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Impact of implantable cardioverter defibrillators on mortality in heart failure receiving quadruple guideline-directed medical therapy: a propensity score-matched study

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Abstract

Background In the contemporary management of heart failure with reduced ejection fraction (HFrEF), the recommended quadruple guideline-directed medical therapy (GDMT) consists of angiotensin receptor-neprilysin inhibitor (ARNI), evidence-based beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter-2 inhibitors (SGLT-2i). This study explored the impact of adding implantable cardioverter-defibrillator (ICD) therapy to this comprehensive regimen in HFrEF patients.

Methods Utilizing deidentified data from the National Electronic Database of the Turkish Ministry of Health, we conducted a nationwide retrospective cohort study on 5450 HFrEF patients receiving quadruple GDMT, including ARNI. Among them, 709 patients underwent additional ICD or cardiac resynchronization therapy defibrillator (CRT-D) implantation. Propensity score matching ensured balanced baseline characteristics between groups. Primary endpoint was determined as all-cause mortality.

Results In the matched cohort, all-cause mortality occurred in 108 out of 619 patients (17.4%) in the GDMT group and 101 out of 619 patients (16.3%) in the ICD group, with a hazard ratio (HR) of 0.74 and a 95% confidence interval (CI) ranging from 0.57 to 0.98. The median follow-up time was 1365 days in the matched cohort, 1283 days in the GDMT group. Subgroup analyses consistently demonstrated benefits, particularly among individuals aged 61 years and older (HR: 0.60, 95% CI: 0.42–0.87, $p=0.006$), those with sinus rhythm (HR: 0.55, 95% CI: 0.34–0.89, $p=0.013$), individuals not using amiodarone (HR: 0.61, 95% CI: 0.42–0.89, $p=0.011$), and those with an estimated glomerular filtration rate lower than 61.9 (HR: 0.66, 95% CI: 0.48–0.91, $p=0.011$).

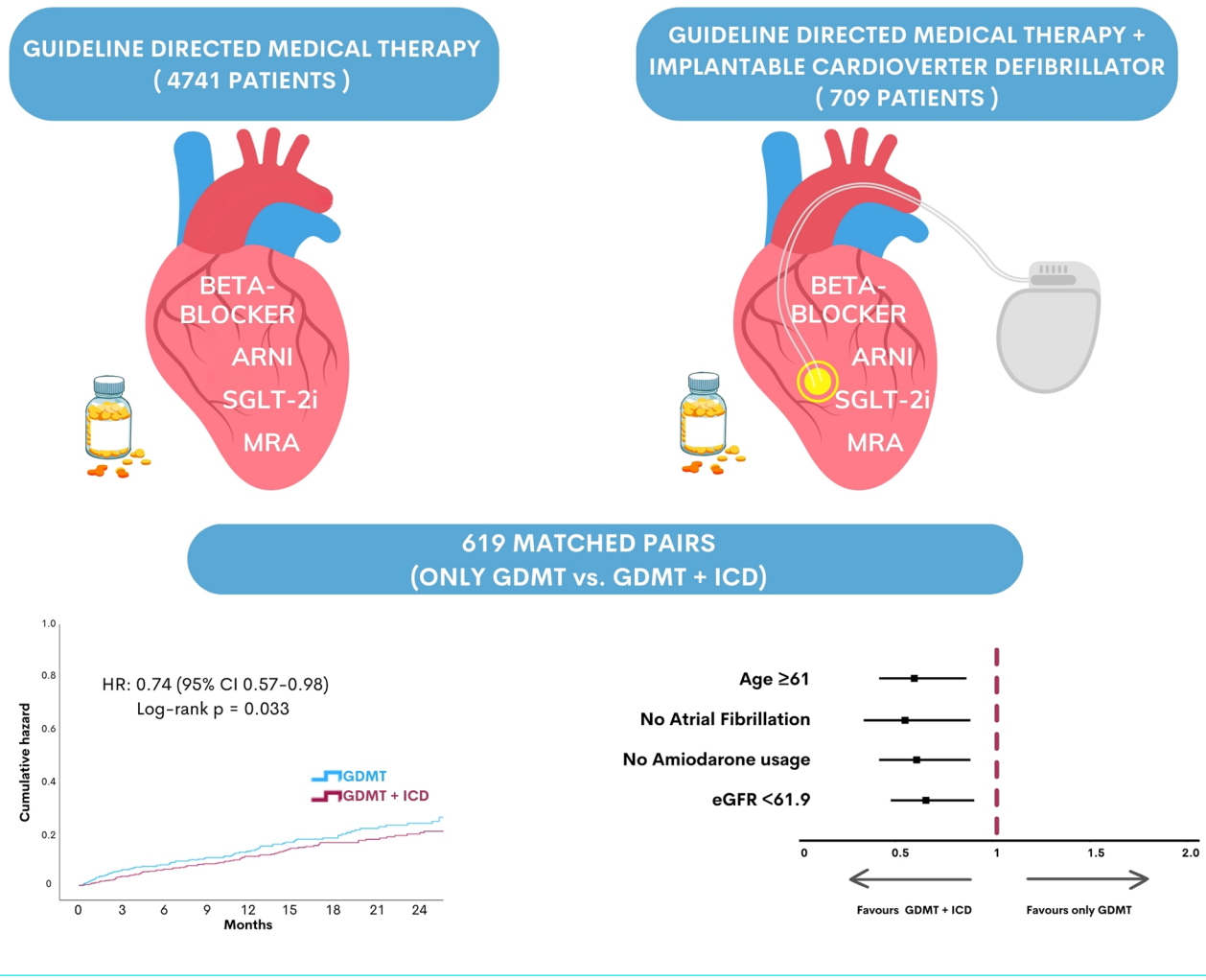
Conclusions This study may offer a glimmer of hope that even after achieving the best current optimal medical therapy, the addition of device therapy could still yield positive outcomes in the management of patients with HFrEF.

