CJC Open 3 (2021) S209–S217

Systematic Review/Meta-analysis

Sex, Race, and Age Differences in Cardiovascular Outcomes in Implantable Cardioverter–Defibrillator Randomized Controlled Trials: A Systematic Review and Meta-analysis

Mohammad K. Syed, BHSc,[a,‡] Hassan I. Sheikh, BHSc-c,[a,‡] Bradley McKay, BHSc,[a] Nicholas Tseng, BSc-c,[b] Maureen Pakosh, BA, MISt,[c] Jessica E. Caterini, MD, PhD,[d] Abhinav Sharma, MD, PhD,[e] Tracey J.F. Colella, RN, PhD,[f,g] Kaja M. Konieczny, MD,[h] Kim A. Connelly, MBBS, PhD,[h] Michelle M. Graham, MD,[i] Michael McDonald, MD,[j] Laura Banks, RKin, PhD,[a,f] and Varinder Kaur Randhawa, MD, PhD[k]

[a] *Faculty of Health Sciences, Ontario Tech University, Oshawa, Ontario, Canada;* [b] *Faculty of Biomedical Sciences, University of Waterloo, Waterloo, Ontario, Canada;* [c] *Library & Information Services, University Health Network, Toronto, Ontario, Canada;* [d] *Queen's University Medical School, Kingston, Ontario, Canada;* [e] *Department of Medicine, McGill University Health Centre, Montreal, Quebec, Canada;* [f] *KITE, Toronto Rehabilitation Institute, University Health Network, Toronto, Ontario, Canada;* [g] *Lawrence S. Bloomberg Faculty of Nursing, Faculty of Rehabilitation Sciences Institute, University of Toronto, Toronto, Ontario, Canada;* [h] *Department of Cardiology, St Michael's Hospital, Toronto, Ontario, Canada;* [i] *Department of Medicine, University of Alberta, Edmonton, Alberta, Canada;* [j] *Division of Cardiology, Peter Munk Cardiac Centre, University Health Network, Toronto, Ontario, Canada;* [k] *Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, USA*

ABSTRACT

Background: Data are limited regarding the use of implantable cardioverter–defibrillators (ICDs) in diverse populations. This study explores cardiovascular (CV) outcomes and mortality from ICD randomized controlled trials (RCTs), by sex, race, and age.

Methods: Five electronic databases (PubMed, Emcare, Embase, MEDLINE, and Cumulative Index to Nursing & Allied Health Literature CINAHL) were searched for dates from their inception to July 12, 2021, for RCTs of ICD therapy in adult patients. Data were analyzed for clinical outcomes, including all-cause or CV death, and heart failure hospitalization (HFH).

RÉSUMÉ

Contexte : Les données sur l'utilisation des défibrillateurs cardioverteurs implantables (DCI) dans diverses populations sont limitées. Cette étude porte sur les résultats cardiovasculaires (CV) et les décès liés aux DCI qui ont été signalés dans le cadre d'essais contrôlés randomisés (ECR), en fonction du sexe, de la race et de l'âge.

Méthodologie : Des recherches ont été effectuées dans cinq bases de données électroniques (PubMed, EmCare, Embase, Medline et CINAHL [Cumulative Index to Nursing & Allied Health Literature]) en ciblant une période allant de la date de leur création jusqu'au 12 juillet 2021 afin de recenser les ECR menés chez des patients adultes ayant reçu un

An implantable cardioverter–defibrillator (ICD), which functions to treat ventricular tachycardia and ventricular fibrillation by delivering shocks and/or anti-tachycardia pacing,[1] is indicated to prevent sudden cardiac death (SCD) in patients who have not previously experienced a ventricular arrhythmia, but are at an increased risk for it (primary prevention), and patients who have experienced a serious ventricular arrhythmia (secondary prevention).[2] Several landmark randomized controlled trials (RCTs) have demonstrated the effectiveness of ICD therapy in the primary and secondary prevention of SCD. For example, the primary prevention **S**udden **C**ardiac **D**eath in **He**art **F**ailure **T**rial (SCD-HeFT) found a 60% reduction in SCD in patients who were randomized to the ICD group, compared with the incidence among those who received placebo or amiodarone therapy.[3] Similarly, a study focused on secondary prevention of SCD, the **A**ntiarrhythmics **V**ersus **I**mplantable **D**efibrillators (AVID) trial, found that ICD use, compared with antiarrhythmic therapy, resulted in a 27% relative risk reduction in death.[4]

Received for publication June 14, 2021. Accepted September 16, 2021.

Ethics Statement: This study was not registered in PROSPERO, but it has adhered to the relevant ethical guidelines.

‡These authors contributed equally to this work.

Corresponding author: Dr Laura Banks, Affiliate Scientist, University Health Network, Assistant Teaching Professor, Faculty of Health Sciences, Ontario Tech University, KITE, Toronto Rehabilitation Institute, Cardiovascular Prevention & Rehabilitation Program, 347 Rumsey Rd, Toronto, Ontario M4G 1R7, Canada. Tel.: +1-416-597-3422; fax: +1-416-425-0301.

E-mail: laura.banks@uhn.ca

See page S217 for disclosure information.

https://doi.org/10.1016/j.cjco.2021.09.015

Results: Among 5 RCTs (mean age: 63 years; 78% male; 76% White) with moderate overall risk of bias, clinical outcomes in patients with an ICD (n = 3260) vs a control group (n = 3685) were compared. No between-group sex differences were observed for all-cause death (odds ratio [OR] 0.86, $P = 0.51$), CV death (OR 0.98, $P = 0.96$), HFH (OR 0.95, $P = 0.87$), or HFH and all-cause death (OR 0.83, $P = 0.51$) in the ICD group, in a comparison of male vs female sex. All-cause death (OR 1.20, $P = 0.67$) did not differ for White vs Black patients receiving ICD therapy. Outcomes data for other non-White, non-Black race groups were often unreported. Most RCTs originated in North America, had male leadership, and were evenly sponsored by industry vs peer-reviewed funding.

