3       | 8      |
| Echouffo 2016    | 3         | 2             | 3       | 8      |
| Eckart 2006      | 3         | 1             | 2       | 7      |
| Exner 2001       | 3         | 2             | 3       | 8      |
| Fumagalli 2014   | 3         | 1             | 3       | 7      |
| Hager 2010       | 3         | 1             | 3       | 7      |
| Hess 2014        | 4         | 1             | 3       | 8      |
| Ho 2005          | 4         | 1             | 2       | 7      |
| Jahangir 2017    | 3         | 1             | 3       | 7      |
| Junttila 2020    | 3         | 1             | 3       | 7      |
| Lee 2007         | 3         | 2             | 3       | 8      |
| Lee.D 2015       | 4         | 1             | 3       | 8      |
| Morani 2013      | 4         | 2             | 3       | 8      |
| Morani 2018      | 3         | 1             | 3       | 7      |
| Perkiomaki 2015  | 3         | 2             | 3       | 8      |
| Rogstad 2018     | 3         | 2             | 3       | 8      |
| Roth 2019        | 4         | 2             | 3       | 9      |
| Ruwald 2013      | 3         | 2             | 3       | 8      |
| Ruwald 2016      | 3         | 1             | 3       | 7      |
| Santangelo 2020  | 3         | 1             | 3       | 7      |
| Seegers 2016     | 4         | 1             | 3       | 8      |
| Sjöblom 2016     | 3         | 1             | 3       | 7      |
| Stein 2009       | 4         | 1             | 2       | 7      |
| Steiner 2016     | 3         | 1             | 3       | 7      |
| Vandenberk 2016  | 3         | 2             | 3       | 8      |
| Wasiak 2020      | 3         | 1             | 3       | 7      |
| Wilson 2017      | 3         | 1             | 3       | 7      |
| Winkler 2019     | 3         | 1             | 3       | 7      |
| Zhang 2014       | 3         | 2             | 3       | 8      |

Average score: 7.55

reported inappropriate shock, ATP and inappropriate ATP. Forest plots showed that diabetes had nonsignificant relationship with the risk of appropriate therapy (HR = 1.10, 95% CI 0.93–1.31, I² = 53%) (Fig. 4A), inappropriate therapy (HR = 0.79, 95% CI 0.45–1.39, I² = 67%) (Fig. 4B), appropriate shock (HR = 0.95, 95% CI 0.70–1.29, I² = 69%) (Fig. 4C) and inappropriate shock (HR = 1.04, 95% CI 0.69–1.56, I² = 0%) (Fig. 4D) in ICD recipients. Meanwhile, no statistically significant difference was found between diabetes and the risk of ATP (HR = 1.36, 95% CI 0.97–1.91, I² = 51%) (Fig. 4E) in ICD recipients. However, Fig. 4F shows that diabetes was associated with a decreased risk of inappropriate ATP (HR = 0.56, 95% CI 0.39–0.79, I² = 0%).

Discussion

The present study systematically and comprehensively reviewed the current available literature, including 36 publications with 162,780 ICD recipients, to assess the potential influence of diabetes on the mortality and risk of ICD therapy. Not as we expected, the meta-analysis indicated that in ICD recipients, diabetes was associated with an increased risk of both all-cause mortality and cardiac mortality, and secondary prevention patients with diabetes may suffer a higher risk of all-cause mortality. Another important discovery was that there were no nonsignificant differences in the proportion of ICD therapies (appropriate therapy, inappropriate therapy, appropriate shock, inappropriate shock and appropriate ATP) between diabetes patients and non-diabetes patients. However, diabetes was associated with a reduced risk of inappropriate ATP. To the best of our knowledge, this study is the first systematic review and meta-analysis to comprehensively assess the cumulative evidence of diabetes associated with mortality and the risk of ICD therapy in ICD recipients. Although there were no randomized controlled trials due to the particularity of the study design, according to the quality evaluation of the NOS, all of the included studies were of high quality. Sensitivity analysis also showed that the results were not affected by any individual studies. The above factors show the robustness of the results.

There is a high proportion of diabetes in HF patients, especially in hospitalized HF patients, and diabetes has been found to be an independent predictor of SCD in HF patients [3, 4]. On the other hand, ICD is an effective method of SCD prevention in patients with HF [6]. Based on the above theory, it can be deduced that diabetes ICD recipients with HF should receive more survival benefits than nondiabetic recipients. However, our pooled results showed that in ICD recipients, diabetes also significantly increased the risk of all-cause mortality and cardiac mortality, especially for patients with ICD implantation for secondary prevention. This result indicates that even with ICD implantation, diabetic patients still have a higher mortality than nondiabetic patients of all-cause or the cardiac mortality, which is consistent with other studies [8, 38, 39]. How to explain the increased mortality of diabetic ICD recipients is a key question. Our following work regarding whether diabetic patients have the higher risk of ICD therapies is very important to address this question, because both inappropriate and appropriate
ICD therapies are associated with an increased risk of subsequent death [44–46].