Keywords Quadruple guideline-directed medical therapy, Implantable cardioverter-defibrillator, Mortality

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Graphical Abstract



Background

In the contemporary approach to Heart Failure with Reduced Ejection Fraction (HFrEF) therapy, there is a robust recommendation that the four cornerstones of angiotensin receptor-neprilysin inhibitor (ARNI), evidence-based beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter-2 inhibitors (SGLT-2i) constitute the fundamental standard for medical therapy in HFrEF patients. Each of these four therapeutic interventions has received the highest class of recommendation due to their distinct contributions to reducing mortality. Importantly, their benefits manifest within days without overlapping [1, 2].

The landmark MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II) showed a significant reduction in all-cause mortality with prophylactic implantable cardioverter defibrillator (ICD) placement in patients with ischemic HFrEF with no arrhythmia qualifier but with previous myocardial infarction (MI) and left ventricular ejection fraction (LVEF) lower than 30% derived benefit from ICD. However, in the MADIT-II trial, 64% of patients used beta-blockers, and 88% used ACEi or angiotensin receptor blockers (ARB) without any MRAs or SGLT-2 inhibitors [3]. More recently, in 2016, the DANISH (Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure) trial enrolled participants with nonischemic cardiomyopathy and LVEF ≤ 35% in either an ICD or standard care arm. While there was no observed reduction in the primary endpoint of total mortality, a notable decrease in the risk of sudden cardiac death (SCD) was evident. In the DANISH trial, the usage rates of beta-blockers, ACEi or ARB, and MRA were 96%, 92%,

and 59%, respectively. Notably, SGLT-2i were not part of the therapeutic regimen in this trial [4].

Nevertheless, the currently available evidence is insufficient to ascertain whether ICD therapy maintains its efficacy in preventing death for patients receiving contemporary guideline-directed medical therapy for HFrEF. In this real-world trial, our objective was to investigate the persistence of the benefit derived from ICD therapy in patients adhering to quadruple guideline-directed medical therapy for HFrEF.

Methods

Data sources and study design

The investigation utilized deidentified data sourced from the National Electronic Database of the Turkish Ministry of Health covering the period between January 1, 2016, and December 31, 2022. TRends-HF cohort analysis involved 2,701,099 adult patients diagnosed with HF [5, 6]. From this comprehensive cohort, we selectively included 5450 patients diagnosed with HFrEF who were receiving quadruple guideline-directed medical therapy (GDMT), including ARNI, as part of our nationwide retrospective cohort study known as TRends-HF (Fig. 1). Patients with HF were identified using specific International Statistical Classification of Diseases (ICD)−10 codes, including I50.0 (congestive HF), I50.1 (left ventricular dysfunction), I50.9 (HF, unspecified), I11.0 (hypertensive heart disease with congestive HF), I13.0 (hypertensive heart and chronic kidney disease with congestive HF), I13.2 (hypertensive heart and chronic kidney disease with congestive HF and renal failure), and I42.0 (dilated cardiomyopathy). Comorbidities were defined according to the ICD-10 codes. The prescribed drugs were confirmed using the ATC system. Laboratory parameters, including estimated glomerular filtration rate (eGFR), N-terminal pro-B type natriuretic peptide (NT-proBNP), hemoglobin, and ferritin, were recorded when initiating quadruple GDMT. The exclusion