Conclusions: Outcomes data are sparse, by sex, race, and age, in current RCTs evaluating ICD therapy. Although ICD patient outcomes did not significantly differ by sex or race, improved data analyses and reporting are needed to determine the relationship between these sociocultural factors and clinical outcomes among distinct ICD patient cohorts.

Résultats : Cinq ECR (âge moyen des patients : 63 ans; 78 % d'hommes; 76 % de race blanche) présentant globalement un risque de biais modéré ont permis de comparer les résultats cliniques obtenus chez les patients ayant reçu un DCI (n = 3 260) et ceux du groupe témoin (n = 3 685). Aucune différence intergroupe entre les sexes n'a été observée pour les décès toutes causes confondues (rapport de cotes [RC] : 0,86, $p = 0,51$), les décès d'origine CV (RC : 0,98, $p = 0,96$) et les hIC (RC : 0,95, $p = 0,87$), ou les hIC et les décès toutes causes confondues (RC : 0,83, $p = 0,51$) au sein du groupe de patients ayant reçu un DCI, dans une comparaison entre les sexes. Aucune différence entre les patients de race blanche et de race noire ayant reçu un DCI n'a été notée pour ce qui est des décès toutes causes confondues (RC : 1,20, $p = 0,67$). Souvent, les données sur les résultats obtenus au sein de groupes de patients de race autre que blanche ou noire n'étaient pas signalées. La plupart des ECR avaient été menés en Amérique du Nord, étaient dirigés par des hommes et commandités à parts égales par l'industrie et des organismes offrant du financement approuvé par les pairs.

Conclusions : Les ECR portant sur l'utilisation des DCI fournissent actuellement peu de données sur les résultats en fonction du sexe, de la race et de l'âge. Les résultats obtenus chez les patients ayant reçu un DCI ne différaient pas significativement selon le sexe ou la race. Néanmoins, des analyses de données et des rapports plus détaillés sont nécessaires pour déterminer la relation entre ces facteurs socioculturels et les résultats cliniques au sein de cohortes distinctes de patients ayant reçu un DCI.

However, few ICD RCTs have reported granular data for cardiovascular (CV) outcomes by sex, race, and age, thereby obscuring the potential survival/morbidity benefits and applicability of ICD therapy in more-diverse patient cohorts with CV diseases. Moreover, data have indicated that diverse patient populations, including women, non-White races, and the elderly, are underrepresented in RCTs evaluating major CV outcomes.[5,6] Therefore, the aim of this study was to bridge this knowledge gap by evaluating independent clinical outcomes data and study characteristics, by sex, race, and/or age, among patients who received an ICD.

Methods

Data sources, search strategy, and study eligibility

This review was conducted following the **P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalyses (PRISMA) guidelines.[7] This study was not registered in the International Prospective Register of Systematic Reviews (PROSPERO), but it has adhered to the relevant ethical guidelines. Five electronic databases (PubMed [non-MEDLINE], Emcare, Embase, MEDLINE [Ovid], and Cumulative Index to Nursing & Allied Health Literature [CINAHL]) were searched by an information specialist (M.P.) using the **P**opulation, **I**ntervention, **C**omparison, **O**utcomes, and **S**tudy (PICOS) framework for all relevant English-language RCTs on ICD therapy in adults (age $\geq$ 18 years) with CV disease, from inception until July 12, 2021. Search terms included "implantable cardioverter-defibrillator" and "ICD"; terms are detailed in the search strategy (Supplemental Table S1). All RCTs and their secondary analyses that evaluated the use of ICD alone compared with a control or comparator group (eg, medical therapy or cardiac resynchronization therapy) were included. Studies were excluded for the following criteria: duplicates, non-RCTs (eg, case reports or observational studies, reviews, or meta-analyses), animal studies, non-English publications, and pediatric (age $<$ 18 years) studies. Reference lists of key studies and reviews were also manually searched for any potentially relevant studies.

Data collection, data extraction, and statistical analyses

Search results were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia),[8] and duplicate studies were removed. Two reviewers (H.I.S. and M.K.S.) independently screened article titles and abstracts, and reviewed full-text articles for study eligibility for data extraction. Standardized data extraction included the following: study characteristics (including authorship and funding-recipient sex and race), trial funding sources, trial origin and enrollment sites, patient characteristics, the intervention and control group details, and 12-month event rates for outcomes by sex (male vs female), race (White, Black, Hispanic, East Asian, Southeast Asian, and other), and age ($\geq$ 65 and $<$ 65 years). Discrepancies at each stage were resolved by consensus, with group discussion involving another reviewer (B.M.). Six studies were excluded for the reasons outlined, or in cases in which reported data could not be appropriately synthesized (Supplemental Table S2). Details for first and corresponding (trial lead) authorship and funding

recipient, including sex, and trial funding sources, were captured as reported in the published article, from the clinicaltrials.gov website, and/or from web sources, such as an institutional biography page when possible. Trial investigators' races were determined through an online search, by evaluating their faculty/clinical profiles and last name origins, with consensus of 2 independent reviewers (H.I.S. and M.K.S.). Lack of data precluded analyses based on age and/or career status (eg, early vs late) at the time of study publication.

Predefined clinical outcomes of interest included the following: all-cause death and heart failure hospitalization (HFH; composite and isolated); arrhythmic death; cardiac/non-arrhythmic death; CV death; and ventricular arrhythmia. The composite 3-point major CV adverse endpoint, which includes myocardial infarction, stroke, and CV death, although it was a predefined outcome of interest, could not be evaluated due to lack of reporting that was disaggregated by the demographic variables. Summary statistics for retrievable data (means or medians) were calculated, along with 12-month event rates for each outcome. These outcomes were reported as an odds ratio (OR) or risk ratio (RR), with a 95% confidence interval (CI), utilizing a random-effects model, given the limitations in reported data availability. A P value (2-sided) of < 0.05 was considered statistically significant. Data from each study were analyzed using Cochrane Review Manager (RevMan, version 5.3, The Nordic Cochrane Centre, Copenhagen, Denmark).[9] As applicable, χ^2 and I^2 tests of heterogeneity were also generated.

