ORIGINAL ARTICLE

Effect of implantable cardioverter-defibrillators in patients with non-ischaemic systolic heart failure and concurrent coronary atherosclerosis

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Abstract

Aims Prophylactic implantable cardioverter-defibrillators (ICD) reduce mortality in patients with ischaemic heart failure (HF), whereas the effect of ICD in patients with non-ischaemic HF is less clear. We aimed to investigate the association between concomitant coronary atherosclerosis and mortality in patients with non-ischaemic HF and the effect of ICD implantation in these patients.

Methods and results Patients were included from DANISH (Danish Study to Assess the Efficacy of Implantable Cardioverter Defibrillators in Patients with Non-Ischaemic Systolic Heart Failure on Mortality), randomizing patients to ICD or control. Study inclusion criteria for HF were left ventricular ejection fraction $\leq$ 35% and increased levels (>200 pg/mL) of N-terminal pro-brain natriuretic peptide. Of the 1116 patients from DANISH, 838 (75%) patients had available data from coronary angiogram and were included in this subgroup analysis. We used Cox regression to assess the relationship between coronary atherosclerosis and mortality and the effect of ICD implantation. Of the included patients, 266 (32%) had coronary atherosclerosis. Of these, 216 (81%) had atherosclerosis without significant stenoses, and 50 (19%) had significant stenosis. Patients with atherosclerosis were significantly older {67 [interquartile range (IQR) 61–73] vs. 61 [IQR 54–68] years; P < 0.0001}, and more were men (77% vs. 70%; P = 0.03). During a median follow-up of 64.3 months (IQR 47–82), 174 (21%) of the patients died. The effect of ICD on all-cause mortality was not modified by coronary atherosclerosis [hazard ratio (HR) 0.94; 0.58–1.52; P = 0.79 vs. HR 0.82; 0.56–1.20; P = 0.30], P for interaction = 0.67. In univariable analysis, coronary atherosclerosis was a significant predictor of all-cause mortality [HR, 1.41; 95% confidence interval (CI), 1.04–1.91; P = 0.03]. However, this association disappeared when adjusting for cardiovascular risk factors (age, gender, diabetes, hypertension, smoking, and estimated glomerular filtration rate) (HR 1.05, 0.76–1.45, P = 0.76).

Conclusions In patients with non-ischaemic systolic heart failure, ICD implantation did not reduce all-cause mortality in patients either with or without concomitant coronary atherosclerosis. The concomitant presence of coronary atherosclerosis was associated with increased mortality. However, this association was explained by other risk factors.

Introduction

Heart failure (HF) aetiology is commonly divided into ischaemic and non-ischaemic, and this division is also reflected in the European guidelines.[1] Prognosis of systolic HF differs due to the aetiology, and it is well established that patients with ischaemic heart disease have poorer prognosis.[2,3] For patients with ischaemic HF, the implantation of an implantable cardioverter-defibrillator (ICD) is associated with a marked reduction in sudden cardiac death (SCD) and all-cause mortality.[4–7] For patients with non-ischaemic systolic HF, no single study has found evidence of benefit of ICD implantation on all-cause mortality.[8–11] However, based on meta-analyses, ICD implantation is recommended as a class I evidence level B treatment for both ischaemic and non-ischaemic HF in the 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic HF.[1]

It is uncertain if concomitant coronary atherosclerosis is related to outcome in patients with non-ischaemic systolic HF and whether the effect of implanting an ICD is different in patients with non-ischaemic HF and coronary atherosclerosis. Patients with non-ischaemic HF and some extent on coronary atherosclerosis may be more similar to patients with ischaemic aetiology of HF than those with no atherosclerosis, and the effect of ICD implantation could potentially differ within these subgroups. Therefore, the aim of this study was to investigate the association between coronary atherosclerosis and all-cause mortality in patients with non-ischaemic systolic HF and the effect of ICD implantation in these patients.