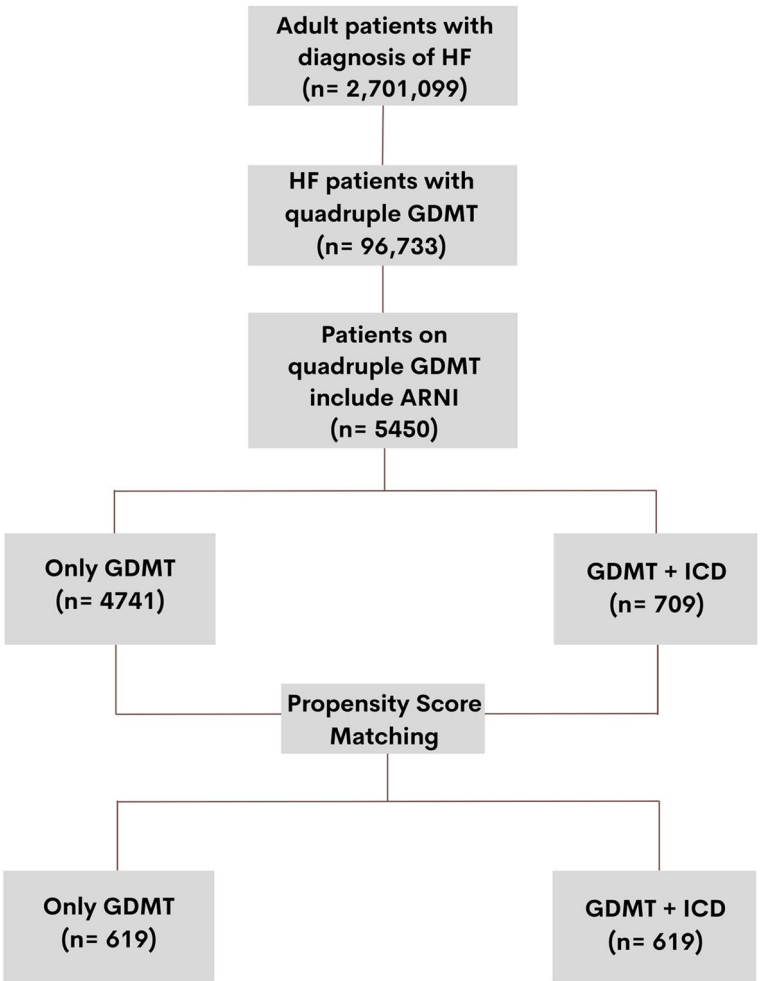


Fig. 1 Flow chart of the study

criteria included patients with heart failure HF who did not undergo quadruple GDMT, patients with GDMT adherence rates below 80%, individuals with a history of ventricular assist device or heart transplantation, those with malignancy, HF patients undergoing renal replacement therapy, and individuals younger than 18 years. Patients were stratified into two groups according to their treatment approach: one group received solely GDMT, while the other group received a combination of device therapy alongside GDMT. Patients assigned to the device group were those who had either an ICD or a cardiac resynchronization therapy defibrillator (CRT-D) prior to admission or during the follow-up period. In our country, the use of ARNI is permitted only in patients with HFrEF. Therefore, all patients included in the study are those with reduced ejection fraction heart failure due to the medical indication requirement. In our study, the follow-up of patients began from the moment they reached quadruple GDMT. Both patients who had a device before GDMT and those who had device implantation during follow-up after GDMT were included in the study. Data on mortality were obtained from the Turkish Death Notification System. The main outcome was all-cause mortality. The study protocol for TRends-HF was approved by the Ministry of Health of Türkiye (approval number: 95741342–020) and conforms to the Declaration of Helsinki. In preparation of this manuscript, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for cohort studies were rigorously followed with the use of a comprehensive checklist.

Statistical analysis

We generated cross-tables to analyze categorical variables across the two therapy modalities. Categorical variables are presented with their respective numbers and percentages, while age variables are expressed as the mean ± standard deviation. Other continuous variables are presented as medians and interquartile ranges (IQRs: 25–75%). To address potential confounding factors arising from unbalanced variables during the initial analysis, we conducted propensity score matching. After conducting appropriate PSM, 619 patients were matched across both groups.

A logistic model was constructed to calculate the propensity score for each patient, considering variables such as age, sex, DM, prior MI, atrial fibrillation (AF), and amiodarone usage for the entire cohort. Before and after propensity score matching, the similarity between groups was confirmed not only by p-value but also by using Cohen's effect size. After propensity score matching, Kaplan–Meier analysis was conducted to determine the hazard ratio (HR) of all-cause mortality for each therapy modality. Survival analysis was performed using Kaplan–Meier curves to estimate the survival probabilities for both the GDMT-only group and the GDMT plus device group. The log-rank test p values are depicted in the hazard curve figure.

