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Long-term clinical outcomes after cardioverter-defibrillator: does etiology of heart failure matter?

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What’s new?

Heart failure etiology is a strong independent predictor of mortality. Significantly worst survival was observed in ICM vs NICM. Other independent predictors for mortality in HF patients post ICD implantation are: age > 65 years, impaired LVEF, chronic kidney disease, atrial fibrillation, diabetes mellitus. It seems that patient with ICM should be follow more frequently after ICD implantation.

Abstract

Background: European and American guidelines for implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy defibrillator (CRT-D) placement in patients with heart failure (HF) remain unchanged despite controversy and ongoing debate about HF etiology. However, currently there are limited data on the long-term follow-up of primary defibrillator therapy with regard to ischemic (ICM) and non-ischemic cardiomyopathy (NICM). The prognostic importance of the etiology is not well established.

Aims: This study investigated the predictive value of the cause of heart failure.

Methods: Between January 2009 and December 2013, 1073 patients with the first implantation of ICD/CRT-D from the Contemporary Modalities In Treatment of Heart Failure Registry (COMMIT-HF) registry, were selected for the study analysis. Study population was divided into two groups: ischemic (n=705, 65.7%) and non-ischemic (n=368, 34.3%). The primary end-point was long-term all-cause mortality.

Results: The median follow-up period was 60.5 months. The primary end-point, death from any cause occurred significantly higher in ICM as compared to NICM group (35.7% vs.
26.6%, $P = 0.008$) Trend towards a higher out-of-hospital mortality in ICM patients was noticed (15.5% vs. 10.6, $P = 0.052$). The multivariate analysis revealed that among others ischemic etiology was an independent factor of long-term mortality (hazard ratio (HR) 1.43, 95% confidence interval (CI) 1.30 - 1.81, $P = 0.003$)

Conclusions: In the real-world population, significantly worse survival of ICM in comparison with NICM is observed. Ischemic heart failure etiology is a strong independent predictor of mortality.

**Keywords:**
heart failure; implantable cardiac defibrillators; ischemic heart disease; non-ischemic cardiomyopathy; prognostic factor;

**Introduction**
Prophylactic cardioverter-defibrillator (ICD) implantation among heart failure (HF) patients with left ventricle eject fraction (LV-EF) ≤35% significantly decrease the relative risk of death and become standard care with I class recommendation in European and American guidelines regardless of HF etiology.[1,2] However despite the worse clinical profile and higher rate of concomitant diseases in ischemic cardiomyopathy (ICM), same clinical evaluation during follow-up after implantation regarding the frequency of in-clinic visits is recommended.[3,4]

In patients with non-ischemic cardiomyopathy (NICM) implantation of ICD in primary prevention are already considered controversial, and is still in the center of the ongoing debate.[5,6] Following the recent publication of the DANISH (Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure) study it is reasonable to ask
if we need to consider HF etiology by the decision of ICD implantation or if we should to rethink guidelines regard this question.[7] On the other hand, recently published metaanalyses, including DANISH, showed without any shadow of doubt the significant reduction in mortality related with ICD implantation in NICM.[8,9]

All of the mentioned above investigations were based on comparison between ICD versus medical therapy. To ours the best knowledge little evidence about long-term mortality after ICD implantation regarding HF etiology coming from real life, all comers registries is still present. Therefore, we conducted a trial of patients with ICM or NICM. The aim of this study was to compare long-term all-cause mortality in patients with an impaired left ventricular according to ischemic and non-ischemic etiology.

**Methods**

*Design of registry*

The Contemporary Modalities In Treatment of Heart Failure Registry (COMMIT-HF) is a prospective, single-center, observational registry (ClinicalTrials.gov, NCT02536443) and has been previously described elsewhere.[10] Data collection is based on national health care provider registry. The study protocol was approved by appropriate institutional review board and ethics committee, patient written consent was not required.