Risk of bias and GRADE

Two reviewers (H.I.S. and M.K.S.) independently assessed the risk of bias within the eligible studies using the Cochrane risk-of-bias tool for RCTs (RoB2)[10]; any discrepancy was resolved by consensus with an additional reviewer (B.M.). The risk of bias was defined as "low," "some concerns," or "high," based on overall and individual assessment for the following 5 domains (Supplemental Fig. S1): bias arising from the randomization process, bias due to deviations from intended intervention, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported results. Overall quality of the evidence in included trials was also assessed independently (H.I.S. and M.K.S.) utilizing the **G**rading of **R**ecommendations, **A**ssessment, **D**evelopment and **E**valuations (GRADE)[11] certainty scale. Individual studies were defined as "very low," "low," "moderate," or "high" certainty, with the assumption of "high" certainty and then down-rated in the presence of serious concerns about study limitations. The limitations that could have led to a lowered rating included risk of bias, indirectness of evidence, heterogeneity, imprecision, and publication bias.

Results

Study selection and risk of bias

The literature search yielded 6875 studies. After 2976 duplicates were removed, 3896 citations were eligible for abstract screening, of which 175 were eligible for further full-text review. Of 25 publications reporting on ICD therapy, there were 11 distinct RCTs; sex- and race-based clinical outcome data were only available from 5 of these ICD RCTs.[12-16] (Fig. 1). The corresponding authors of the 6 remaining trials were approached for relevant data disaggregated by sex, race, and age, for potential inclusion in the study analyses. However, only one author responded, and this author no longer had access to the data. Therefore, no new data could be added. Consequently, study characteristics and results of the excluded trials were also extracted to determine if the included trials were still representative of ICD trials as a whole. Moreover, similarities between the included vs excluded study cohorts suggested adequate representation by the included studies of ICD trials in general (Supplemental Table S2). Prespecified study characteristics of the eligible ICD RCTs included study authorship and funding recipient, trial funding sources, trial origin and site locations, patient characteristics, and outcomes data in the trial intervention and control arms. Trial information, patient characteristics by sex, race, and age, and outcomes data are summarized in Table 1. Although no studies reported CV outcomes and mortality based on dichotomized age ≥ 65 or < 65 years, Køber et al.[14] reported all-cause death in those aged < 59 years, ≥ 59 to < 68 years, and ≥ 68 years.

Using RoB2 to assess the methodological quality, 4 studies[12,13,15,16] showed "some concerns" overall, and one study[14] showed "high" bias. Most risk of bias was related to deviations from the intended intervention, in cases in which personnel or patients could not be blinded to certain variables due to the nature of device[14,17] implantations. A visual plot of the individual risk of bias domains and summary report is shown in Supplemental Fig. S1. GRADE assessment of the included studies yielded an overall "high" quality of evidence. Funnel-plot analyses for publication bias are shown for data regarding clinical outcomes by sex (Supplemental Fig. S2); inadequate data points from a limited number of studies precluded such plots for clinical outcomes by race or age. The χ^2 and I^2 tests highlighting limited statistical heterogeneity in clinical outcomes were also generated (Fig. 2 and Supplemental Fig. S3). Limited heterogeneity was observed in part, as data for the various clinical outcomes was from a single trial.

Study patient demographics

Descriptive baseline data on 7125 adult patients (n = 3260 patients with an ICD; n = 3865 in the control group) from 5 ICD RCTs are reported in Table 2. The percent composition of female sex was lower, relative to that of male sex (23% vs 78%), within the ICD group, which was comprised primarily of White patients (76%), with a mean age of 63 ± 4 years. Similar study patient characteristics were noted within the control group, which consisted of 23% of female sex and 77% White patients, also with a mean age of 63 ± 4 years. Comprehensive race data were not reported in all studies; for instance, one study reported all non-White patients as being in the "other" category, without further qualifying the "other" ethnic distribution among patients, if present.[15]

Cardiovascular outcomes and mortality, by sex, race, and age

CV outcomes and mortality data have been reported as ORs, by sex (n = 4 studies) and race (n = 1 study), in Tables 3 and 4, between ICD treatment arms. Mortality data,

