Efficacy and safety of implantable cardioverter-defibrillator implantation in the elderly—The I-70 Study: A randomized clinical trial

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BACKGROUND There is conflicting evidence on the efficacy of primary prevention implantable cardioverter-defibrillator (ICD) implantation in the elderly.

OBJECTIVE The purpose of this study was to determine the efficacy and safety of ICD implantation in patients 70 years and older.

METHODS Patients (n = 167) aged 70 years or older and eligible for ICD implantation were randomly assigned (1:1) to receive either optimal medical therapy (OMT) (n = 85) or OMT plus ICD (n = 82).

RESULTS Of the 167 participants (mean age 76.4 years; 165 men), 144 completed the study protocol according to their assigned treatment. Average participant follow-up was 31.5 months. Mortality was similar between the 2 groups: 27 deaths in OMT vs 26 death in ICD (unadjusted hazard ratio 0.92; 95% confidence interval 0.53–1.57), but there was a trend favoring the ICD over the first 36 months of follow-up. Rates of sudden death (7 vs 5; $P = .81$) and all-cause hospitalization (2.65 events per participant in OMT vs 3.09 in ICD; $P = .31$) were not statistically significantly different. Eleven participants randomized to ICD received appropriate therapy. Five participants received an inappropriate therapy that included at least 1 ICD shock.

CONCLUSION The study did not recruit to target sample size, and accumulated data did not show benefit of ICD therapy in patients 70 years or older. Future studies similar in design might be feasible but will need to contend with patient treatment preference given the large number of patients who do not want an ICD implanted. Further research is needed to determine whether the ICD is effective in prolonging life among elderly device candidates.

KEYWORDS Elderly; Electrophysiology; Heart failure; Implantable cardioverter-defibrillator; Primary prevention

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Introduction

Prophylactic use of the implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death (SCD) has been shown to improve survival in a generalized cohort of patients with heart failure and reduced ejection fraction.[1,2] However, there is conflicting evidence on the efficacy of primary prevention ICD implantation in the elderly, with numerous published calls for a study to address this question.[3–9] Nevertheless, there is no specific contraindication of advanced age in the American College of Cardiology/American Heart Association/Heart Rhythm Society practice

Information on the Study Groups in given in the Supplemental Appendix. ClinicalTrials.gov Identifier: NCT02121158. **Address reprint requests and correspondence:** Dr Michael Wininger, Cooperative Studies Program, VA Connecticut Healthcare System, 950 Campbell Avenue (151A), West Haven, CT 06516. E-mail address: michael.wininger@va.gov.

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KEY FINDINGS

- The most common reason patients declined participation in the study was a preference not to have an implantable cardioverter-defibrillator (ICD) implanted, which may help explain the apparent underutilization of ICD therapy in the elderly.
- Among those participants assigned to receive an ICD vs those not assigned to receive an ICD, all-cause mortality and observed differences in all-cause mortality were not statistically significant (primary outcome), although there seems to be a trend toward lower mortality in the ICD group.
- Among those participants assigned to receive an ICD vs those not assigned to receive an ICD, all-cause mortality and observed differences in cardiac mortality and all-cause hospitalization were not statistically significant (secondary outcomes).

guidelines that would preclude ICD prescription[10] or Medicare reimbursement for older patents.[11] Yet in a study of Medicare beneficiaries, only 8.1% of 10,318 ICD-eligible elderly patients (mean age 78 years) received an ICD for primary prevention of SCD,[12] and a recent all-ages cohort study of 144,074 eligible veterans with incident heart failure and reduced ejection fraction (mean age 71 years) estimated utilization at <20%.[13] It is likely equipoise about the efficacy of ICD therapy in the elderly on the part of both patients and providers that contributes to this underutilization. It is widely anticipated that a landmark clinical trial testing the efficacy of ICD in older patients would be pivotal in reconciling the gap between device eligibility and device adoption.

The primary objective of the I-70 Study (Efficacy and Safety of ICD Implantation in the Elderly trial) was to determine whether primary prevention of SCD using ICD implantation in addition to optimal medical therapy (OMT) is effective in reducing all-cause mortality compared to OMT alone in patients aged 70 years or older, who are eligible for ICD therapy according to current Centers for Medicare & Medicaid Services criteria.

Methods

Patient population

Veterans aged 70 years or older who qualified for ICD implantation per Centers for Medicare & Medicaid Services criteria were eligible for study recruitment. Before left ventricular ejection fraction (LVEF) was measured, patient volunteers were required to be in stable condition on an OMT regimen, including titration of heart failure therapies and adherence to a healthy lifestyle (eg, smoking cessation, dietary management, exercise). There was no minimum interval for establishing stability; this was left to the determination of the study team. The qualifying LVEF had to be measured within 6 months of randomization, and participants were excluded if they were within 40 or 90 days of a myocardial infarction or revascularization, respectively. Patients with a pre-existing conventional single- or dual-chamber pacemaker were included; however, those with an existing defibrillator or either had been or were judged to be a good candidate for a cardiac resynchronization therapy (CRT)–pacemaker were excluded. The research reported in this paper adhered to CONSORT guidelines. This study was approved through the VA Office of Research and Development and the VA Central Institutional Review Board. The Central Institutional Review Board conducted annual continuing review, and a data monitoring committee reviewed the study on an approximately biannual basis. All participants provided written informed consent and privacy authorization.