In our study we included patients hospitalized with a diagnosis of systolic HF (left ventricle ejection fraction (LVEF) ≤ 35%). We excluded patients with acute coronary syndrome. Baseline characteristics of all individuals were collected by hospital records. All implanted devices data were annotated. All therapeutic interventions were individualized and based on European Society of Cardiology Heart Failure Treatment and Cardiac Pacing and Cardiac Resynchronization Therapy guidelines.[4]
Study population

There were 1429 consecutive patients with heart failure included in the COMMIT-HF registry between January 2009 and December 2013. For our study analysis we selected 1073 patients with the first implantation of cardioverter-defibrillator or cardiac resynchronization therapy defibrillator (ICD/CRT-D). Patients were considered as patients with ischemic HF etiology if they had a history of myocardial infarction (including Q-wave or enzyme-positive), previous coronary artery interventions. All patient with risk factors for coronary artery disease (CAD), > 45 years old underwent coronaryography. Nonobstructive coronary lesions with no history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) surgery were insufficient for classification as ICM. The study population was divided into two groups: ischemic (n=705, 65.7%) and non-ischemic (n=368, 34.3%). The exclusion criteria were as follows: congestive heart failure (CHF) as a complication of valvular heart disease, patients with implanted devices in other cardiovascular centres, patients who received their ICD for other reasons than CAD or NICM (idiopathic ventricular fibrillation, hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, long-QT syndrome).

Data analysis and end-points of the study

The following variables were analyzed: gender, age, length of stay, type of prevention, type of implanted device (ICD, CRT-D), etiology of heart failure, functional class according to New York Heart Association (NYHA) score, co-morbidities, previous revascularization in case of CAD, electrocardiographic parameters and medication. The primary end-point of this study was long-term all-cause mortality.

Statistical analysis

Continuous variables with normal distribution were presented as mean standard deviation (SD) non-normal variables were reported as median.
The categorical variables are presented as percentages. The continuous variables were compared using the T-test or Mann–Whitney U test. Chi-squared test was used for categorical variables. The twelve-month mortality was analyzed using the Kaplan-Meier method. The prognostic relevance of the baseline variables on the occurrence of death in the observation period was assessed with multivariable Cox proportional hazards regression models with results expressed as adjusted hazard ratios (HR) and 95% confidence intervals (CI). We used a $P$-value of $\leq 0.3$ in univariate analysis to include a variable in the multivariable analysis model. Stepwise regression method with backward elimination was used in further analysis. A two-sided $P$-value $\leq 0.05$ was considered significant. The SAS software (version 9.4 SAS Institute, Cary, North Carolina) was used for all calculations.

**Results**

Baseline characteristics

The baseline clinical characteristics of the study groups are presented in Table 1.

The ICM group contained more males than the NICM group (85.6% vs 74% $P < 0.001$) and were older (64±10 vs. 53±13 $P < 0.001$). Among others, diabetes mellitus, chronic kidney disease, arterial hypertension, hypercholesterolemia were more frequent in ICM patients (42.1% vs. 32.6 $P = 0.003$; 31.9% vs 19.3 % $P < 0.001$; 58.9% vs. 40.2% $P < 0.001$; 34.1% vs. 21.2% $P < 0.001$ – respectively). The echocardiographic findings of the study groups are presented in Table 2.

Significantly greater was left ventricular end systolic diameter (LVESD), diastolic diameter (LVEDD), left ventricle end systolic and diastolic volume (LVESV and LVEDV), left atrium area, in the NICM group as compared with ICM group (52.3mm vs. 56mm $P < 0.001$; 64mm vs. 67.3mm $P < 0.001$; 152 ml vs.168 m. $P < 0.001$; 27cm2 vs. 30cm2 $P = 0.01$ respectively). In this group left ventricular fraction (LVEF) was significantly lower (24 % vs 26% $P < 0.001$). Regarding to valve diseases no significant differences between groups were noted.
Similarly, several significant differences in pharmacotherapy at baseline were noticed (Table 3).

Impact of HF etiology on long-term prognosis

The median follow-up period was 60.5 months (interquartile range from 43 to 77), and no patients were lost to follow-up for the primary outcome. The primary end-point, death from any cause, occurred significantly higher in ICM as compared to NICM group (35.7% vs. 26.6%, \( P = 0.008 \)) (Table 4, Figure 2). Trend towards a higher out-of-hospital mortality in ICM patients was noticed (15.5% vs. 10.6, \( P = 0.05 \)), whereas cardiovascular and non-cardiovascular mortality rate were comparable in studied groups (Table 4).