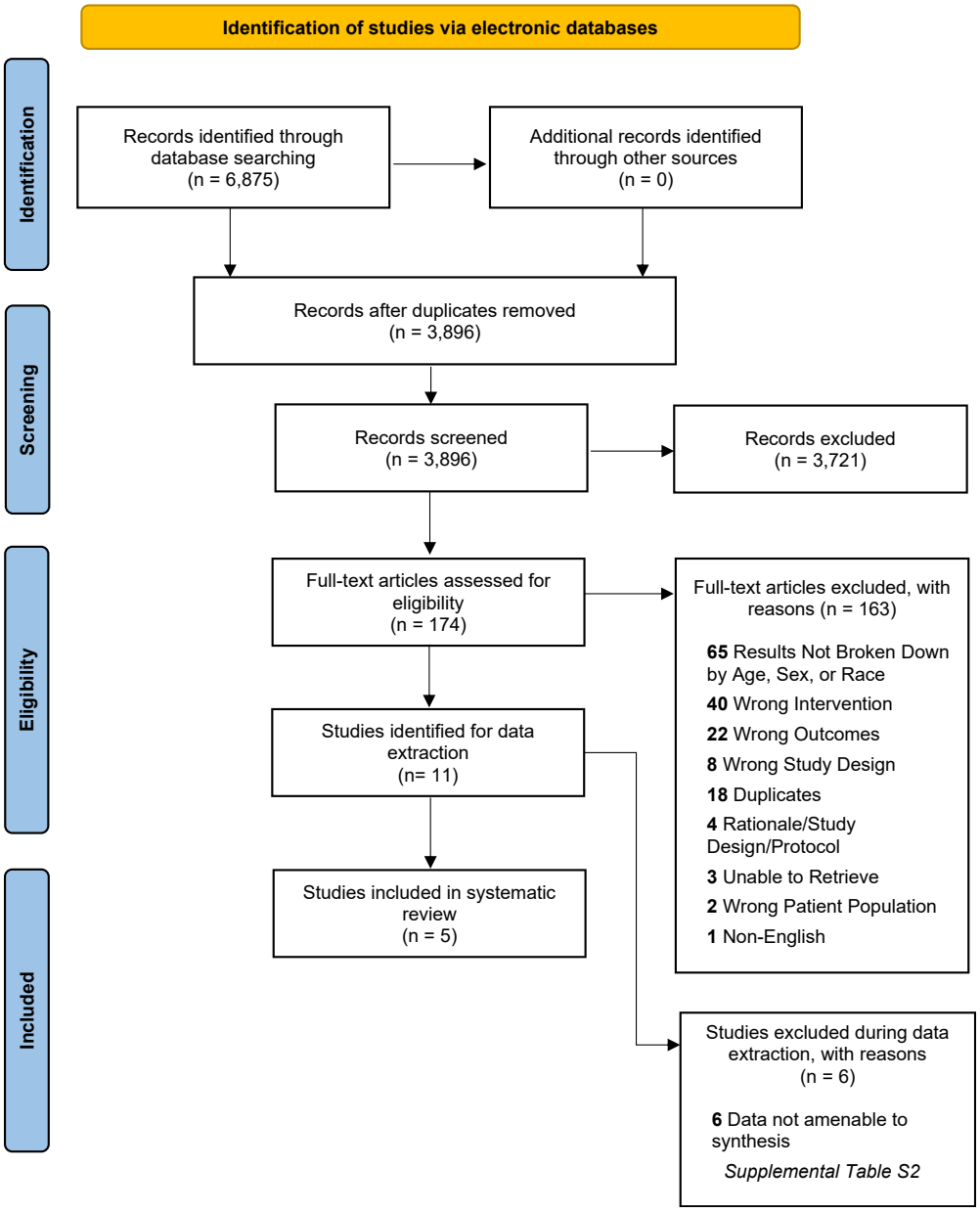

Figure 1. Study flow diagram: **P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalyses (PRISMA) protocol recommendations were used to determine study inclusion.

by sex, are further reported as RRs in forest plots (Fig. 2), between ICD treatment arms, and between ICD and control arms (Supplemental Fig. S3). Data for age were commonly dichotomized into age groups of $\geq$ 65 years and $<$ 65 years, which limited age-related data analysis. Within the ICD group, women, relative to men, had lower odds (nonsignificant difference) of CV death (OR 0.98, 95% CI 0.47-2.07, $P = 0.96$; $n_{studies} = 1$; $n_{subjects} = 904$), HFH (OR 0.95, 95% CI 0.51-1.78, $P = 0.87$; $n_{studies} = 1$; $n_{subjects} = 904$), and composite HFH and all-cause death (OR 0.83, 95% CI 0.49-1.42, $P = 0.51$; $n_{studies} = 1$; $n_{subjects} = 904$). All-cause death, by sex, within ICD arms was the only dataset with a sufficient number of studies for pooled analysis, which showed that the difference between men and women was also nonsignificant, with lower odds in women (OR 0.86, 95% CI 0.55-1.35, $P = 0.51$; $n_{studies} = 3$; $n_{subjects} = 2289$; $\chi^2 = 0.58$; degrees of freedom = 2; $I^2 = 0\%$). Although also a nonsignificant difference, one study reported that women had higher odds of non-arrhythmic CV death within its ICD group, in comparison to men (OR 1.78, 95% CI 0.29-10.92, $P = 0.53$; $n_{subjects} = 229$). Only all-cause death between intervention groups was evaluated for race, due to limited data points: Black adults had nonsignificant higher odds of all-cause death, relative to White adults, within ICD arms (OR 1.18, 95% CI 0.56-2.57, $P = 0.66$; $n_{studies} = 1$). Finally, Køber et al.[14] published the only study reporting any outcome comparison by age. The difference in all-cause death between the ICD and control groups was nonsignificant in all age groups ($<$ 59

Table 1. Summary of included implantable cardioverter–defibrillator (ICD) randomized controlled trials

Study characteristic	Vorobiof[16] (2006)*	Albert[12] (2008)	Russo[15] (2008)	Køber[14] (2016)	De Waard[13] (2019)
Trial name	MADIT-II	DEFINITE	SCD-HeFT	DANISH	RAFT
Trial sites/ region	North America, Europe	North America	North America, Australia	Europe	North America, Europe, Australia, Asia
No. of trial sites	76	NR	148	5	34
Eligible age, y	> 21	NR	≥ 18	NR	NR
Enrollment by sex (male vs female)	1039 (84), 197 (16)	326 (71), 132 (29)	1933 (76.7), 588 (23.3)	809 (72.5), 307 (27.5)	1490 (83), 308 (17)
Male enrollment by race (White, Black, Hispanic, other)	934 (93.7) White, 63 (6.3) Black	232 (71), 69 (21), 20 (6), 5 (2)	1527 (79) White, 406 (21) reported as non-White race	NR	NR
Female enrollment by race (White, Black, Hispanic, other)	140 (78.2), White 39 (21.8) Black	77 (58%, 49 (37), 6 (5), 0 (0)	406 (69) White, 182 (31) reported as non-White race	NR	NR
Mean age, y	64 ± 10	58.3	60 (median)	63.5 (median)	66.1 ± 9.4
Patient population	Past MI, LVEF < 0.30	LVEF < 36%, HF, or arrhythmias	NYHA class II or class II chronic, stable CHF, and LVEF ≥ 35%	LVEF < 36%, arrhythmias, HF, or non-ischemic DCM	NYHA class II HF, LVEF < 30%, prolonged QRS duration, sinus rhythm/AF/AFL < 60 bpm at rest, or planned ICD for indicated prevention of SCD
Trial subgroup	MI	Non-ischemic DCM	SCD, CHF	Systolic HF	HF, ventricular arrhythmia
Primary outcome(s)	Death from any cause†	Death from any cause	Death from any cause†	Death from any cause	Death from any cause or HFH†
Secondary outcome(s)	N/A	Sudden death from arrhythmia†	Arrhythmic death	SCD, CV death, cardiac arrest, sustained ventricular tachycardia, and change in quality of life	Death from any cause, death from any CV cause, and HFH
Treatment arm	ICD	ICD	ICD	ICD	ICD
Control arm	Conventional medical therapy	Standard medical therapy	Amiodarone or placebo	Usual clinical care	ICD-CRT
No. of patients (treatment vs control)	1232 (742† vs 490)	458 (229† vs 229)	2521 (Tx1: 845, Tx2: 829† vs 847)	1116 (556 vs 560)	1798 (904 vs 894†)
Overall quality of the evidence (GRADE)‡			⊕⊕⊕⊕ High (n = 5 studies)		