Methods

Study design and patients

The DANISH study (Danish Study to Assess the Efficacy of Implantable Cardioverter Defibrillators in Patients with Non-Ischaemic Systolic Heart Failure on Mortality) was a randomized controlled multicentre trial investigating the effect of ICD implantation in patients with non-ischaemic systolic HF. To be included in the study, patients should have left ventricular ejection fraction ≤ 35% and increased levels (>200 pg/mL) of N-terminal pro-brain natriuretic peptide (NT-proBNP). Coronary artery disease (CAD) as the cause of HF had to be ruled out prior to inclusion into the study. This was performed by coronary angiography (96% of patients), computed tomography angiography, or nuclear myocardial perfusion imaging. Patients could have diffuse atherosclerosis, one-vessel, or two-vessel disease on the qualifying coronary angiogram if the investigator did not find that the degree of CAD could explain the severely reduced left ventricular ejection fraction. Coronary obstruction was defined as of atherosclerosis of >50% and fractional flow reserve < 0.8 (where available). Pa-

tients were randomized to ICD or control. Design and main results have been published previously. No overall effect on all-cause mortality was found with ICD implantation.[11,12]

Patients were included in the study only after providing informed consent, and the study was performed according to the principles of the Declaration of Helsinki. The regional scientific ethics committee for the capital region (H-D-2007-0101) and the Danish Data Protection Agency approved the study.

Follow-up and endpoints

To be included in DANISH, patients should be in optimal medical treatment for HF. No minimum duration of HF was required. The primary endpoint was death from any cause, and the secondary endpoints were cardiovascular (CV) death and SCD. All endpoints were adjudicated according to previously reported criteria by a clinical endpoint committee.[11] The definition of SCD was unexpected death in a previously stable patient, death occurring within an hour of onset or worsening of symptoms, or unwitnessed death, in patients who had no sign of life-threatening disease or symptoms when seen alive < 72 h before death, and when circumstances suggested sudden death (e.g. when a patient was found in bed). End of follow-up was 30 June 2016, and patients without an event were right censored at this time.

Statistics

Baseline characteristics of the groups were compared with $\chi 2$ test for categorical variables and Wilcoxon two-sample test for continuous variables. Patients were considered to have coronary atherosclerosis if the invasive cardiologist described diffuse atherosclerosis or coronary stenosis and proportional hazards regression was used to assess the relationship between coronary atherosclerosis and mortality and between ICD implantation and mortality in patients with and without coronary atherosclerosis. Data are presented as hazard ratios with 95% confidence intervals (CIs). Two-sided *P* values < 0.05 were considered statistically significant. Multivariable models were adjusted for age, gender, diabetes, hypertension, smoking, and estimated glomerular filtration rate (eGFR). SAS software Version 9.4 (SAS Institute) and R software Version 3.3.1 (R Project for Statistical Computing) were used for analyses.

Results

Coronary angiography data were available in 838 (75%) of the 1116 patients included in DANISH, and all these patients were included in this subgroup analysis. In total, 266 (32%) had cor-

onary atherosclerosis, 216 (81%) of whom were reported by the individual invasive centres as having atherosclerosis without significant stenoses, and 50 (19%) with significant stenosis. Data on stenosis location were not available. *Table 1* shows baseline characteristics of patients with and without coronary atherosclerosis. Patients with coronary atherosclerosis were significantly older, more often men and in a higher New York Heart Association class. Furthermore, prevalence of comorbidities (diabetes mellitus, hypertension, atrial fibrillation, and renal impairment) was higher in the group with coronary atherosclerosis. Cause of HF differed between the groups and median NT-proBNP, median systolic blood pressure, and median QRS duration were higher in patients with coronary atherosclerosis. However, rate of ICD implantation did not differ between groups. Also, no difference was found between groups regarding medical treatment of HF, left ventricular ejection fraction, cardiac resynchronization therapy implantation, or body mass index.