Significant differences between ICM and NICM group when considering the incidence of stroke (6.2% vs 2.2%, \( P = 0.005 \)) and myocardial infarction (MI) (25.7% vs 1.1% \( P < 0.001 \)) were recorded (Table 4).

The multivariate analysis revealed that independent risk factors for mortality in HF patients post ICD implantation are: age > 65 years, impaired LVEF (hazard ratio for 1% increase in EF), chronic kidney disease (with glomerular filtration rate < 60 ml/min/1.73 m²), atrial fibrillation (AF), diabetes mellitus. An ischemic heart failure etiology was a strong independent factor of long-term mortality (HR 1.43, 95% CI 1.30 - 1.81, \( P = 0.003 \)) (Figure 3).

Discussion

This study is unique insofar as it provides comparison between two different HF etiologies in patients with ICD regarding long-term follow-up. We compared directly ICM and NICM as opposed to draw a parallel to one of the etiology with medical therapy. Additionally, the study population comes from all comers registry, situated in real-life environment.

The overarching goal of this study was to evaluate the relationship between HF etiology and long-term prognosis in large cohort of patients with implanted in primary prevention of
sudden cardiac death ICD. Thus, we performed a retrospective, observational, follow-up study, on 1073 real-life patients, treated with an ICD/CRT-D and evaluated the difference in all-cause mortality as well as risk factors. All patients were optimally medically treated and received ICD according to the current guidelines. The main clinical implications of our study were as follows: first, patients with ischemic heart failure etiology as compared to NICM have significantly worse clinical profile during implantation; second, after primary prophylactic ICD implantation, all-cause, long-term mortality is higher in ICM group in comparison with NICM; third, ischemic etiology is a strong independent predictor of all-cause mortality; finally, other independent predictors for mortality in HF patients post ICD implantation are: age > 65 years, impaired LVEF, chronic kidney disease (with glomerular filtration rate < 60 ml/min/1.73 m²), atrial fibrillation, diabetes mellitus. Winkler et al. in their ICD/CRTD population also observed similar results, thought age and chronic kidney disease was significant only in univariate analysis.[11] Advanced age (>65 years), the presence of AF and impaired LVEF were risk factors in univariate and multivariate analyses previously presented by Stein et al.[12]

Although, many of the published guidelines differentiate between the etiologies with respect to the level of evidence on which their recommendations are made and give ICDs for primary prevention a 1A recommendation for an ischemic etiology, and 1B for a non-ischemic etiology, the same clinical evaluation during follow-up after implantation regarding the frequency of in-clinic visits is recommended.[4,13]

In the humble opinion of the authors, this trial may be a premise for clinicians that in patients with ischemic HF etiology more frequent direct evaluation during follow-up and/or
remote monitoring standard of care strategy after ICD implantation should be implemented. In our opinion, this thesis, apart from the presented study outcomes, is also suggestively supported by trial comprised above 1000 patients with ICM enrolled in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) as showed as 9.5% of study population suffered from ischemic events (IEs) during follow-up, mainly associated with acute coronary syndromes.[14] The development of IEs after CRT-D implantation was independently associated with more than twofold increase in the risk for subsequent HF and death.

Discrepant outcomes, with neutral impact of ischemic etiology on mortality as compared with NICM in two previously published investigations [15,16] need to be stressed. Nevertheless, this could be explained by the few dissimilarities with our trial: first, lower number of subjects were included - together in both trials 925 as compared to 1073 of patients evaluated in the presented study; second, in only one study CRT-D in one-third of patients was present, while in the second study patients with CRT-D were excluded; finally, in both studies we refer to, the long-term follow-up period was shorter as against to our trial (mean: 40 vs 31 vs 60 months respectively).