Trial design

A detailed description of the study design is given in the Supplemental Appendix. Summarily, the I-70 Study was designed in a 2-stage format: a pilot phase involving 6 Veterans Affairs Medical Centers followed by an expanded phase that would include a larger number of sites, contingent on demonstration of adequate enrollment at the pilot sites. Following continuous review of study enrollment data during 52 months of recruitment, the trial was determined by the study sponsor, the VA Office of Research and Development, Cooperative Studies Program, to have recruited at an insufficient rate to justify expansion and subsequently was closed to enrollment on February 11, 2020.

Trial procedures

Participants were assigned to receive either OMT+ICD or OMT without ICD, in a 1:1 allocation. Randomization was performed according to a pre-established assignment scheme, with permuted blocks of size 2, 4, or 6. Randomization was stratified by medical center and Charlson Comorbidity Index,[14,15] measured at baseline and dichotomized according to a score of <3 vs ≥3 points. After randomization, all study participants underwent follow-up per routine clinical practice. Participants randomized to OMT received an additional visit with the study team at 1–4 months to match the postoperative clinic appointment for ICD recipients. All participants completed biannual phone-based follow-ups conducted by centralized personnel, who collected information pertaining to quality of life, adverse events, and changes to medication. All devices implanted under the study protocol were monitored remotely through the VA National Cardiac Device Surveillance Program. Device programming was prescribed per study protocol (Supplemental Appendix A) to minimize ventricular pacing, reduce risk of inappropriate therapy, and improve quality of life, based on published studies, as each device manufacturer's features allowed.[16,17] Programming changes that departed from these parameters at the time of implant (whether intentionally or unintentionally) were considered a protocol deviation. After the day of implantation, programming changes were allowed

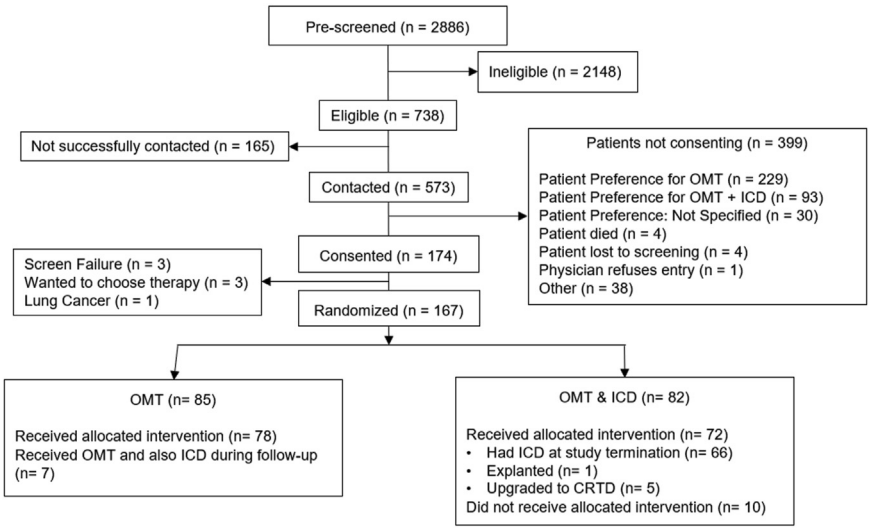

Figure 1 Enrollment and randomization of patients. CRTD = cardiac resynchronization therapy with defibrillator; ICD = implantable cardioverter-defibrillator; OMT = optimal medical therapy.

based on clinical indications, such as development of heart block, development of slow ventricular tachycardia, and syncope with ventricular tachycardia/ventricular fibrillation. Patients requiring CRT were considered ineligible for the study; however, patients who developed a clinical indication for a nonstudy therapy were not withdrawn. Ultimately, the programming parameters after implantation and other case management decisions were left to the discretion of the treating clinician.

Outcomes and safety

The primary outcome measure of the I-70 Trial was death from any cause. Secondary and exploratory objectives were ascertainment of the influence of age vs comorbidity as determinants of mortality outcomes, quality of life, rates of SCD, and all-cause hospitalization. Causes of death were adjudicated by a 3-member panel naïve to the assigned treatment, after reviewing death certificates, hospitalization records, and witness reports. Nonserious adverse events were monitored for 30 days postrandomization (OMT) or postimplantation (ICD). Serious adverse events were monitored for the entire duration of follow-up. An extended description of the study statistical considerations is given in Supplemental Appendix B.

