Circulation: Heart Failure

RESEARCH LETTER

Diabetes and Implantable Cardioverter Defibrillator in Nonischemic Systolic Heart Failure: An Extended Follow-Up Analysis of DANISH

Seiko Nakajima Doi, MD, PhD; Jens Jakob Thune, MD, PhD; Jens Cosedis Nielsen, MD, DMSc; Jens Haarbo, MD, DMSc; Lars Videbæk, MD, PhD; Rasmus Rørth, MD, PhD; Søren Lund Kristensen, MD, PhD; Niels Eske Bruun, MD, DMSc; Finn Gustafsson, MD, DMSc; Hans Eiskjær, MD, DMSc; Christian Hassager, MD, DMSc; Jesper Hastrup Svendsen, MD, DMSc; Dan Eik Høfsten, MD, PhD; Christian Torp-Pedersen, MD, DMSc; Steen Pehrson, MD, DMSc; Lars Køber, MD, DMSc; Jawad Haider Butt, MD

Individuals with heart failure (HF) and diabetes generally have more severe HF and more comorbidities than those with HF and no diabetes, and the former may therefore have an increased risk of competing causes of death to arrhythmic death.

In the DANISH trial (The Danish Study to Assess the Efficacy of Implantable Cardioverter Defibrillators [ICDs] in Patients With Nonischemic Systolic Heart Failure on Mortality), primary prophylactic ICD implantation, compared with usual care, significantly reduced the rate of sudden cardiovascular death, but not all-cause mortality.[1] We have previously examined the effect of ICD implantation according to diabetes status in the DANISH trial and found no statistically significant interaction between diabetes and the effect of ICD implantation.[2] However, given that diabetes is a chronic disease, which can cause various systemic adverse effects over the long term, we conducted an extended follow-up study of the DANISH trial, adding 4 years of additional follow-up, to examine the long-term effects of primary prophylactic ICD implantation, according to diabetes status.

The data that support the findings of this study are available from the corresponding author on reasonable request. The design of the DANISH trial has been published and described previously.[1,3] In brief, 1116 patients with nonischemic HF with reduced ejection fraction (HFrEF) were enrolled from 5 ICD-implanting centers in Denmark and randomized in a 1:1 ratio to ICD implantation or usual care. In the present analysis with extended follow-up, patients were followed from randomization until death or May 18, 2020, whichever came first, and no patients were lost to follow-up. The primary outcome was death from any cause, and secondary outcomes were cardiovascular death and sudden cardiovascular death. The protocol was approved by the ethics committee in the Capital Region of Denmark (H-D-2007-0101), and all participants gave written informed consent.

The effect of ICD implantation versus usual care was evaluated using the Kaplan-Meier estimator, Aalen-Johansen estimator, and Cox proportional hazards regression models, stratified according to center and status with respect to cardiac resynchronization therapy implantation. Data were analyzed according to the intention-to-treat principle. A *P*-value of 0.05 was considered statistically significant.

At baseline, 211 (18.9%) patients had diabetes. Baseline characteristics, including data on the management of diabetes, are presented in our previous report.[2] During a median follow-up of 9.5 years (interquartile range, 7.9–10.9), there was a statistically significant interaction between diabetes and the effect of ICD implantation on death from any cause; ICD implantation, compared with

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Correspondence to: Jawad H. Butt, MD, Department of Cardiology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark. Email jawad_butt91@hotmail.com