Subsequent to propensity score matching, subgroup analysis was carried out within the matched cohort. Hazard ratios and 95% confidence intervals were calculated for each subgroup to provide a more detailed examination of the outcomes. Groups were selected based on the median values of the groups and any comorbidities that may be associated. All the statistical analyses were performed using SPSS version 29.0 (IBM Corp., Armonk, NY, USA) and E-PICOS AI (MedicReS, NY). p value < 0.05 was considered to indicate statistical significance.

Results

This study included a cohort of 5450 patients who were diagnosed with heart failure and who underwent quadruple GDMT, including ARNI. Within this cohort, 709 patients underwent additional implantation of CRT-D or ICD alongside GDMT [484 patients (68.3%) received ICD, while 225 patients (31.7%) underwent CRT-D]. The remaining 4741 patients were solely administered GDMT. The baseline characteristics of the study population are summarized in Table 1. Patients in the GDMT group were older (61.3 ± 11.4 vs. 59.3 ± 10.8, $p < 0.001$) and were more likely to be female (31.0% vs. 19.6%, $p < 0.001$). Patients in the ICD group had a significantly greater prevalence of prior MI (46.1% vs. 39.8%, $p < 0.001$) and atrial fibrillation (62.5% vs. 56.2%, $p = 0.002$) than did those in the GDMT group (Table 1).

Patients in the ICD group exhibited a greater median NT-proBNP (3023 [980–8300] vs. 1939 [682–5229], $p < 0.001$). There was no statistically significant difference observed among the groups in terms of the eGFR, ferritin level, or hemoglobin level (Table 1). Patients in the GDMT group were much less likely to use amiodarone (26.6% vs. 44.4%, $p < 0.001$), digoxin (38.4% vs. 45.3%, $p < 0.001$), and statins (78.8% vs. 82.1%, $p = 0.044$) than were those in the ICD group (Table 1).

We identified 619 matched pairs of patients based on propensity score matching analysis. After propensity score matching analysis, the baseline characteristics considered for propensity score calculation were equally distributed between the two groups (Table 2). After propensity analysis, among the patients in the ICD group, 201 (32.5%) had CRT-D. The median follow-up time was 1365 (1333–1411) days in the matched cohort. The median follow-up period was found to be 1283 (1194–1373) days in the GDMT group. All-cause mortality occurred in 108 of 619 patients (17.4%) in the GDMT group and 101 of 619 patients (16.3%) in the ICD group

Table 1 Patient demographic properties and baseline characteristics

	GDMT group (*n* = 4741)	ICD group (*n* = 709)	Total (*n* = 5450)	*p* value
Age (years)	61.3 ± 11.4	59.3 ± 10.8	61.0 ± 11.3	< 0.001
Female, *n* (%)	1472 (31.0)	139 (19.6)	1611 (29.6)	< 0.001
Diabetes mellitus, *n* (%)	3715 (78.4)	560 (79.0)	4275 (78.4)	0.706
Prior MI, *n* (%)	1888 (39.8)	327 (46.1)	2215 (40.6)	0.001
Atrial fibrillation, *n* (%)	2666 (56.2)	443 (62.5)	3109 (57.0)	0.002
Anemia, *n* (%)	1947 (41.1)	310 (43.7)	2257 (41.4)	0.180
Hypothyroidism, *n* (%)	1123 (23.7)	167 (23.6)	1290 (23.7)	0.938
Hyperthyroidism, *n* (%)	324 (6.8)	65 (9.2)	389 (7.1)	0.240
Dyslipidemia, *n* (%)	4098 (86.4)	629 (88.7)	4727 (86.7)	0.950
Pulmonary embolism, *n* (%)	494 (10.4)	72 (10.2)	566 (10.4)	0.829
Stroke, *n* (%)	287 (6.1)	38 (5.4)	325 (6.0)	0.467
NT-proBNP (pg/mL)	1939 (682–5229)	3023 (980–8300)	2063 (733–5673)	0.003
eGFR (CKD-EPI)	66 (47–86)	64 (45–83)	65 (47–86)	0.126
Hemoglobin levels (g/dL)	13.2 (10.8–15.8)	13.4 (10.6–15.7)	13.2 (10.7–15.8)	0.534
Ferritin, (ng/mL)	60 (27–118)	73 (31–135)	61 (28–120)	0.261
Digoxin, *n* (%)	1820 (38.4)	321 (45.3)	2141 (39.4)	< 0.001
Statin, *n* (%)	3736 (78.8)	582 (82.1)	4318 (79.2)	0.044
Amiodarone, *n* (%)	1259 (26.6)	315 (44.4)	1574 (28.9)	< 0.001
CRT-D, *n* (%)		225 (31.7)		