Values are n (%), unless otherwise indicated.

AF, atrial fibrillation; AFL, atrial flutter; bpm, beats per minute; CHF, congestive heart failure; CRT, cardiac resynchronization therapy; CV, cardiovascular; DANISH, **D**anish Study to **A**ssess the Efficacy of ICDs in Patients with **N**on-**is**chemic Systolic **H**eart Failure on Mortality; DCM, dilated cardiomyopathy; DEFINITE, **Def**ibrillators in **N**on-**I**schemic Cardiomyopathy **T**reatment **E**valuation Trial; GRADE, **G**rading of **R**ecommendations, **A**ssessment, **D**evelopment, and **E**valuations; HF, heart failure; HFH, heart failure hospitalization; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MADIT-II, **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial II; MI, myocardial infarction; NR, not reported; NYHA, New York Heart Association; RAFT, **R**esynchronization–Defibrillation for **A**mbulatory Heart **F**ailure **T**rial; RCT, randomized controlled trial; SCD, sudden cardiac death; SCD-HeFT, **S**udden **C**ardiac **D**eath in **He**art **F**ailure **T**rial; Tx, treatment.

*Vorobiof et al.[16] reported data on MADIT-II and included 1073 White patients, 102 Black Patients, and 37 Hispanic patients, and 20 patients categorized as 'other'. However, race characteristics were only documented for White and Black patients, so not all participants are included for those characteristics.

†Indicates significance at $P < 0.05$.

‡Studies were assessed for all-cause death only.

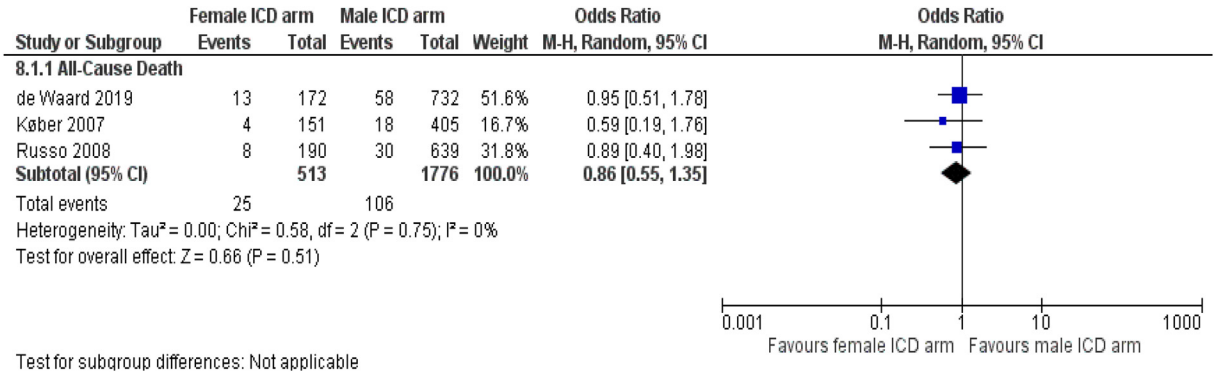

Figure 2. Reported all-cause death by sex between implantable cardioverter–defibrillator (ICD) treatment arms. Shown are forest plot analyses for all-cause death by sex between ICD treatment arms. Only all-cause death was included in Forest plot analyses due to limited availability of data regarding cardiovascular outcomes. CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel method.

years, RR 1.85, 95% CI 0.47-7.26, $P = 0.38$; ≥ 59 to < 68 years, RR 1.10, 95% CI 0.42-2.89, $P = 0.85$; and ≥ 68 years, RR 0.92, 95% CI 0.39-2.12, $P = 0.84$).

Study characteristics of trial leads and sites

Table 5 reports study details for trial leads, sites, and authorship of included studies. Most trials originated in North America and enrolled subjects from 4 sites in North America, 3 sites in Europe, 2 sites in Australia, and 1 site in Asia. These studies were evenly supported by industry partners and peer-reviewed grant support; this funding support was given predominantly to White men from North America (80%). The corresponding and first authors were both male in 2 studies (40%), and both female in 3 studies (60%); they were White in 4 studies (80%) and Asian in 1 study (20%). Important to note is that the data for this analysis were provided mainly from secondary-analysis publications, which more often had female vs male lead authors. By contrast, the primary RCT analyses were more often published by male lead authors.