Sample size projection

The primary outcome of the I-70 Trial was all-cause mortality analyzed as time to event. The primary hypothesis was that the ICD arm will yield a 25% reduction in hazard ratio (HR 0.75; 23.5% relative risk reduction in the annual mortality rate). We assumed 15% annual mortality in the OMT arm, annual drop-in rate of 3.5% from OMT to OMT+ICD, dropout rate of 1% from OMT+ICD to OMT (year 1 only), and annual loss to follow-up of 1%. The study was designed to uphold a 1:1 allocation, 5% 2-sided type I error, and 90% power. Considering a staged design (pilot at 6 sites, followed by a planned expansion to a total of 27 sites), the target sample size was 1,462.

Primary analysis

All analyses were performed according to the intention-to-treat principle. Cumulative survival rates for the treatment arms were calculated using the Kaplan-Meier method. All-cause mortality was analyzed as time to event with the log-rank test, stratified by site and by Charlson co-morbidity index (<3 or ≥ 3). The start time for all time-to-event analyses was defined as the date of randomization, and participants who did not experience an event were right-censored at the date of last contact, date withdrawn, or date of study exit. The treatment effect was estimated with a Cox proportional hazards model stratified by Charlson score (<3 vs ≥ 3). Before fitting the Cox proportional hazards model, the proportional hazards assumption was tested using a treatment by time interaction term. In addition, the treatment by Charlson stratum interaction was tested in a Cox proportional hazards model.

Analysis of ICD therapies

Patients who received a study-assigned ICD were monitored for device therapies by remote monitoring and in-person interrogation either scheduled or after clinical events. ICD therapy episodes were analyzed for the arrhythmia triggering detection, therapy type (antitachycardia pacing vs shock), and therapy outcome. All therapy events were reviewed by a separate 3-member committee. Designation as appropriate vs inappropriate therapy was made after review of all available data in the interrogation. An episode was defined as appropriate if ventricular tachycardia or ventricular fibrillation was present at the time of detection and resulted in a single or multiple shocks, or antitachycardia pacing.

Table 1 Patient characteristics at baseline

	OMT (n = 85)	OMT + ICD (n = 82)	Total (N = 167)
Age (y)	74.1 [72–89]	75.0 [72–82]	74.6 [72–80]
Male sex	84 (98.8)	81 (98.8)	165 (98.8)
Race			
African-American	12 (14.1)	15 (18.3)	27 (16.2)
White	73 (85.9)	67 (81.7)	140 (83.8)
Heart failure			
Ischemic	59 (69.4)	60 (73.2)	119 (71.3)
Nonischemic	26 (30.6)	22 (26.8)	48 (28.7)
Diabetes	37 (43.5)	38 (46.3)	75 (44.9)
Hypertension	80 (94.1)	74 (90.2)	154 (92.2)
Renal disease	8 (9.4)	9 (11.0)	17 (10.2)
Smoking	16 (18.8)	9 (11.0)	25 (15.0)
Atrial fibrillation	37 (43.5)	47 (57.3)	84 (50.3)
Body mass index (kg/m^2)	29.0 [24.7–32.8]	28.9 [25.5–32.1]	29.0 [25.1–32.5]
Left ventricular ejection fraction (%)	30 [27–33]	30 [27–33]	30 [27–33]
New York Heart Association class			
I	2 (2.4)	4 (4.9)	6 (3.6)
II	62 (72.9)	58 (70.7)	120 (71.9)
III	21 (24.7)	20 (24.4)	41 (24.6)
Systolic BP (mm Hg)	122 [111–138]	128 [115–141]	125 [112–138]
Diastolic BP (mm Hg)	72 [63–78]	73 [64–82]	72 [64–79]
Resting heart rate (bpm)	68 [60–81]	69 [62–78]	68 [61–80]
ACE inhibitor or ARB	70 (82.4)	74 (90.2)	144 (86.2)
Aldosterone receptor blocker	29 (34.1)	25 (30.5)	54 (32.3)
Aspirin	57 (67.1)	54 (65.9)	111 (66.5)
Beta-blocker	81 (95.3)	82 (100)	163 (97.6)
Diuretic	60 (70.6)	57 (69.5)	117 (70.1)
Statin	73 (85.9)	67 (81.7)	140 (83.8)
Digoxin	6 (7.1)	6 (7.3)	12 (7.2)
Hydralazine + nitrate	6 (7.1)	11 (13.4)	17 (10.2)
Antiarrhythmic drug	7 (8.2)	5 (6.1)	12 (7.2)
Six-minute walk test distance (m)	306 [243–374]	293 [197–360]	305 [216–369]
BNP (pg/mL)			
Median [Q1–Q3]	245 [158–824]	264 [130–435]	255 [155–497]
No. (%)	15 (17.6)	17 (20.7)	32 (19.2)
NT-proBNP (pg/mL)			
Median [Q1–Q3]	1200 [710–2600]	1290 [716–2800]	1250 [708–2670]
No. (%)	70 (82.4)	65 (79.3)	135 (80.8)
Serum creatinine (mg/dL)	1.2 (1.0, 1.5)	1.2 (1.1, 1.6)	1.2 (1.0, 1.5)

Values are given as median [Q1–Q3] or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; ICD = implantable cardioverter-defibrillator; NT-proBNP = N-terminal pro–brain natriuretic peptide; OMT = optimal medical therapy.