The first two primary prevention ICD trials (Cardiomyopathy Trial (CAT) and Amiodarone Vs Implantable Cardioverter-Defibrillator (AMIOVIRT) trial) were stopped untimely, partly because mortality rates that were lower than predicted.[17,18] Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) demonstrated a mortality benefit of prophylactic ICD placement in various patient groups, including both ischemic and non-ischemic cardiomyopathy. Amiodarone compared with placebo, was associated with a similar risk of death and ICD group manifested decreased risk of death during a five years follow up. Outcomes did not vary according to ischemic or non-ischemic HF etiology.[19]
The 2004 Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial studied 458 patients with non-ischemic dilated cardiomyopathy with LVEF ≤35%, NYHA class II-III symptoms, and a history of non-sustained ventricular tachycardia (nsVT). In DEFINITE trial ICD implantation jointly with standard medical therapy resulted in decreased mortality compared with standard medical therapy. The reduction was significant only among patients with NYHA class III.[20]

More recently published, DANISH (Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure) trial questions ICD implantation in non-ischemic HF etiology. Køber et al. found that prophylactic ICD implantation in patients with symptomatic systolic HF not caused by coronary artery disease does not significantly reduce significantly rate of death from any cause than standard clinical care. However, in the subgroup of patients who were younger than 68 years of age, the rate of death from was significantly lower in the ICD group than in the control group.[7] The neutral influence on all-cause mortality in this trial could be partially explained by the high percentage of CRT-D patients enroled in the trial (nearly 60%) and its potential positive electromechanical, hemodynamic and clinical response as presented in land-mark trials.[21] Additionally, latterly published meta-analyses of randomized control trials compared implantation of ICD in primary prevention with medical treatment in NICM patients, comprising DANISH trial found that primary prevention ICDs reduce all-cause mortality in patients with left ventricular dysfunction both ICM and NICM.[9,22]

**Limitations**

The most important limitation is that this study is a single-centre observational study derived from a real-life practice with inherent weakness related to retrospective analysis. The results of our multivariate analysis may be biased due to the potential impact of important
factors that are not available in our database. Nevertheless, all data on primary and secondary outcomes were obtained without loss to follow-up.

Conclusions

In the presented study significantly worst survival in ICM in comparison with NICM in real-world population was observed. Ischemic heart failure etiology was a strong independent predictor of long-term mortality. In our beliefs for patients with ICM and implanted ICD in primary prevention of sudden cardiac death, more frequent clinical evaluation (including remote monitoring for instance), should be considered. Well-designed randomized control trials are required to reassess our findings and mentioned above thesis.
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Table 1. Baseline clinical characteristics.

| Variable                        | Etiology                                                                 |
|---------------------------------|---------------------------------------------------------------------------|
|                                 | Ischemic | Non-ischemic | P value |
|                                 | (n=705)  | (n =368)     |         |
| Age, years (SD)                 | 64 (10.2) | 52.8(12.9)   | <0.001  |
| Male, %                         | 604 (85.6%) | 273 (74%)    | <0.001  |
| NYHA II, %                      | 282 (41.7 %) | 147(42.1%)   | 0.93    |
| NYHA III, %                     | 267 (39.4%) | 136 (39%)    | 0.93    |
| ICD, %                          | 487 (69.1%) | 240 (65.2%)  | 0.23    |
| CRT/D, %                        | 218 (30.9%) | 128 (34.8%)  | 0.22    |
| DM, %                           | 297 (42.1%) | 120(32.6%)   | 0.003   |
| Chronic kidney disease, %       | 225 (31.9%) | 81 (19.3%)   | <0.001  |
| AF, %                           | 164 (24%)  | 111 (31.4%)  | 0.01    |
| Hypertension, %                 | 403 (58.9%) | 142 (40.2%)  | <0.001  |
| Hypercholesterolemia, %         | 233 (34.1%) | 75 (21.2%)   | <0.001  |
| Mix Hyperlipidemia, %           | 112 (16.4%) | 35 (9.9%)    | 0.21    |
| Stroke, %                       | 64 (9.4%)  | 15 (4.2%)    | 0.005   |
| Mean (SD) Hospitalization time, | 7.2 (5.5)  | 8.1 ( 8.4)   | 0.81    |
| days                            |           |              |         |

AF – atrial fibrillation; CRTD -cardiac resynchronization therapy defibrillator; DM – diabetes mellitus; GFR-glomerular filtration rate; ICD-implantable cardioverter-defibrillator; NYHA - New York Heart Association Classification; SD – standard deviation;
Table 2. Basic echocardiographic parameters.