During a median follow-up of 64.3 months [interquartile range (IQR) 47–82], 174 (21%) of the patients included in this subgroup analysis died. Treatment with ICD did not affect all-cause mortality in patients with or without coronary atherosclerosis [hazard ratio (HR) 0.94; 0.58–1.52; P = 0.79 vs. HR 0.82; 0.56–1.20; P = 0.30], P for interaction = 0.67. In univariable analysis, coronary atherosclerosis significantly predicted of all-cause mortality (HR, 1.41; 95% CI 1.04–1.91; P = 0.03), (*Figure 1*). This did not change when adjusting for hypertension (HR, 1.42; 95% CI 1.04–1.95; P = 0.03) or smoking (HR, 1.41; 95% CI 1.04–1.91; P = 0.03) However, the association between coronary atherosclerosis and all-cause mortality disappeared when adjusting for other CV risk factors (age, gender, diabetes, or eGFR) as well as in a multiple analysis adjusting for multiple CV risk factors (age, gender, diabetes, hypertension, smoking, and eGFR) (HR 1.05, 0.76–1.45, P = 0.76). Unadjusted and adjusted hazard ratios are shown in *Figure 2*.

Table 1 Characteristics of the patients at baseline

	Patients without coronary atherosclerosis (N = 572)	Patients with coronary atherosclerosis (N = 266)	P value
Age (IQR), year	61 (54–68)	67 (61–73)	<0.0001
Male gender, no. (%)	402 (70)	206 (77)	0.03
Body mass index (IQR), kg/m^2	27.1 (23.9–30.5)	26.5 (23.9–30.2)	0.27
NT-proBNP (IQR), pg/mL	1120 (533–2198)	1424 (654–2742)	0.02
Estimated GFR (IQR), mL/min/1.73 m^2	75 (60–94)	73 (54–90)	0.01
QRS duration (IQR), ms	144 (112–166)	151 (120–167)	0.04
Left ventricular ejection fraction (IQR), %	25 (20–30)	25 (20–30)	0.93
Blood pressure (IQR), mmHg			
Systolic	121 (109–135)	128 (114–142)	<0.001
Diastolic	73 (65–81)	74 (66–83)	0.38
NYHA class, no. (%)			
II	326 (57)	128 (48)	0.02
III	238 (42)	136 (51)	
IV	8 (1)	2 (1)	
Coexisting conditions, no. (%)			
Diabetes mellitus	97 (17)	79 (30)	<0.0001
Hypertension	146 (26)	114 (43)	<0.001
Permanent atrial fibrillation	101 (18)	63 (24)	0.03
Ever smoker	453 (79)	207 (78)	0.65
Means of exclusion of ischemic cause of heart failure, no. (%)			
Myocardial scintigraphy	2 (1)	0 (0)	0.34
CT angiogram	18 (3)	2 (1)	0.03
Coronary angiography	556 (97)	264 (99)	0.06
Cause of heart failure, no. (%)			
Idiopathic	457 (80)	191 (72)	<0.01
Valvular	20 (4)	7 (3)	
Hypertension	50 (9)	41 (15)	
Other	45 (8)	27 (10)	
Medications, no. (%)			
ACE-inhibitor or ARB	553 (97)	255 (96)	0.56
Beta blocker	525 (92)	248 (93)	0.47
Aldosterone receptor antagonist	325 (57)	143 (54)	0.41
Amiodarone	37 (6)	13 (5)	0.37
Device therapy, no. (%)			
Cardiac resynchronization therapy	343 (60)	164 (62)	0.64
Implantable cardioverter-defibrillator	276 (48)	137 (52)	0.38

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CT, computed tomography; GFR, glomerular filtration rate; IQR, interquartile range; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.