Categorical variables are presented as *n* (%). Continuous variables are presented as the mean (SD) or median (IQR). *CRT*, cardiac resynchronization therapy; *GDMT*, guideline-directed medical therapy; *GFR*, glomerular filtration rate; *IQR*, interquartile range; *MI*, myocardial infarction; *NT-proBNP*, N-terminal pro-B type natriuretic peptide

Table 2 Patient demographic properties and baseline characteristics after propensity score matching

	GDMT group (*n* = 619)	ICD group (*n* = 619)	*p* value
Age (years)	59.8 ± 0.4	59.8 ± 0.4	1.00
Female, *n* (%)	114 (18.4)	114 (18.4)	1.00
Diabetes mellitus, *n* (%)	515 (83.2)	515 (83.2)	1.00
Prior MI, *n* (%)	283 (45.7)	283 (45.7)	1.00
Atrial fibrillation, *n* (%)	397 (64.1)	397 (64.1)	1.00
Anemia, *n* (%)	237 (38.3)	266 (43.0)	0.093
Hypothyroidism, *n* (%)	140 (22.6)	139 (22.5)	0.946
Hyperthyroidism, *n* (%)	51 (8.2)	56 (9.0)	0.613
Dyslipidemia, *n* (%)	564 (91.1)	560 (90.5)	0.694
Pulmonary embolism, *n* (%)	66 (10.7)	61 (9.9)	0.640
Stroke, *n* (%)	41 (6.6)	36 (5.8)	0.556
NT proBNP (pg/mL)	2017 (771–4981)	3236 (1101–8368)	0.014
eGFR (CKD-EPI)	67 (49–86)	64 (44–82)	0.051
Hemoglobin levels, (g/dL)	13.7 (11.5–16.6)	13.4 (10.6–15.7)	0.075
Ferritin, (ng/mL)	65.3 (29.0–127.3)	70.2 (29.8–129.1)	0.494
Digoxin, *n* (%)	264 (42.6)	290 (46.8)	0.137
Statin, *n* (%)	498 (80.5)	523 (84.5)	0.062
Amiodarone, *n* (%)	256 (41.4)	256 (41.4)	1.00
CRT-D, *n* (%)		201 (32.5)	

Categorical variables are presented as *n* (%). Continuous variables are presented as the mean (SD) or median (IQR). *CRT*, cardiac resynchronization therapy; *GDMT*, guideline-directed medical therapy; *GFR*, glomerular filtration rate; *IQR*, interquartile range; *MI*, myocardial infarction; *NT-proBNP*, N-terminal pro-B type natriuretic peptide

(HR: 0.74, 95% CI: 0.57–0.98, $p=0.033$) (Fig. 2, Additional file 1: Fig. S1, Central Illustration). In our study, the median time from achieving GDMT to device implantation was 92 days. The average follow-up duration for the group of patients who received a device after reaching GDMT was 808 days.

Figure 3 illustrates the relationship between the two groups and all-cause mortality risk in the prespecified subgroups. The effect of ICD therapy on all-cause mortality was more favorable across prespecified subgroups, including patients aged 61 years and older (HR: 0.60, 95% CI: 0.42–0.87, $p=0.006$), patients without atrial fibrillation (HR: 0.55, 95% CI: 0.34–0.89, $p=0.013$), patients using amiodarone (HR: 0.61, 95% CI: 0.42–0.89, $p=0.011$), and patients with an eGFR under 61.9 (HR: 0.66, 95% CI: 0.48–0.91, $p=0.011$) (Fig. 3, Central Illustration).

Discussion

The present study marks a significant milestone as the initial inquiry revealing the complementary benefit associated with ICDs in reducing all-cause mortality. Notably, this effect was detected in patients with HFrEF who concurrently underwent quadruple GDMT, which included ARNI, beta-blockers, MRA, and SGLT-2 inhibitors. The findings of our study contribute to the ongoing discourse on the efficacy of ICD therapy in the context of contemporary HFrEF management. Our investigation focused on a cohort of patients adhering to the recommended quadruple GDMT comprising an ARNI, beta-blockers, MRA, and SGLT-2 inhibitors. The literature extensively supports the individual and combined benefits of ARNI, BB, MRA, and SGLT-2i in reducing mortality among HFrEF patients [7–15]. However, the role of ICD therapy in the era of contemporary medical therapy has been a subject of debate, with limited evidence on its effectiveness in conjunction with the latest therapeutic standards.