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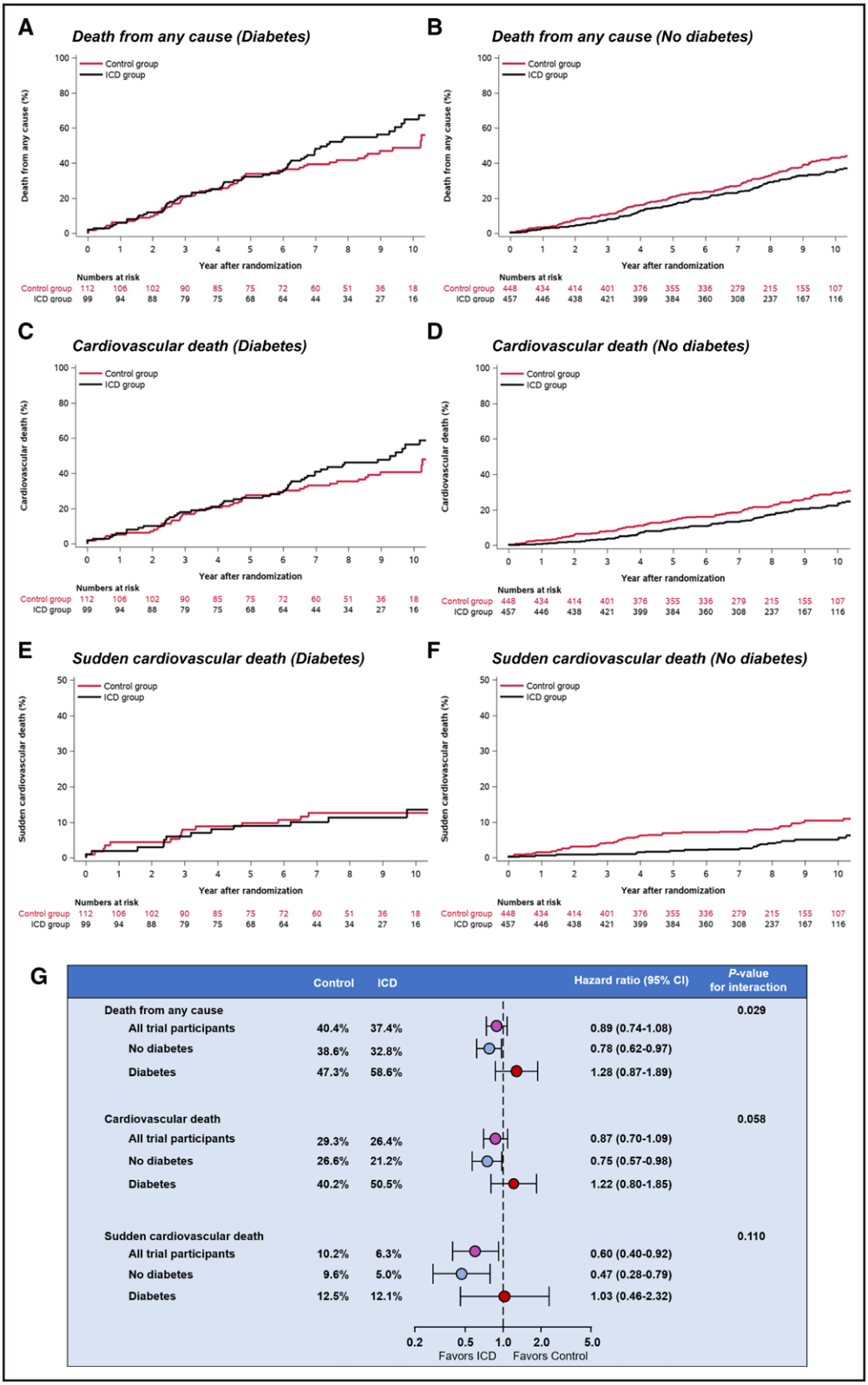

Figure. Effect of implantable cardioverter defibrillator (ICD) implantation compared with usual care according to diabetes. **A** through **F**, Cumulative incidence of death from any cause (using the Kaplan-Meier estimator), cardiovascular death, sudden cardiovascular death (using the Aalen-Johansen estimator, taking the competing risk of other causes of death into account) among patients with and without ICD. **G**, Cox regression models were stratified according to center and cardiac resynchronization therapy implantation (preexisting or planned). Because there was a difference between the ICD and control arm according to diabetes status at baseline with respect to certain key variables, we also adjusted these analyses for age, log of NT-proBNP (N-terminal pro-B-type natriuretic peptide) level, estimated glomerular filtration rate, and a history of hypertension, atrial fibrillation, and chronic obstructive pulmonary disease. In addition, an interaction term between diabetes and treatment assignment was included as a covariate in the models.