Figure 1 Cumulative incidence curves of all-cause mortality according to ICD treatment and the presence of coronary atherosclerosis. Patients with coronary atherosclerosis had an increased risk of all-cause mortality hazard ratio 1.41 (95% confidence interval, 1.04–1.91); *P* = 0.03. ICD, implantable cardioverter defibrillators.
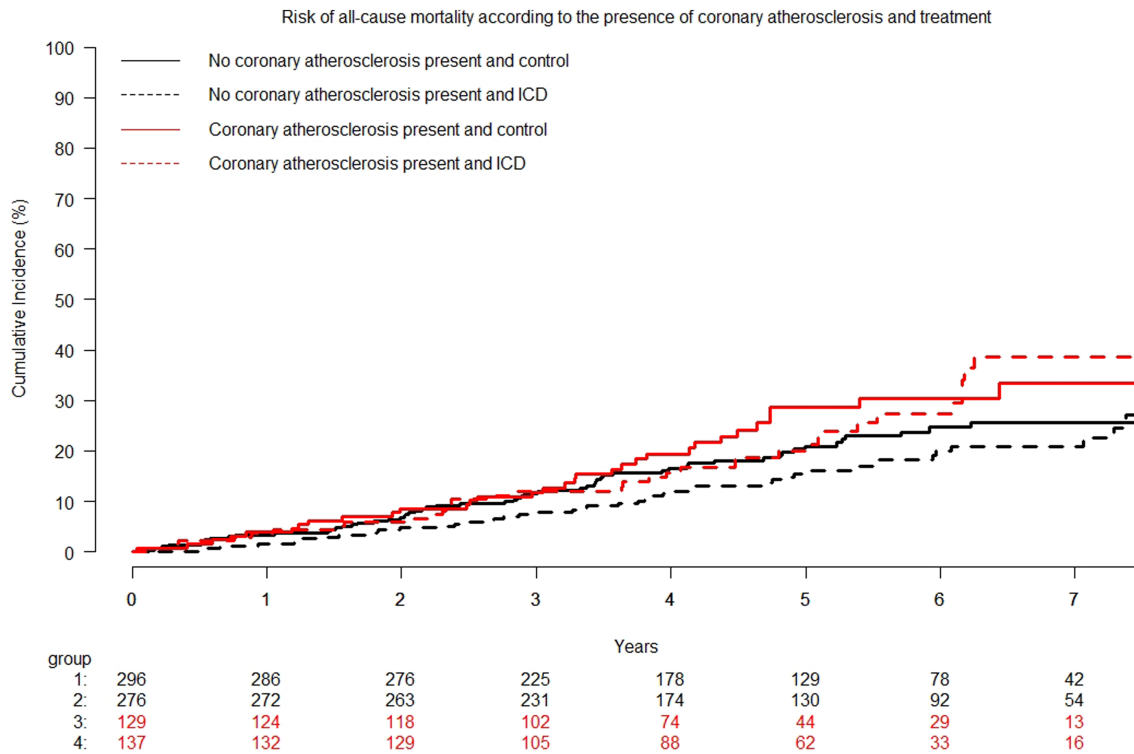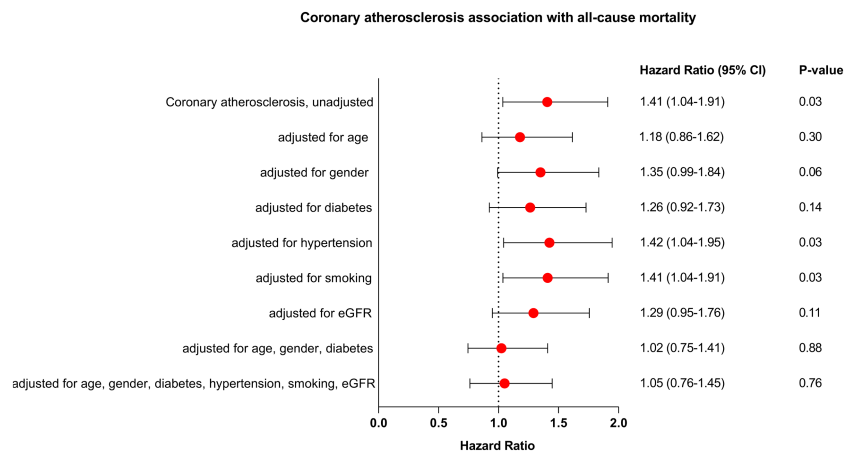

Figure 2 Coronary atherosclerosis association with all-cause mortality. eGFR denotes estimated glomerular filtration rate. CI, confidence interval.