Results

Patient characteristics

From August 6, 2015, to December 5, 2019, a total of 174 participants were enrolled at 6 VA Medical Centers, with 167 participants being randomly assigned to a study treatment (Figure 1).

Baseline characteristics of the 167 study participants are listed in Table 1. Median [interquartile range] age of the patients was 74.6 [72–80] years, 165 participants (98.8%) were men, and 140 (83.8%) were white. Median LVEF was 30% [27%–33%]. A total of 120 participants (71.9%) had New York Heart Association functional class II symptoms. In 119 participants (71.3%), cardiomyopathy was ischemic-type. Participants were treated with guideline-directed medical therapy for heart failure: 97.6% beta-adrenergic blockers, 86.2% angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and 32.3% aldosterone receptor antagonists. Those participants taking antiarrhythmic medications were primarily prescribed amiodarone, although some received sotalol or dofetilide. Several participants were observed to change antiarrhythmic therapy during the study follow-up.

Therapy adoption and adherence

Among participants assigned to OMT+ICD, 72 (88%) underwent ICD implantation a median of 10 [6–60] days after randomization. Among those assigned to the OMT+ICD therapy, 9 (11%) changed their minds about receiving the ICD after randomization, and 1 participant assigned to ICD died before device implantation. One participant assigned to ICD later underwent device explantation because

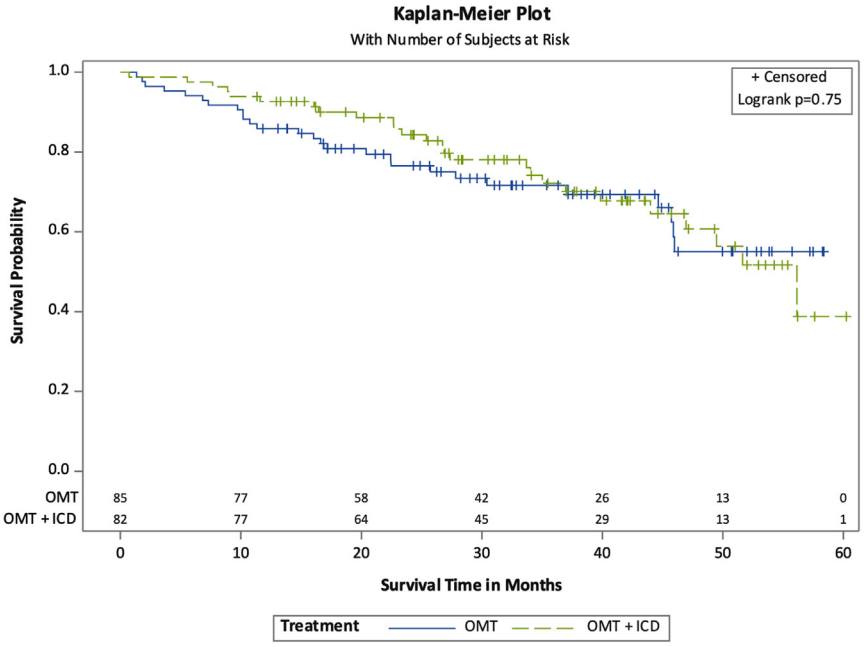

Figure 2 Time-to-event curves for death from any cause. *Green line* indicates OMT+ICD. *Blue line* indicates OMT. ICD = implantable cardioverter-defibrillator; OMT = optimal medical therapy.

of an infected pocket. Five patients with an ICD implanted per protocol were later upgraded to a CRT-defibrillator. Among participants randomized to receive OMT without ICD, 7 (8%) underwent ICD implantation during follow-up. Formal records for crossover were not collected, but this was commonly an outcome for participants who developed a clinical indication for an ICD as a secondary prevention therapy.

Outcomes

Median duration of follow-up was 31.5 [18.8–44.8] months (range 22 days to 61 months). Vital status was known for all study participants at the time of the last study follow-up. In total, 53 participants (32%) died during the study follow-up period: 26 (32%) in the ICD group and 27 (32%) in the OMT group (unadjusted HR 0.915; 95% confidence interval 0.534–1.568; $P = .746$). Figure 2 shows Kaplan-Meier survival curves of the 2 treatment groups. The annual mortality rate was 11.6% per year for the ICD group and 12.6% per year for the OMT group overall, with the curves seeming to separate at 36 months.

Of the 53 deaths, 32 (60%) were from cardiovascular causes including 12 (23%) due to SCD (Table 2). There were no statistically significant differences between the 2 treatment groups in terms of cause-specific mortality. No participants in the ICD arm died of device infection. An extended summary of the observed causes of mortality is given in Supplemental Table S1.

Figure 3 shows a forest plot of the primary outcome measure of all-cause mortality. No subgroup showed benefit from either OMT+ICD or OMT. Subgroups with <20 patients are not shown.