Table 2. Study patient characteristics by sex, race, and age from included implantable cardioverter–defibrillator randomized controlled trials (ICD RCTs)

Characteristic	ICD arm (n = 3260)	Comparator arm (n = 3018)*	Comparator arm 2 (n = 847)
Age, y			
Mean	62.9 ± 4.0	63.1 ± 4.3	NR
Median	62.1	61.7	59.1
Sex, % of n			
Male	77.5	77.5	77.0
Female	22.5	22.5	23.0
Race, % of n			
White	75.8	77.1	NR
Black	17.3	16.9	NR
Hispanic	5.7	5.7	NR
East Asian	0	0.4	NR
Southeast Asian	NR	NR	NR
Other†	12.0	12.0	24.0

NR, not reported.

*Comparator arm included either standard medical therapy, usual clinical care, treatment with amiodarone, conventional medical therapy, or ICD-CRT. Comparator arm 2 was composed of a placebo arm from Russo et al.[15]

†"Other" includes all non-White races as reported in one study, but these were unspecified by Russo et al.[15]

Discussion

This study sought to investigate CV outcomes and mortality, by sex, race, and age, among patients implanted with an ICD. Only 45% (5 of 11 studies) reported data on age, sex, and race. Among these 5 ICD RCTs that met the study inclusion criteria, no sex- or race-specific differences in pooled CV outcomes were observed in patients implanted with an ICD, in terms of all-cause death, CV death, and HFH. Additionally, data on these CV outcomes and mortality were not reported based on the prespecified age cutoff of 65 years, and thus could not be pooled for evaluation. Interesting to note is that the majority of trials originate and are carried out largely in North America, followed by Europe.

The primary RCTs had predominantly White male leadership, supported evenly by industry and peer-reviewed funding. Many of the secondary-analysis publications that provided data for the current analysis had female lead authors, in contrast to the primary-analysis publications, which had mainly male lead authors. Expanding on the origins and sites of trials, as well as the diversity of funding recipients and trial leadership, may improve recruitment diversity via enhanced patient–physician concordance. Higher patient–physician concordance may be associated with greater levels of trust, which in turn has the potential to enhance the generalizability of study outcomes to a more-diverse group of patients, owing to the increased enrollment.[18] As well, patient–physician concordance (eg, patients identifying with physicians in terms of personal beliefs, values, and/or communication style) may be associated with improved health outcomes, trusting relationships that lead to greater shared decision-making and intent to adhere to recommendations, and overall satisfaction with care.[19-21]

Future prospective studies with more granular analyses and reporting are warranted to evaluate the relationship between diverse sociocultural variables and clinical outcomes among patients requiring ICD therapy.

Sex differences in CV outcomes and mortality post-ICD implantation

We reported no sex differences in CV outcomes and mortality following 1-year post-ICD implantation in male vs female patients. Notably, although we included 4 studies that had ICD outcomes reported by sex, women tended to be

Table 3. Clinical outcomes by sex in implantable cardioverter–defibrillator (ICD) randomized controlled trial treatment arms

Clinical outcome*	Total, n	Male sex, n	Female sex, n	Odds ratio (95% CI)	*P*
ICD arm					
All-cause death and HFH	108/904	90/732	18/172	0.83 (0.49, 1.42)	0.51
All-cause death	131/2289	106/1776	25/513	0.86 (0.55, 1.35)	0.51
HFH	71/904	58/732	13/172	0.95 (0.51, 1.78)	0.87
CV death	48/904	39/732	9/172	0.98 (0.47, 2.07)	0.96
CV death (non-arrhythmic)	5/229	3/166	2/63	1.78 (0.29, 10.92)	0.53
Arrhythmic death	2/229	2/166	0/63	0.52 (0.03, 10.94)	0.67
Ventricular arrhythmia	133/904	111/732	22/172	0.82 (0.50, 1.34)	0.43
Comparator arm					
All-cause death and HFH	88/894	80/758	8/136	0.53 (0.25, 1.12)	0.10
All-cause death	130/2299	109/1801	21/498	0.68 (0.42, 1.10)	0.12
HFH	52/894	48/758	4/136	0.45 (0.16, 1.26)	0.13
CV death	39/894	34/758	5/136	0.81 (0.31, 2.12)	0.67
CV death (non-arrhythmic)	6/229	3/160	3/69	2.38 (0.46, 12.10)	0.30
Arrhythmic death	7/229	5/160	2/69	0.92 (0.17, 4.90)	0.93
Ventricular arrhythmia	125/894	113/758	12/136	0.55 (0.29, 1.03)	0.06
Comparator arm 2					
All-cause death	50/847	41/655	9/192	0.75 (0.35, 1.57)	0.44

CV, cardiovascular; HFH, heart failure hospitalization.
* Number of events per total patients in group at 1 year, unless otherwise stated.

underrepresented (only 23%). Albert et al.[12] did not report any sex differences following ICD therapy, but they acknowledged that their study was inadequately powered. Similarly, Russo et al.,[15] included in our analysis, suggested that men may exhibit a greater reduction in mortality risk than women; however, the smaller sample size of women may explain the treatment differences observed. Previous work on sex-based differences in outcomes following ICD implantation also reported that men, but not women, demonstrated a reduction in mortality.[22] Therefore, future research also must be adequately powered to detect sex differences for clinical outcomes following ICD therapy.

Race differences in CV outcomes and mortality post-ICD implantation

We reported no significant race differences in CV outcomes and mortality following 1-year post-ICD implantation; yet, RCTs in our analysis included primarily White participants and/or were inadequately powered to evaluate race-based differences following ICD therapy. As an example, a substudy of the **M**ulticenter **A**utomatic **D**efibrillatory **I**mplantation **T**rial (MADIT-II) reported that ICD therapy was associated with a reduction in all-cause death, CV death, and SCD in White but not Black participants; however, Black participants were greatly underrepresented in the trial (8% of enrollees).[16] As with sex, enhanced reporting of race-related data is imminently required, along with targeted recruitment efforts to better understand how ICD therapy impacts clinical outcomes in ethnically diverse patient groups. Resource allocation and ongoing access to clinical care, based on the regional interplay of different races and the universality of healthcare insurance coverage, also may be critical influencers of the ultimate effectiveness of ICD therapy among these diverse populations.