Our study revealed a noteworthy reduction in all-cause mortality associated with ICD therapy among HFrEF patients receiving quadruple GDMT. According to the matched cohort analysis, patients with ICDs had a 26% lower risk of all-cause mortality than those with only GDMT. These findings align with earlier landmark trials, such as the MADIT-II, which demonstrated the benefit of ICDs in reducing all-cause mortality in ischemic HFrEF patients [3]. Importantly, our study extends this observation to a contemporary cohort receiving the best optimal medical therapy, which includes ARNI, BB, MRA, and SGLT-2i.

In this study, it is essential to acknowledge that the absolute risk reduction in all-cause mortality between the ICD and GDMT-only groups was indeed modest, with a 1.1% difference. This minimal absolute difference could be attributed to the relatively small number of patients, which may limit the statistical power to detect larger effects. However, despite this modest reduction, our

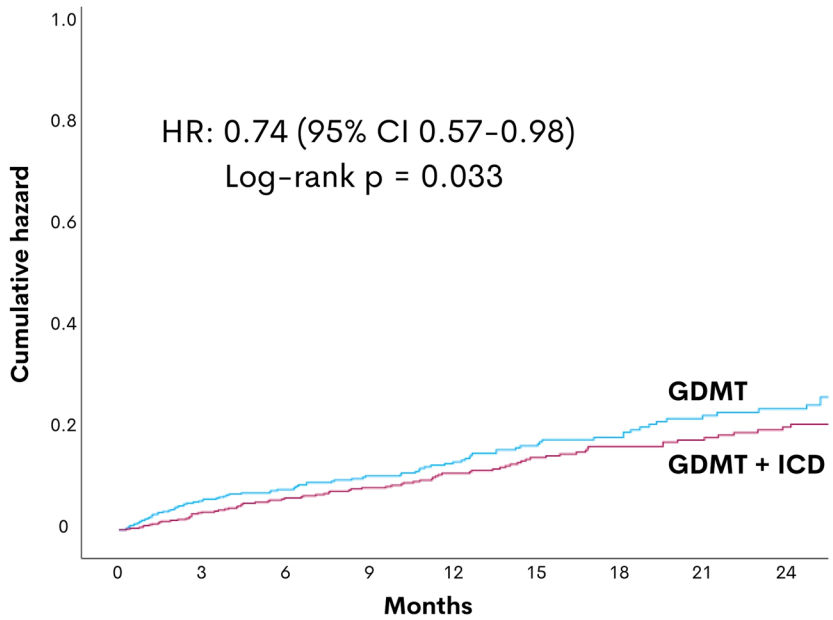


Fig. 2 Kaplan–Meier-reconstructed curves for the hazard risk of all-cause mortality