| Variable                  | Etiology                        |  |  |  |
|---------------------------|---------------------------------|---|---|---|
|                           | **Ischemic** n=705  | **Non-ischemic** n=368 | **P value** |
| LVEF, % (SD)              | 26 (5.7)                        | 24 (5.6)                  | <0.001      |
| Diastolic LV diameter, mm (SD) | 64.7 (8.8)                  | 67.3 (9.3)                | <0.001      |
| Systolic LV diameter, mm (SD) | 52.3 (9.9)                  | 56 (10.7)                | <0.001      |
| LVEDV, ml (SD)            | 201.9 (86.1)                    | 219.5 (87.2)              | <0.001      |
| LVESV, ml (SD)            | 152.5 (74.3)                    | 168.7 (168.7)             | <0.001      |
| Severe MVR, %             | 67 (11%)                        | 49 (15.8%)                | 0.05        |
| Severe TVR, %             | 31 (6.9%)                       | 27 (10.7%)                | 0.1         |
| Severe AVR, %             | 1 (0.8%)                        | 0 (0.0%)                  | 0.73        |
| Severe AVS, %             | 4 (14.8%)                       | 1 (10%)                   | 0.87        |
| LAA, cm2 (SD)             | 27 (6.6)                        | 30.1 (9.6)                | 0.01        |

AVR – aortic valve regurgitation; AVS – aortic valve stenosis; LAA- left atrium area; LV - left ventricle; LVEDV – left ventricle end diastolic volume; LVEF – left ventricle ejection fraction; LVESV - left ventricle end systolic volume; MVR – mitral valve regurgitation; TVR – tricuspid valve regurgitation;
Table 3. Pharmacotherapy at enrollment.

| Variable        | Etiology |          |          |          |
|-----------------|----------|----------|----------|----------|
|                 | Ischemic | Nonischemic |          | P value  |
|                 | n=705    | n=368    |          |          |
| Beta-blockers   | 681 (97.0%) | 357 (97.3%) | 0.95    |          |
| ACE – I         | 531 (76.2%) | 281 (77.2%) | 0.76    |          |
| Sartans,        | 59 (8.5%) | 29 (8.1%) | 0.89    |          |
| Diuretics (loop)| 572 (81.6%) | 327 (89.1%) | 0.002   |          |
| Diuretics (thiazide) | 29 (10.2%) | 39 (13.7%) | 0.2     |          |
| MRAs            | 594 (84.9%) | 338 (92.1%) | 0.001   |          |
| Statins         | 615 (88.1%) | 194 (53.7%) | <0.001  |          |
| Ant Pl          | 619 (88.4%) | 117 (32.5%) | <0.001  |          |
| OAC             | 210 (30.1%) | 152 (42%) | <0.001  |          |

ACE – I – angiotensin enzyme converting inhibitor; AntPl – anti platelets; ARBs - angiotensin receptor blockers; MRAs-Mineralocorticoid Receptor Antagonists; OAC – oral anticoagulants;
| Variable                        | Etiology                  | P value |
|--------------------------------|---------------------------|---------|
|                                | Ischemic: n=705           | Non-ischemic: n=368 |         |
| Mortality, (%):                |                           |         |
| - All cause                    | 252 (35.7)                | 98 (26.6) | 0.008   |
| - Cardiovascular               | 115 (16.3)                | 44 (11.9) | 0.1     |
| - Non-cardiovascular           | 28 (4.0)                  | 15 (4.1)  | 0.81    |
| - Out-of-hospital              | 109 (15.5)                | 39 (10.6) | 0.052   |
| Stroke, (%)                    | 44 (6.2)                  | 8 (2.2)   | 0.005   |
| Myocardial infarction, (%)     | 40 (5.7)                  | 4 (1.1)   | 0.0005  |
| Cardiology outpatient visits – | Mean (SD)                 |         |
|                                | 10.3 (7.3)                | 10.1 (7.6) | 0.55    |
| HF re-hospitalization - Mean   | 3.34 (3.8)                | 3.27 (3.8) | 0.6     |

HF: heart failure; SD – standard deviation;
Figure 1. Study flow chart.
Figure 2. Kaplan-Meyer estimates of long-term all-cause mortality.

Figure 3. Predictors of all-cause mortality in the entire study population (Cox proportional hazards model results).