Table 4. All-cause death by race in implantable cardioverter–defibrillator (ICD) randomized controlled trials

Clinical outcome* All-cause death	White race, n	Black race, n	Odds ratio (95% CI)	*P*
ICD arm	59/646	7/65	1.18 (0.56, 2.47)	0.66
Comparator arm	43/427	4/37	1.08 (0.37, 3.20)	0.89

CI, confidence interval.
* Number of events per total patients in group at one year unless otherwise stated. No race-specific data were reported in the study with the second comparator arm.

Age differences in CV outcomes and mortality post-ICD implantation

We were unable to report on age-related CV outcomes and mortality differences following 1-year post-ICD implantation, as these data were not reported based on the prespecified age cutoff of $\geq$ 65 or $<$ 65 years, in any of the 5 RCTs included in this review. One study highlighted a sign of mortality benefit of ICD therapy in those aged $\geq$ 68 years. Additional studies are warranted to understand whether this effect is "real," given the clinical implications of resource allocation, the risks vs benefits of ICD therapy, and the ongoing device care needs that may result in multiple device generator or lead revisions in a patient who is much younger than age 65 years at the time of initial ICD implantation. Furthermore, although population-level analyses provide some insight as to the ICD therapy risk–benefit balance, it may not translate directly to an individual patient. The healthcare team should understand that although individual risk–benefit may depend in part on age, for instance, there are other covariables, such as comorbidities and frailty, that can influence individual patient survival and relative risk of arrhythmic vs non-arrhythmic death with ICD therapy.

Clinical implications and future considerations

Our study findings suggest that diverse populations, including women, non-Whites, and elderly patients, need to be included and reported on in larger RCTs focused on clinical outcomes in patients with CV disease who require ICD therapy. There is persistent underrepresentation and/or underreporting of study data by sex, race, and age. As an example, recent clinical trials with CV outcomes (conducted

Table 5. Study details for trial leads, sites, and authorship of included implantable cardioverter–defibrillator randomized controlled trials

Parameter	Frequency	Parameter	Frequency
Trial origin		Trial enrollment sites	
North America	4 (80)	North America	4 (40)
Europe	1 (20)	Europe	3 (30)
Australia	0	Australia	2 (20)
Asia	0	Asia	1 (10)
Africa	0	Africa	0
South America	0	South America	0
First author by sex		Corresponding author by sex	
Male	2 (40)	Male	2 (40)
Female	3 (60)	Female	3 (60)
First author by race		Corresponding author by race	
White	4 (80)	White	4 (80)
Black	0	Black	0
Hispanic	1 (20)	Hispanic	0
Asian	0	Asian	1 (20)
Southeast Asian	0	Southeast Asian	0
Other	0	Other	0
First author by site		Corresponding author by site	
North America	4 (80)	North America	4 (80)
Europe	1 (20)	Europe	1 (20)
Australia	0	Australia	0
Asia	0	Asia	0
Africa	0	Africa	0
South America	0	South America	0
Funding recipient by sex*		Funding sponsor by trial†	
Male	5 (100)	Industry	3 (50)
Female	0	Peer-reviewed	3 (50)
Funding recipient by race*		Funding recipient by site*	
White	4 (80)	North America	4 (80)
Black	0	Europe	1 (20)
Hispanic	0	Australia	0
Asian	1 (20)	Asia	0
Southeast Asian	0	Africa	0
Other	0	South America	0

Values are n (%).

*Funding recipient/s were those acknowledged from the article, when possible, or was considered to be the corresponding study lead as listed at clinicaltrials.gov, if not otherwise stated.

†One study, Tang et al.,[17] reported funding from both sources.

between 2010 and 2017) reported that 38% of participants were female, an improved representation in stroke and heart failure trials.[5] However, there is also evidence for low female enrollment in CV device trials, as described by Gong et al.,[23] who reported only 29% female enrollment in device trials. Nguyen et al.[24] evaluated age and female representation in the most-cited RCTs in cardiology from 1996-2015 and reported similar trends. Although the mean age and percentage of women increased significantly over this time, this increase was not enough to close the enrollment gap of older adults and women.

Further, Barra et al.[25] highlight in their analysis that women may benefit from ICD therapies differently than do men; for example, ICD therapy may not be associated with improved survival in female trial patients, compared with optimal medical therapy. Meanwhile, Conen et al.[26] reported that although women had a lower risk of death than men, they experienced more inappropriate shock therapy. Notably, 3 of the 5 trials included in this study were conducted prior to this report,[5] but the more recent ICD trials (published in 2016[14] and 2019[13]) included in our analysis had less than 30% of participants who were female. Therefore, this study serves as a call-to-action to improve representation of a diverse patient group in CV-outcome RCTs, particularly as it may inadvertently impact patient outcomes.[8]

Our findings suggest that major ICD RCTs focusing on clinical outcomes were primarily led by investigators who were male and/or White, as primary recipients of industry or peer-reviewed funding. Although secondary-analysis publications among these studies include more women, few authorships involved non-Whites. Similarly, non-White minorities continue to be underrepresented in CV-outcome RCTs. Ultimately, the scientific community needs to overcome critical barriers to RCT enrollment to improve data reporting on diverse groups of patients with CV disease.[27,28] In particular, RCT investigators should prioritize a number of goals,[28] including the recruitment and training of diverse coordinator and investigator research teams, and sex, race and age equity in clinical trial recruitment. Furthermore, economic incentives from government and industry commitments may enable trial design to be more inclusive of a diversity of patients in clinical CV trials.[14]

Limitations

A few limitations of this study need to be considered. Only 5 ICD RCTs reported event rates for CV outcomes and mortality, to allow for summative analysis, limiting the overall generalizability of the results. The current authors were unable to retrieve data for the 6 excluded studies, for inclusion into the analyses; yet, study demographics are similar between the included vs excluded studies. Furthermore, 1-year estimates were extracted in some studies that reported on event numbers over longer-term follow-up periods; thus, the results of those studies may be reflected less accurately. Additionally, not all of the studies reported full patient demographics or clinical outcomes based on sex, race, or age-based categories. As a result, baseline characteristics may not be comprehensive, and a more robust meta-analysis for all CV outcomes and mortality, and a more comprehensive statistical heterogeneity, could not be achieved, due to such data-reporting inconsistencies.