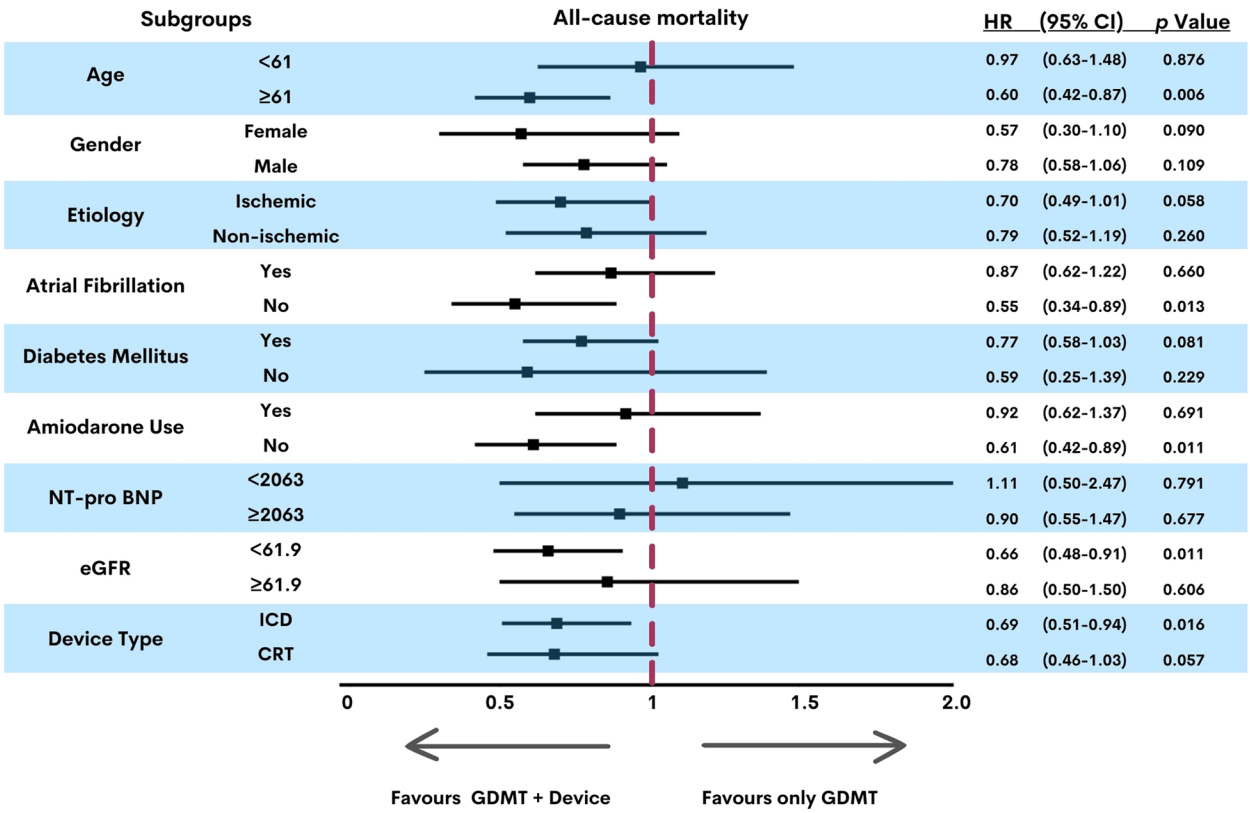


Fig. 3 All-cause mortality outcomes according to prespecified subgroup. Central Illustration: Overall survival results, categorized by predefined subgroups, among individuals with heart failure and reduced ejection fraction, comparing the effectiveness of optimal medical therapy alone versus optimal medical therapy combined with an implantable cardioverter-defibrillator

subgroup analyses identified specific patient populations who appeared to derive greater benefit from ICD therapy, such as those over 61 years of age, patients without atrial fibrillation, those with lower eGFR, and patients using amiodarone. These findings suggest that ICD therapy may confer a survival advantage for specific subsets of HFrEF patients receiving quadruple GDMT. Importantly, this differential benefit highlights the potential of tailored approaches in HFrEF management, where ICD implantation is considered based on individual patient characteristics rather than uniformly applied. Thus, while the overall absolute reduction was limited, ICD therapy remains valuable for certain high-risk HFrEF populations when integrated with comprehensive medical therapy.

The favorable impact of ICD therapy persisted across various subgroups, reinforcing its potential benefits in specific patient populations. Notably, older individuals (61 years and older), those without atrial fibrillation, individuals using amiodarone, and those with an eGFR less than 61.9 displayed a more pronounced reduction in all-cause mortality with ICD therapy. In our study, the addition of ICD therapy to the GDMT in patients with ischemic heart failure tended to reduce mortality, supporting the findings of the MADIT II study [3]. On the other hand, in patients with nonischemic etiology of HF, the addition of ICD therapy to GDMT did not improve all-cause mortality, consistent with the findings of the DANISH study [4].

The DEFINITE study examined the effect of ICDs on individuals with nonischemic dilated cardiomyopathy and revealed that those who received an ICD had a lower mortality rate during an average follow-up of 29 months [16]. However, the medical treatment for patients in this study primarily consisted of beta-blockers and ACE inhibitors. Moreover, the MUSTT study showed a survival benefit for patients with ischemic heart failure who took beta-blockers due to their antiarrhythmic effects [17]. However, contemporary heart failure management has shown that other medications also contribute to these effects. Since our study included patients with strong medical management, including ARNI and SGLT-2 inhibitors known for their anti-sudden death and anti-arrhythmic effects, we provide more up-to-date data on this topic.

The DINAMIT study examined the use of prophylactic ICD after acute myocardial infarction in the early

period and found no significant difference in all-cause mortality between the groups [18]. Similarly, this study's background medical treatment primarily consisted of beta-blockers and ACEi. Our study included patients who received ICD implantation for both primary and secondary prophylaxis, and we observed that ICD implantation tended to be more beneficial for individuals with ischemic heart failure than GDMT. However, this trend did not reach statistical significance.

In our study, we found that the use of an ICD in addition to optimal medical therapy did not have a positive effect on all-cause mortality in patients who were using amiodarone. Amiodarone is a traditional medical treatment for preventing fatal arrhythmias in patients with a reduced ejection fraction, but its efficacy in patients with heart failure has been inconsistent across various studies [19, 20]. The SCD-HeFT study showed that ICD usage was superior to amiodarone in patients with an LVEF < 35% and New York Heart Association (NYHA) classes 2–3 [21]. In our study, after propensity score matching, the rate of amiodarone use was similar in both groups. Previous studies have shown low utilization rates of optimal medical therapy, and the effectiveness of amiodarone in patients with heart failure needs to be reevaluated. In our subgroup analysis, we found that ICD implantation significantly improved survival in patients with HFrEF who did not receive amiodarone. Therefore, in patients receiving GDMT, especially if amiodarone usage is restrictive, ICD implantation is considered a significant opportunity for improving survival.