Device therapies

Of the 78 participants implanted with ICD, 15 experienced ICD therapy during follow-up. Of these participants, 11 had appropriate ICD therapy with a total of 47 therapy episodes, including 6 participants who had at least one ICD shock. Furthermore, 5 participants had a total of 17 inappropriate therapy events, including at least 1 ICD shock in all 5 participants. One participant had both appropriate and inappropriate therapy. The annualized rate of appropriate ICD therapy was 0.22 therapies per year per participant (0.16 appropriate shock per year per participant). The annualized rate of inappropriate therapy was 0.08 therapies per year per participant (0.03 inappropriate shock per year per participant).

Among the 26 participants in the OMT+ICD group who died during study follow-up, 9 received ICD therapy before death; all were categorized as appropriate therapy.

Adverse events

Supplemental Table S2 summarizes the safety profile of this study. Within 30 days postrandomization (OMT) or postimplantation (ICD), 19 participants (OMT 11; ICD 8) were observed to endure 29 serious adverse events (OMT 15; ICD 14), none of which were fatal (not shown in Supplemental Table S2). The 3 most common serious adverse effects encountered over the life of the study were complications of heart failure (21.3%); nonspecific infection,

typically influenza or pneumonia (16%); and myocardial infarction (5%).

Discussion

Need

There is conflicting evidence on the efficacy of primary prevention ICD therapy in the elderly. ICD therapy outcomes in the elderly may differ from those in younger patients in large part because of the increased prevalence of other causes of mortality with age. It has also been suggested that the proportion of patients who are at risk for potentially preventable SCD decreases with age and has changed over time.[18–22] Given the dynamic view of sudden death as a cause of mortality in older patients with heart failure and the complexities of managing patients with competing risks, a definitive trial of the ICD in this population is needed.[3,23–25] Although our study was terminated before reaching its full target sample size, there is significant value in our reporting on the outcome trends observed and the lessons learned in performing this trial that might inform future investigators.

Willingness to consent

Older patients are significantly less likely to participate in research, including noninvasive trials in heart failure,[26] because of a variety of factors.[27,28] Study team members were able to contact 573 veterans who were deemed to be eligible after preliminary medical record screening over 22.8 site-years of operation (average of 25 veterans per site per year). However, <30% (174/593) provided consent. Of patients who declined enrollment, the most common reason was a preference not to have an ICD implanted followed by a group that preferred ICD implant. This suggests that the predilection of this population of older veterans for choosing their own treatment course rather than being randomized to treatment reflects what has been seen in other landmark interventional clinical trials.[29] This issue is an important factor to be aware of when planning a future trial to address this question.

Trends

This trial was stopped after having enrolled 11% of the target sample size because of a slower than expected rate of enrollment. The results observed are noteworthy and might provide insight on design parameters and potential outcome effects from future fully enrolled trials. There seems to be a separation of the survival curves over the first 36 months (Figure 2). Whether this reflects a true survival benefit of the ICD in this population can only be resolved with a fully enrolled trial. The data shown in Figure 2 contrast the late separation of the curves in the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) studies, in which the survival curve of the ICD group did not separate for 12 to 18 months. Our findings raise the possibility that sudden death potentially treated by an ICD might be a more imminent risk in the elderly population with heart failure than it is in younger patients. Similarly, the high prevalence of risk factors for competing mortality with aging may have caused the curves to converge back together sooner than seen in these 2 primary prevention studies.[1,2] We recognize that differences in our outcomes may reflect advancements in background medical care and/or the quality of care available to veterans through the VA health care system.

Table 2 Summary of mortality

	OMT (n = 27)	OMT + ICD (n = 26)	Total (N = 53)
Cardiovascular death	18 (66.7)	14 (53.8)	32 (60.4)
Sudden cardiac death	7 (25.9)	5 (19.2)	12 (22.6)
Congestive heart failure	11 (40.7)	8 (30.8)	19 (35.8)
Stroke	1 (3.7)	2 (7.7)	3 (5.7)
Other	3 (11.1)	3 (11.5)	6 (11.3)
Noncardiovascular death	7 (25.9)	12 (46.2)	19 (35.8)
Infection	4 (14.8)	9 (34.6)	13 (24.5)
Trauma	0 (0.0)	2 (7.7)	2 (3.8)
Cancer	2 (7.4)	1 (3.8)	3 (5.7)
Other	5 (19.2)	7 (26.9)	12 (23.1)
Unknown	2 (7.4)	0 (0.0)	2 (3.8)

Values are given as n (%). Percentages are column based, that is, percent of all deaths within the study arm. Deaths of 5 participants were attributable to both cardiovascular and noncardiovascular causes.

ICD = implantable cardioverter-defibrillator; OMT = optimal medical therapy.

We chose to stratify patients based on the Charlson Comorbidity Index (CCI) to adjust for the competing risks of mortality beyond age. The CCI is held in generally high regard as a measure of general health status to account for comorbid conditions at the time of enrollment.[14,30,31] Unexpectedly, there were no significant differences or notable trend in survival detected between CCI 1–2 and CCI 3+ subgroups in the entire study population or in either intervention group. The lack of statistical association may be due to the limited power, but it also may suggest that the underlying severe cardiac disease present in all of these study participants is the dominant predictor of mortality.