A systematic approach was used, including a formal search strategy and consensus between 2 coauthors (H.I.S. and M.K.S.), to retrieve trial investigators' race. Investigator race data were not solicited, and therefore, discrepancies may exist. Lastly, this study analyzed data from only ICD RCTs and not population-based registries or studies. Subsequent research could investigate the interactions of sex, race, and age in their impact on ICD efficacy, and compare data from ICD RCTs with population-based data such as that from registries.

Conclusions

Our study findings suggest no significant sex- or race-based differences in CV outcomes and mortality, utilizing cases in which some such data were reported; age-related differences could not be surmised due to lack of reported data. However, future RCTs with explicit data reporting with analyses by sex, race, and age are warranted to determine the association

between these sociocultural factors and CV outcomes and mortality among patients who receive an ICD. As well, the diversification of trial leadership, trial origin, and trial sites should be considered as a means to enhance patient–physician concordance to make progress toward improving recruitment of diverse patient populations.

Acknowledgements

The authors thank Dr Katherine Allan for her input on this article.

Funding Sources

The authors have no funding sources to declare.

Disclosures

The authors have no conflicts of interest to disclose.

References

1. DiMarco JP. Implantable cardioverter–defibrillators. N Engl J Med 2003;349:1836-47.
2. Glikson M, Friedman PA. The implantable cardioverter defibrillator. Lancet 2001;357:1107-17.
3. Chia P-L, Foo D. Overview of implantable cardioverter defibrillator and cardiac resynchronisation therapy in heart failure management. Singapore Med J 2016;57:354-9.
4. Kedia R, Saeed M. Implantable cardioverter-defibrillators: indications and unresolved issues. Tex Heart Inst J 2012;39:335-41.
5. Jin X, Chandramouli C, Allocco B, et al. Women's participation in cardiovascular clinical trials from 2010 to 2017. Circulation 2020;141:540-8.
6. Sardar MR, Badri M, Prince CT, et al. Underrepresentation of women, elderly patients, and racial minorities in the randomized trials used for cardiovascular guidelines. JAMA Intern Med 2014;174:1868-70.
7. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336-41.
8. Covidence Systematic Review Software [program]. Melbourne, Australia: Veritas Health Innovation.
9. Review Manager 5 [program]. 5.3 version. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014: The Cochrane Collaboration.
10. Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
11. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383-94.
12. Albert CM, Quigg R, Saba S, et al. Sex differences in outcome after implantable cardioverter defibrillator implantation in nonischemic cardiomyopathy. Am Heart J 2008;156:367-72.
13. de Waard D, Manlucu J, Gillis AM, et al. Cardiac resynchronization in women: a substudy of the resynchronization-defibrillation for ambulatory heart failure trial. JACC Clin Electrophysiol 2019;5:1036-44.
14. Køber L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375:1221-30.
15. Russo AM, Poole JE, Mark DB, et al. Primary prevention with defibrillator therapy in women: results from the Sudden Cardiac Death in Heart Failure Trial. J Cardiovasc Electrophysiol 2008;19:720-4.
16. Vorobiof G, Goldenberg I, Moss AJ, et al. Effectiveness of the implantable cardioverter defibrillator in Blacks versus Whites (from MADIT-II). Am J Cardiol 2006;98:1383-6.
17. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. N Engl J Med 2010;363:2385-95.
18. Street RL, O'Malley KJ, Cooper LA, et al. Understanding concordance in patient-physician relationships: personal and ethnic dimensions of shared identity. Ann Fam Med 2008;6:198-205.
19. Blanchard J, Nayar S, Lurie N. Patient–provider and patient–staff racial concordance and perceptions of mistreatment in the health care setting. J Gen Intern Med 2007;22:1184-9.
20. Greenwood BN, Carnahan S, Huang L. Patient-physician gender concordance and increased mortality among female heart attack patients. Proc Natl Acad Sci U S A 2018;115:8569-74.
21. Traylor AH, Schmittdiel JA, Uratsu CS, et al. Adherence to cardiovascular disease medications: does patient-provider race/ethnicity and language concordance matter? J Gen Intern Med 2010;25:1172-7.
22. Narasimha D, Curtis AB. Sex differences in utilisation and response to implantable device therapy. Arrhythm Electrophysiol Rev 2015;4:129-35.
23. Gong IY, Tan NS, Ali SH, et al. Temporal trends of women enrollment in major cardiovascular randomized clinical trials. Can J Cardiol 2019;35:653-60.
24. Nguyen QD, Peters E, Wassef A, et al. Evolution of age and female representation in the most-cited randomized controlled trials of cardiology of the last 20 years. Circ Cardiovasc Qual Outcomes 2018;11:e004713.
25. Barra S, Providência R, Boveda S, et al. Do Women Benefit Equally As Men from the Primary Prevention Implantable Cardioverter-Defibrillator?. Oxford, UK: Oxford University Press, 2018.
26. Conen D, Arendacká B, Röver C, et al. Gender differences in appropriate shocks and mortality among patients with primary prophylactic implantable cardioverter-defibrillators: systematic review and meta-analysis. PLoS One 2016;11:e0162756.
27. Clark LT, Watkins L, Piña IL, et al. Increasing diversity in clinical trials: overcoming critical barriers. Curr Prob Cardiol 2019;44:148-72.
28. Ortega RF, Yancy CW, Mehran R, et al. Overcoming lack of diversity in cardiovascular clinical trials: a new challenge and strategies for success. Circulation 2019;140:1690-2.

Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2021.09.015.