ICD therapies mainly include shock and ATP. Several previous studies showed different results regarding whether diabetes increases the risk of ICD therapies. Steiner et al. showed that diabetes was not associated with an increased risk of appropriate or inappropriate ICD therapies [31, 32, 39]. However, Ruwald et al. found that patients with diabetes had a 58% increased risk of appropriate therapy and a 46% decreased risk of inappropriate therapy [33]. For ICD shock and ATP, the conclusions are also not consistent [15, 24, 33, 39]. Our cumulative meta-analysis showed that diabetes ICD recipients do not have a higher risk of ICD therapies, including appropriate therapy, inappropriate therapy, appropriate shock, inappropriate shock and appropriate ATP, than nondiabetic ICD recipients. This means that the higher mortality in diabetic ICD recipients is

![Fig. 2](image-url)
not caused by ventricular arrhythmias or ICD therapies. Therefore, a possible reason for the increased mortality in diabetes recipients may be the comorbidities related to diabetes, independent of the effects of ICD therapy [24]. Our study found that diabetes was associated with a reduced risk of inappropriate ATP. The underlying mechanism for this phenomenon is not clear, and the possible reasons are that diabetic patients are less likely to experience exercise-induced sinus tachycardia due to reduced activity, and their cardiovascular reflexes are reduced due to autonomic nervous dysfunction and neuropathy [33].
Fig. 4  The influence of diabetes on appropriate therapy (A), inappropriate therapy (B), appropriate shock (C), inappropriate shock (D), appropriate ATP (E) and inappropriate ATP (F) in ICD recipients compared with non-diabetes. ICD implantable cardioverter-defibrillator ATP anti-tachycardia pacing
Our results show that diabetes is significantly associated with an increased risk of mortality in ICD recipients. On the other hand, diabetes has no effect on the risk of ICD therapies. This suggests that the increased risk of mortality caused by diabetes in ICD recipients may be due to adverse pathophysiological changes and related complications caused by diabetes itself rather than arrhythmias.

Our results showed that the all-cause mortality of secondary prevention patients with diabetes was higher than diabetic primary prevention patients. A study suggested that secondary prevention patients have a higher risk of death than primary prevention patients [47], which is consistent with our finding. The results indicated that secondary prevention patients may have a vulnerable myocardium resulting from more risk factors, therefore, the vulnerable myocardium may be more likely to be damaged by diabetic complications, resulting in a higher risk of mortality. In addition, the survival benefits of ICD treatment for diabetes recipients are limited. ICD is effective in treating ventricular tachyarrhythmias; however, HF patients with diabetes may be at increased risk of mortality through mechanisms other than arrhythmias that can be treated by ICD. Our results also suggest that for these diabetes ICD recipients, more aggressive treatment should be applied to treat the adverse pathophysiological changes and complications caused by diabetes, rather than just focusing on the treatment of arrhythmias. For example, many anti-diabetic medications have been shown to improve the prognosis of diabetic patients with HF. For example, dapagliflozin, a sodium–glucose cotransporter 2 inhibitor, can significantly reduce cardiac and all-cause mortality in diabetic patients with HF [48]. Real-world studies have shown that metformin also significantly reduces mortality in diabetic patients with HF [49].

Our research has several advantages. First, to the best of our knowledge, this is the first systematic review and meta-analysis to comprehensively assess the cumulative evidence of diabetes associated with mortality and the risk of ICD therapy in ICD recipients. Second, we strictly followed the PRISMA guidelines to carry out this study. Third, all of the included studies were of high quality, and sensitivity analysis also showed the robustness of the results. Finally, such a large sample (36 studies containing 162,780 patients) can ensure the reliability of the study results. However, several limitations should be considered. First, due to the particularity of the study design, no randomized controlled trials were included. Second, there was relatively high heterogeneity among the included articles, such as in the outcomes of all-cause mortality, appropriate and inappropriate therapy, appropriate shock and ATP, which may mainly due to the individual characteristics of each included studies. Hence, we tried several ways to reduce the impact of heterogeneity on the results, including using random effects models, performing sensitivity analysis and subgroup analysis. Third, although most of the included studies adjusted for a range of confounding variables, we could not rule out an effect of residual confounding variables on the results, which may also account for the heterogeneity existence in the outcomes above.

Conclusions
In summary, our study shows that diabetes is associated with an increased risk of mortality in ICD recipients, especially in the secondary prevention patients, but diabetes has no significant effect on the risks of ICD therapies. These results indicate that the increased mortality of ICD recipients with diabetes may not be caused by arrhythmias. The survival benefits of ICD treatment for diabetic ICD recipients are limited, and more aggressive treatment should be sought to reduce mortality.

Abbreviations
ICD: Implantable cardioverter-defibrillator; HRs: Hazard ratios; CIs: Confidence intervals; HF: Heart failure; SCD: Sudden cardiac death; ATP: Anti-tachycardia pacing; LVEF: Left ventricular ejection fractions; NOS: Newcastle–Ottawa Scale; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NYHA: New York Heart Association; RevMan: Review Manager.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12933-022-01580-y.

Additional file 1: Figure S1. Funnel plot of the outcome (all-cause mortality). Figure S2: Sensitivity of the outcome (all-cause mortality).

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HLL, JZH and WZ to the acquisition of data, analysis and interpretation of data, and drafting of the article. RW contributed to interpretation of data. KH contributed to the conception and design of the study, analysis and interpretation of data, and revising the article. All authors read and approved the final manuscript.

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Author details
1 Department of Cardiovascular Medicine, The Second Affiliated Hospital of Nanchang University, No. 1, Minde Road, Nanchang 330006, Jiangxi, China.
2 Jiangxi Key Laboratory of Molecular Medicine, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China.

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