Our findings related to patient safety in receiving an ICD were consistent with previous research supporting therapeutic guidelines in this population. Our annual mortality rates (12.6% and 11.6% in OMT and ICD groups, respectively) were less than some commonly noted estimates of mortality in subgroups of older patients, which ranged in ages from late 60s to >80 years.[7,32–34] We limited the scope of the collection of nonserious adverse events to those specific to ICD implantation and occurring within 30 days. Thus, for the participants who received OMT+ICD to report more adverse events is not surprising. Most importantly, the observation that the risk of serious adverse events was comparable in the 2 groups (Supplemental Table S1) suggests that ICD therapy may not add meaningfully to the risk profile of these patients.

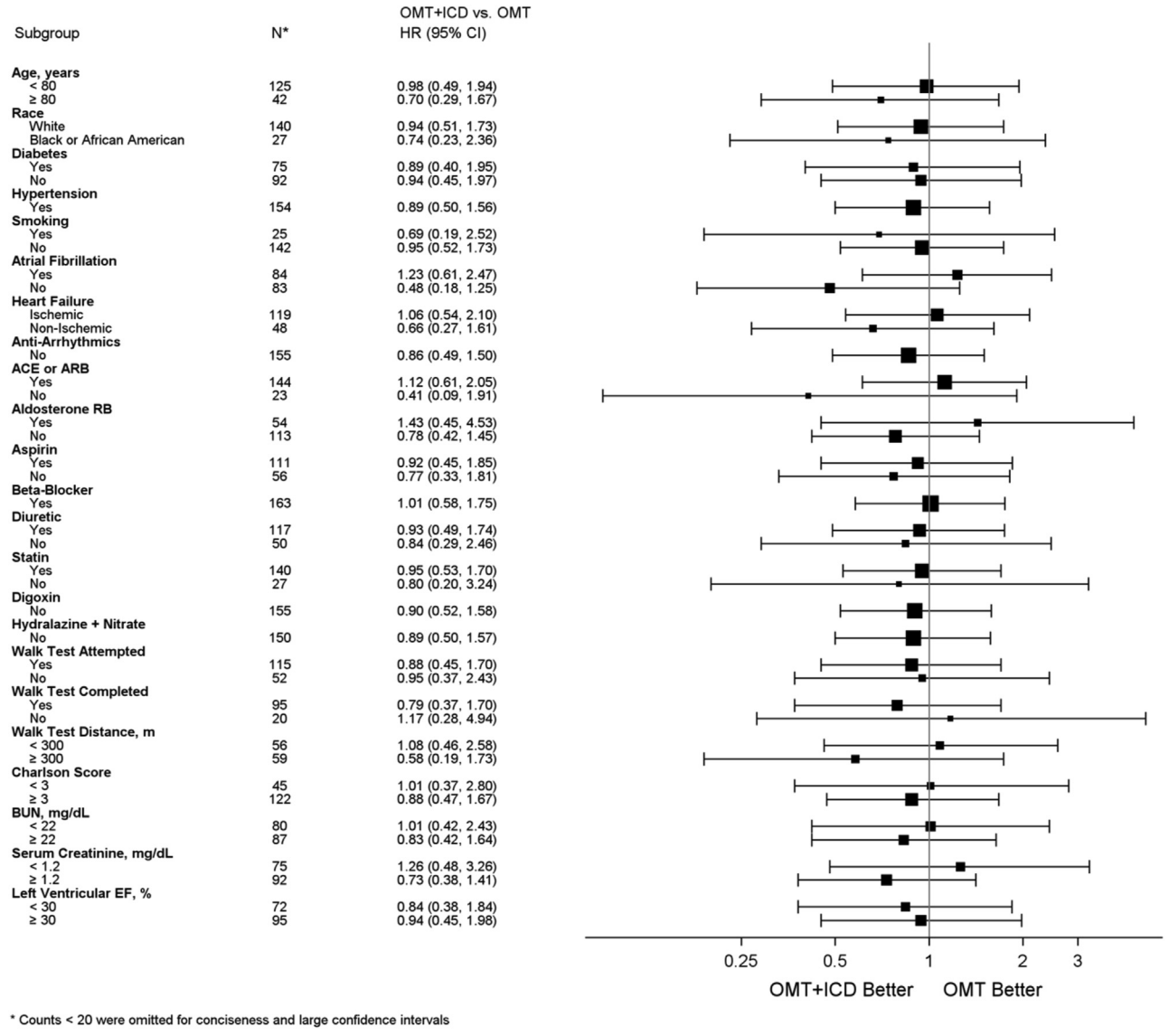

Figure 3 Rate of death from any cause (primary outcome) in subgroups. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BUN = blood urea nitrogen; CI = confidence interval; EF = ejection fraction; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; OMT = optimal medical therapy.