No difference was found in CV death between patients with and without coronary atherosclerosis [HR 0.92 (95% CI, 0.63–1.36); *P* = 0.69] (*Figure 3*) The risk of SCD also did not differ between the two groups [HR 0.71 (95% CI, 0.37–1.35); *P* = 0.29] (*Figure 4*). There was no significant statistical interaction between treatment effect of ICD and presence of coronary atherosclerosis on CV death (*P* for interaction = 0.53) or SCD (*P* for interaction = 0.11) (*Figures 3 and 4*). Finally, there was no indication of a difference in results when patients with coronary atherosclerosis were divided into those with and without obstructive coronary artery disease on the qualifying coronary angiogram. Descriptive data

Figure 3 Cumulative incidence curves of the risk of cardiovascular death according to ICD treatment and the presence of coronary atherosclerosis. The presence of coronary atherosclerosis was not associated with the risk of cardiovascular death HR 0.92 (95% CI, 0.63–1.36); *P* = 0.69. ICD, implantable cardioverter defibrillators.
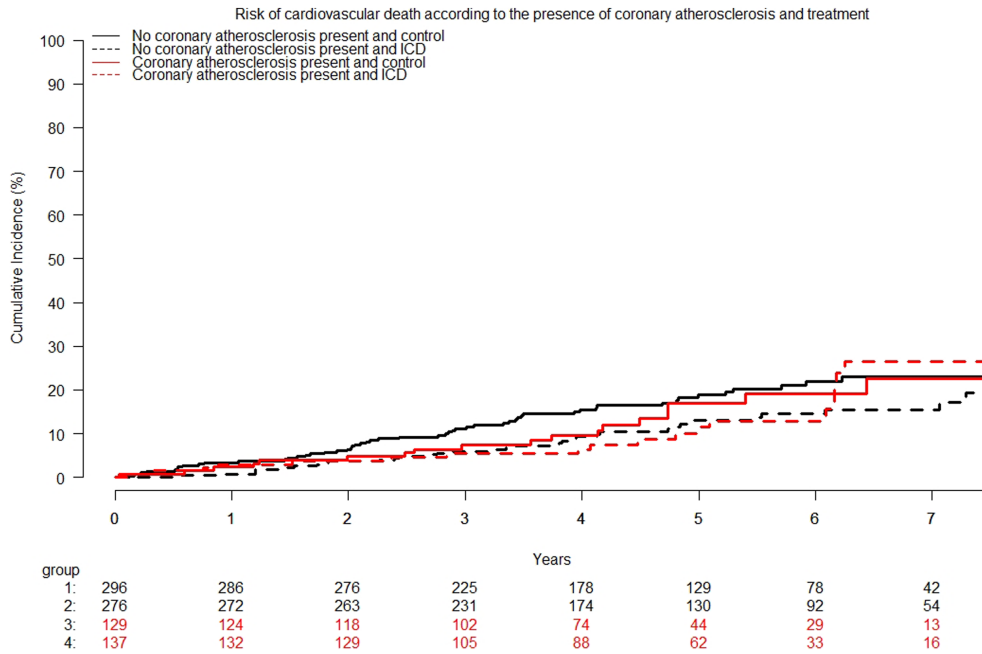

Figure 4 Cumulative incidence curves of the risk of sudden cardiac death according to ICD treatment and the presence of coronary atherosclerosis. The presence of coronary atherosclerosis was not associated with the risk of cardiovascular death hazard ratio 0.71 (95% confidence interval, 0.37–1.35); *P* = 0.29. ICD, implantable cardioverter defibrillators; SCD, sudden cardiac death.
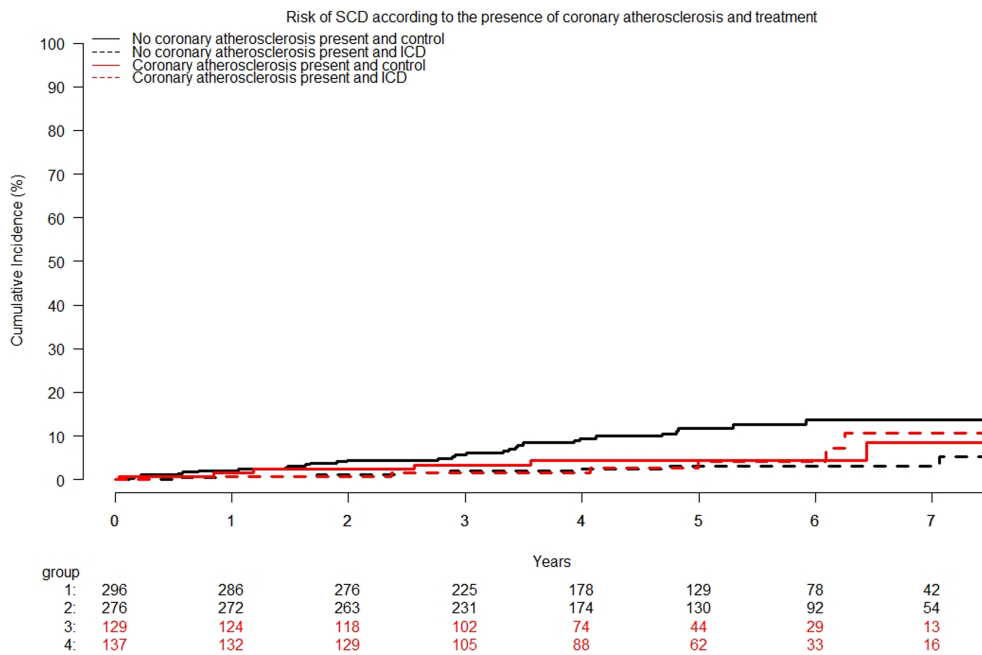
Table 2 Cause of death stratified by level of coronary obstruction