usual care, reduced the rate of death from any cause in patients without diabetes, but not in those with diabetes (hazard ratio, 0.78 [95% CI, 0.62–0.97] versus 1.28 [0.87–1.89], respectively; $P_{interaction}$=0.029). Although there was no statistically significant interaction between diabetes and the effect of ICD implantation on cardiovascular death ($P_{interaction}$=0.058) and sudden cardiovascular death ($P_{interaction}$=0.110), the potential differential effect of ICD implantation according to diabetes status was also observed for these outcomes (cardiovascular death: hazard ratio 0.75 [0.57–0.98] versus 1.22 [0.80–1.85] in patients without and with diabetes, respectively; sudden cardiovascular death: hazard ratio 0.47 [0.28–0.79] versus 1.03 [0.46–2.32], respectively; Figure).

Due to the cumulative benefit of evidence-based, disease-modifying therapies, the incidence of sudden cardiac death has declined in patients with HFrEF during the past decades.[4] The incidence is expected to decline even further with the addition of angiotensin receptor-neprilysin-inhibitors and sodium-glucose cotransporter-2 inhibitors to the pharmacological armamentarium, although neither of these drug classes were indicated for the treatment of HFrEF during the enrollment period of the DANISH trial.

Our data confirm the findings from a previous meta-analysis of 4 landmark primary prevention ICD trials[5] and extend those from our previous analysis by increasing the number of events and subsequently the statistical power.[2] There may be several explanations for the differential effects of ICD implantation in patients with and without diabetes. An ICD can prevent sudden cardiovascular death caused by ventricular tachyarrhythmia, and severe bradycardia, but cannot provide protection against other causes of death, including sudden cardiovascular death not caused by such arrhythmia. Because patients with diabetes have more severe HF and more comorbidities than those without diabetes, they may, perhaps, be less likely to die suddenly due to arrhythmias. Therefore, due to competing risk of nonarrhythmic causes of death, patients with HF and diabetes may derive less benefit of ICD therapy than those without diabetes. Furthermore, sodium-glucose cotransporter-2 inhibitors, which were indicated for the treatment of diabetes during follow-up in the DANISH trial, have been shown to reduce the risk of sudden cardiac death in patients with HFrEF and may have contributed, at least to some extent, to the lack of a beneficial effect of ICD implantation in patients with diabetes. Nevertheless, the findings from the present report, along with previous analyses from other trials, suggest that individuals with nonischemic HFrEF without diabetes may derive benefit from ICD implantation. However, this question can only be answered definitively in a clinical trial specifically designed and powered to answer this question.

ARTICLE INFORMATION

Affiliations

Department of Cardiology, Copenhagen University Hospital - Rigshospitalet, Denmark (S.N.D., R.R., S.L.K., F.G., C.H., J.H.S., D.E.H., S.P., L.K., J.H.B.). Department of Clinical Medicine, University of Copenhagen, Denmark (J.J.T., N.E.B., F.G., C.H., J.H.S., D.E.H., L.K.). Department of Cardiology, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Denmark (J.J.T.). Department of Cardiology, Aarhus University Hospital, Denmark (J.C.N., H.E.). Department of Clinical Medicine, Aarhus University, Denmark (J.C.N.). Department of Cardiology, Copenhagen University Hospital - Herlev and Gentofte, Hellerup, Denmark (J.H.). Department of Cardiology, Odense University Hospital, Svendborg, Denmark (L.V.). Department of Cardiology, Aalborg University Hospital, Denmark (N.E.B.). Department of Cardiology, Zealand University Hospital, Roskilde, Denmark (N.E.B.). Department of Cardiology, Nordsjællands Hospital, Hillerød, Denmark (C.T.-P.). Department of Public Health, University of Copenhagen, Denmark (C.T.-P.).

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