Equipoise

It should be noted that some VA medical centers did not agree to randomization to not receive ICD patients who, under current guidelines, qualified for ICD implant despite the lack of definitive evidence of ICD efficacy in this age group and the call for a study such as I-70 in many published papers and editorials.[5–9] This situation is an inherent challenge in all studies that test the efficacy of a widely accepted therapy, but there are numerous examples in which widely accepted therapies have been ineffective or, even worse, harmful.[35] Furthermore, we acknowledge the large number of of participants (13%) who did not complete the study protocol according to their assigned therapy at the time of randomization. For some participants, a crossover to device therapy was a response to a newly developed clinical indication. We did not collect data as to why participants, particularly those who did not receive their assigned device, did not complete the study per protocol; however, anecdotally we report that these participants were more likely to attribute this to logistics than to lack of equipoise.

Considerations in redesign

A brief synopsis of our study timeline is given in Supplemental Appendix C. The study was determined to be infeasible because, given the observed recruitment rate seen in the pilot study sites, the target enrollment could not be achieved in an acceptable amount of time, even if all interested VA sites were included in a full study. When it became apparent that the study was infeasible in its original design, other avenues for study reconfiguration were considered. Lowering the

minimum age of inclusion from 70 to 65 years was discarded because of the lack of clinical equipoise for patients aged <70 years, as there already is convincing evidence of device efficacy in these younger patients. After extensive deliberation, the study's Executive Committee determined that inclusion of CRT-eligible patients would be untenably complex because participant pool heterogeneity, potential dilution of the differential benefit, the implications of implanting a biventricular device (without defibrillator function or with defibrillator function turned off) vs withholding the device altogether, and the unclear field-level equipoise, in aggregate, posed a prohibitive barrier to study redesign.[36] It was believed that these potential redesigns suggestions would have interfered with the integrity of the study's primary objectives and raised serious ethical questions.

Study limitations

The primary limitation of this study is that it did not enroll to target sample size. Another limitation is that, being a VA-based trial, the population is predominantly male and may differ from the general population in other ways. However, there are many examples of large VA-based clinical trials in cardiovascular disease that have provided the same results as those performed in other more diverse populations (eg, prevention of atrial fibrillation, stroke, bypass surgery, hypertension). Another limitation of the study is the crossover rate. It is inevitable that, in a study such as this, a certain number of patients in the OMT arm will develop an indication for secondary prevention ICD. Such crossover was built into our power calculation and will need to be accounted for in future studies. The failure to implant patients randomized to ICD based on patient refusal after randomization is also an inherent risk in studies involving potential randomization to an invasive procedure. Every effort was made at the time of consent to ensure patients were willing to accept their randomization, and the fact that so many patients refused entry into the study because they had a treatment preference is a testimony to the effectiveness of that effort. Nonetheless, some patients refused implant after consent and randomization. This type of crossover will need to be anticipated in future trials.

Study participants were free to receive their implant and follow-up care from a different VA medical center, or even a non-VA facility, as is their right through the VA Choice program. Within the I-70 Trial operations, we were able to reduce the risk of survivorship bias by identifying incipient cases and excluding patients who were eligible for ICD implantation for secondary prevention or patients seeking a generator change on an extant ICD. Although beyond the scope of this report, members of this study team are working separately on a causal inference line of inquiry to emulate this clinical trial across the full VA healthcare system, with an interest in maximizing sample size and study generalizability.

Conclusion

The I-70 Trial was terminated early because of inability to recruit at the anticipated rate and thus did not achieve the target sample size to definitively evaluate the effect on survival with OMT compared to OMT+ICD among ICD-eligible individuals >70 years of age. However, the trial gathered valuable data pertaining to recruitment and patient outcomes in a population of older study participants and showed compelling trends. Although the number of older veterans with heart failure in the VA health care system provided a potentially large recruitment pool, many patients chose not to participate. A large number of patients refused entry into the study because they did not want an ICD implanted, while a smaller group refused because they wanted an ICD implanted. Nevertheless, a trial of this sort with a similar design would be feasible with a larger population to recruit from and perhaps a longer duration of patient follow-up. We urge other investigators to build off this study to implement a definitive study or to continue adding to the accumulating evidence related to the safety and efficacy of ICD implantation in older patients.

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Patient Consent: All participants provided written informed consent and privacy authorization.

Ethics Statement: The research reported in this study adhered to CONSORT guidelines. This study was approved through the VA Office of Research and Development and the VA Central Institutional Review Board (CIRB).

Data Availability Statement: Individual deidentified participant data, including data dictionaries, are available to requesting individuals through Data Use Agreement through the VA Cooperative Studies Program via the corresponding author.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2024.04.010.

References

1. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–237.
2. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–883.
3. Hauser RG. Underutilization of implantable cardioverter-defibrillators in older patients. JAMA 2015;313:2429.
4. Kong MH, Peterson ED, Fonarow GC, et al. Addressing disparities in sudden cardiac arrest care and the underutilization of effective therapies. Am Heart J 2010;160:605–618.e1.
5. Phurrough S, Farrell J, Chin J. Decision Memo for Implantable Cardioverter Defibrillators (ICDs). Centers for Medicare & Medicaid Services; June 2003. Report No. CAG-00157N. Available at: http://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=39&fromdb=true. Accessed May 28, 2024.