Limitations

While our findings suggest a continued benefit of ICD therapy in the contemporary era of HFrEF management, it is essential to acknowledge the limitations of our study. The retrospective nature of the investigation and the reliance on deidentified data introduce inherent biases. There are inherent limitations in studies based on ICD-10 coding in terms of data accuracy. Particularly in ICD-10 coding, there may be diagnostic inaccuracies due to coding errors, differences in coding practices, evolving diagnostic criteria, and issues in accurately defining subgroups. While increasing the sample size can mitigate some of these issues, random errors tend to have less significance in larger sample groups. Given the sample size of our study and considering other studies based on ICD-10 codes, we believe that this issue may be less pronounced in our research. Additionally, the absence of data on certain variables, such as cause-specific mortality and device programming details, limits the depth of our analysis. The inability to separately analyze major adverse cardiovascular events (MACE) and distinguish hospitalizations specifically due to heart failure from the data in the national registry database represents another limitation of this study. A notable limitation of our study is the potential for selection bias, as patients receiving ICD therapy may have been chosen based on clinical factors, such as relatively better life expectancy. Although we employed propensity score matching to balance baseline characteristics between groups and mitigate the impact of confounding factors, residual selection bias may still exist. Another limitation in our study is that the reported laboratory values represent the values at the time of initial treatment initiation during diagnosis. There is insufficient data available on laboratory values that could be obtained during follow-up. The patients included in the study are those with HFrEF due to the requirement of medical indication, but the lack of available average LVEF values is another limitation of the study. Due to the methodological planning of the study, and the fact that it is not an RCT, the power to compare the medical therapy group with the medical therapy + ICD group is limited. Differences in follow-up durations between patients who received device implantation and those who did not represent another limitation. Although propensity score matching was used to address these differences, variability in follow-up periods remains an issue that needs to be considered.

Conclusions

Contemporary HFrEF management, incorporating ARNI, BB, MRA, and SGLT-2i, is the gold standard, demonstrating significant mortality reductions individually and in combination. Our real-world study reveals continued positive outcomes of ICD therapy in reducing all-cause mortality among HFrEF patients receiving quadruple GDMT, including ARNI, BB, MRA, and SGLT-2i. The survival benefits appear to be more pronounced in specific subgroups, such as older patients, those without atrial fibrillation, individuals with lower eGFR, and those using amiodarone. These results underscore the importance of a tailored approach to device therapy in HFrEF, prioritizing ICD/CRT use for patients who exhibit particular risk profiles.

Abbreviations

ACEi	Angiotensin-converting enzyme inhibitors
AF	Atrial fibrillation
ARB	Angiotensin receptor blockers
ARNI	Angiotensin receptor-neprilysin inhibitor
BB	Beta-blocker
CV	Cardiovascular
CRT-D	Cardiac resynchronization therapy defibrillator
DANISH	Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
GDMT	Guideline-directed medical therapy
HF	Heart failure

ICD	Implantable cardioverter defibrillator
ICD-10	International Statistical Classification of Diseases—10
HFrEF	Heart Failure with Reduced Ejection Fraction
LVEF	Left ventricular ejection fraction
MADIT-II	Multicenter Automatic Defibrillator Implantation Trial II
MI	Myocardial infarction
MRA	Mineralocorticoid receptor antagonist
NYHA	New York Heart Association
NT-proBNP	N-terminal pro-B type natriuretic peptide

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03761-w.

Additional file 1: Fig S1 - Kaplan-Meier reconstructed curves of all-cause mortality risk extended to 5 years.

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Authors' contributions
AS, AC and MBY conceptualized and designed the study.AS, ITC, DU, EAK, NA, MMU and SB contributed to data collection and data curation, methodology and statistical analysis. AS, AC, DU and ITC contributed to the interpretation of the results, and AS wrote the frst draft of the manuscript. All authors contributed relevant intellectual content, critically revised, and edited the manuscript. All authors read and approved the fnal manuscript.

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Data availability
The data used for this study are available upon reasonable request, appropriate ethical approval, and data protection arrangements. Data from the National Database are protected by the Turkish Ministry of Health, which prevents open access to the personal data of the study. To obtain deidentifed data for research purposes, interested researchers can contact the Republic of Türkiye Ministry of Health, Ankara, Türkiye (https://sgb.saglik.gov.tr).

Declarations

Ethics approval and consent to participate
The Ministry of Health of Türkiye Ethics Committee granted ethical approval to access data from National Database (approval number: 95741342–020).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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