	No coronary atherosclerosis (N = 572)	Coronary atherosclerosis (N = 216)	One-vessel disease (N = 37)	Multi-vessel disease (N = 13)
All-cause mortality, no. (%)	108 (19)	52 (24)	9 (24)	5 (38)
Cardiovascular death, no. (%)	90 (16)	28 (13)	5 (14)	3 (23)
Sudden cardiac death, no. (%)	39 (7)	9 (4)	1 (3)	2 (15)

One-vessel or multi-vessel disease was defined as coronary obstruction of >50% and fractional flow reserve < 0.8 (where available) in one or more coronary arteries, respectively.

on cause of death stratified by level of coronary obstruction are shown in *Table 2*.

Discussion

The current study is a substudy to DANISH investigating 838 patients with available coronary angiography data. The study demonstrated that in patients with non-ischaemic systolic HF, ICD implantation was not associated with changes in mortality risk, independent of concomitant coronary atherosclerosis. The concomitant presence of coronary atherosclerosis was significantly associated with increased all-cause mortality. However, in multivariable analyses, this association was no longer significant after adjusting for traditional CV risk factors associated with atherosclerosis and well known to predict mortality.

In a recent registry study by Braga et al, the authors found significant association between non-obstructive coronary artery disease and death from any cause in patients with reduced ejection fraction, also when adjusting for baseline comorbidities.[13] However, 13% of patients with non-obstructive coronary artery disease had a history of myocardial infarction and would likely not have been included in the DANISH trial. It is uncertain whether results would have been similar if patients with history of AMI were excluded from the study by Braga et al.

The presence of atherosclerosis in patients with systolic HF of non-ischaemic aetiology did not indicate an increased effect of ICD implantation. An explanation may be that the increased risk of malignant arrhythmia is mainly caused by large areas of ischemic scar tissue with border zone ischaemia and re-entry pathways in the infarct region.[14–16] Therefore, atherosclerosis without history of prior myocardial infarction may not presuppose the same benefit of ICD implantation.

In perspective, the effect of ICD implantation in patients with systolic HF on current state of the art optimized guideline directed medical therapy has been called into question. Evidence-based medications for the treatment of systolic HF have improved over the last two decades, and correspondingly, the rates of sudden death have declined consistently and substantially over time among ambulatory patients with

systolic HF who were enrolled in clinical trials. These declining rates of sudden death may undermine the benefits of ICD implantation.[17]

Some limitations of the current study should be addressed. This is a post hoc analysis, and randomization to ICD or control was not stratified by atherosclerosis burden. Also, details on the performed coronary angiography were only available from the invasive centres for 75% of the patients included in DANISH. We had limited statistical power to assess whether there was in a difference in outcomes for patients with obstructive versus non-obstructive coronary atherosclerosis.

In conclusion, no association was found between ICD implantation and all-cause mortality either in patients with non-ischemic systolic HF with or without concomitant coronary atherosclerosis. The concomitant presence of coronary atherosclerosis was univariably associated with increased all-cause mortality. However, this association was explained by the presence of other well-established CV risk factors.

Conflict of interest

Funding

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