6. Epstein AE. Subject of the year: who are we missing, who are we overtreating, and who is best served? Refining the prescription of implantable cardioverter-defibrillator therapy. J Interv Card Electrophysiol 2009;26:91–94.
7. Heidenreich PA, Tsai V. Is anyone too old for an implantable cardioverter-defibrillator? Circ Cardiovasc Qual Outcomes 2009;2:6–8.
8. Santangeli P, Di Biase L, Russo AD, et al. Meta-analysis: age and effectiveness of prophylactic implantable cardioverter-defibrillators. Ann Intern Med 2010;153:592.
9. Kong MH, Al-Khatib SM, Sanders GD, Hasselblad V, Peterson ED. Use of implantable cardioverter-defibrillators for primary prevention in older patients: a systematic literature review and meta-analysis. Cardiol J 2011;18:503–514.
10. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;51:e1–e62.
11. Jensen TS, Chin J, Ashby L, Dolan D, Canos D, Hutter J. National Coverage Determination for Implantable Cardioverter Defibrillators (ICDs). Centers for Medicare & Medicaid Services (CMS); 2018. Available at: https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=288. Accessed May 28, 2024.
12. Pokorney SD, Miller AL, Chen AY, et al. Implantable cardioverter-defibrillator use among medicare patients with low ejection fraction after acute myocardial infarction. JAMA 2015;313:2433.
13. Sandhu AT, Kohsaka S, Turakhia MP, Lewis EF, Heidenreich PA. Evaluation of quality of care for US veterans with recent-onset heart failure with reduced ejection fraction. JAMA Cardiol 2022;7:130.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383.
15. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613–619.
16. Wilkoff BL, Williamson BD, Stern RS, et al. Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients. J Am Coll Cardiol 2008;52:541–550.
17. Chevalier P, Verrier P, Kirkorian G, Touboul P, Cottraux J. Improved appraisal of the quality of life in patients with automatic implantable cardioverter defibrillator: a psychometric study. Psychother Psychosom 1996;65:49–56.
18. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. Circulation 2001;104:2158–2163.
19. Arias E. United States Life Tables, 2004. Centers for Disease Control and Prevention. National Vital Statistics Reports. December 2007;56(9). Available at: https://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_09.pdf. Accessed May 28, 2024.
20. Arias E, Heron M, Xu J. United States Life Tables, 2014. Centers for Disease Control and Prevention. National Vital Statistics Reports. August 2017;66(4). Available at: https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_04.pdf. Accessed May 28, 2024.
21. Wininger M. Decay in mortality rates among landmark cardiovascular trials. Int J Cardiol 2019;288:100.
22. Saba S, Ravipati LP, Voigt A. Recent trends in utilization of implantable cardioverter-defibrillators in survivors of cardiac arrest in the United States. Pacing Clin Electrophysiol 2009;32:1444–1449.
23. Tung P, Albert CM. Causes and prevention of sudden cardiac death in the elderly. Nat Rev Cardiol 2013;10:135–142.
24. Mulrow CD, Cornell JA, Herrera CR, Kadri A, Farnett L, Aguilar C. Hypertension in the elderly. Implications and generalizability of randomized trials. JAMA 1994;272:1932–1938.
25. Wolfe SM. Underrepresentation of the elderly in randomized controlled trials. Public Citiz Health Lett 2012;28:1–7.
26. Pressler SJ, Subramanian U, Shaw RM, Meyer LE, Stoudemire K, Gradus-Pizlo I. Research in patients with heart failure: challenges in recruitment. Am J Crit Care 2008;17:198–203.
27. Briel M, Olu KK, von Elm E, et al. A systematic review of discontinued trials suggested that most reasons for recruitment failure were preventable. J Clin Epidemiol 2016;80:8–15.
28. Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: a review. Contemp Clin Trials Commun 2018;11:156–164.
29. Buxton AE, Lee KL, DiCarlo L, et al. Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death. N Engl J Med 2000;342:1937–1945.
30. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245–1251.
31. Frenkel WJ, Jongerius EJ, Mandjes-van Uitert MJ, van Munster BC, de Rooij SE. Validation of the Charlson comorbidity index in acutely hospitalized elderly adults: a prospective cohort study. J Am Geriatr Soc 2014;62:342–346.
32. Chan PS, Nallamothu BK, Spertus JA, et al. Impact of age and medical comorbidity on the effectiveness of implantable cardioverter-defibrillators for primary prevention. Circ Cardiovasc Qual Outcomes 2009;2:16–24.
33. Goldenberg I, Vyas AK, Hall WJ, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2008;51:288–296.
34. Groeneveld PW, Farmer SA, Suh JJ, Matta MA, Yang F. Outcomes and costs of implantable cardioverter-defibrillators for primary prevention of sudden cardiac death among the elderly. Heart Rhythm 2008;5:646–653.
35. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989;321:406–412.
36. Anantha Narayanan M, Vakil K, Reddy YN, et al. Efficacy of implantable cardioverter-defibrillator therapy in patients with nonischemic cardiomyopathy. JACC Clin Electrophysiol 2017;3:962–970.