



# Appropriate Shocks and Mortality in Patients With Versus Without Diabetes With Prophylactic Implantable Cardioverter Defibrillators

*Diabetes Care* 2020;43:196–200 | <https://doi.org/10.2337/dc19-1014>

M. Juhani Juntila,<sup>1</sup> Ari Pelli,<sup>1</sup> Tuomas V. Kenttä,<sup>1</sup> Tim Friede,<sup>2,3</sup> Rik Willems,<sup>4</sup> Leonard Bergau,<sup>5</sup> Marek Malik,<sup>6</sup> Bert Vandenberk,<sup>4</sup> Marc A. Vos,<sup>7</sup> Georg Schmidt,<sup>8</sup> Bela Merkely,<sup>9</sup> Andrzej Lubinski,<sup>10</sup> Martin Svetlosak,<sup>11</sup> Frieder Braunschweig,<sup>12</sup> Markus Harden,<sup>2</sup> Markus Zabel,<sup>3,5</sup> Heikki V. Huikuri,<sup>1</sup> and Christian Sticherling,<sup>13</sup> for the EU-CERT-ICD Investigators

## OBJECTIVE

Diabetes increases the risk of all-cause mortality and sudden cardiac death (SCD). The exact mechanisms leading to sudden death in diabetes are not well known. We compared the incidence of appropriate shocks and mortality in patients with versus without diabetes with a prophylactic implantable cardioverter defibrillator (ICD) included in the retrospective EU-CERT-ICD registry.

## RESEARCH DESIGN AND METHODS AND RESULTS

A total of 3,535 patients from 12 European EU-CERT-ICD centers with a mean age of  $63.7 \pm 11.2$  years (82% males) at the time of ICD implantation were included in the analysis. A total of 995 patients (28%) had a history of diabetes. All patients had an ICD implanted for primary SCD prevention. End points were appropriate shock and all-cause mortality. Mean follow-up time was  $3.2 \pm 2.3$  years. Diabetes was associated with a lower risk of appropriate shocks (adjusted hazard ratio [HR] 0.77 [95% CI 0.62–0.96],  $P = 0.02$ ). However, patients with diabetes had significantly higher mortality (adjusted HR 1.30 [95% CI 1.11–1.53],  $P = 0.001$ ).

## CONCLUSIONS

All-cause mortality is higher in patients with diabetes than in patients without diabetes with primary prophylactic ICDs. Subsequently, patients with diabetes have a lower incidence of appropriate ICD shocks, indicating that the excess mortality might not be caused primarily by ventricular tachyarrhythmias. These findings suggest a limitation of the potential of prophylactic ICD therapy to improve survival in patients with diabetes with impaired left ventricular function.

An implantable cardioverter defibrillator (ICD) treatment is widely recommended for primary prevention of sudden cardiac death (SCD) among patients with reduced left ventricular ejection fraction (LVEF) (1). These recommendations are mainly based on the results of two landmark studies performed almost two decades ago (2–4). Since then, medical treatment of heart failure and patient risk profiles have changed significantly. Currently, most ICD recipients will never receive an appropriate ICD shock. This concept has urged clinical scientists to search risk parameters other than LVEF for the purpose of identifying patients who would actually benefit from primary ICD therapy. Furthermore, the randomized Danish Study to Assess the Efficacy of ICDs in Patients With Non-ischemic Systolic Heart Failure on Mortality (DANISH) recently

<sup>1</sup>Research Unit of Internal Medicine, Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland

<sup>2</sup>Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany

<sup>3</sup>German Center for Cardiovascular Research (DZHK), partner site Göttingen, Göttingen, Germany

<sup>4</sup>Department of Cardiovascular Sciences, University of Leuven and University Hospitals Leuven, Leuven, Belgium

<sup>5</sup>Department of Cardiology and Pneumology, Heart Center, Division of Cardiology, University Medical Center Göttingen, Göttingen, Germany

<sup>6</sup>National Heart and Lung Institute, Imperial College, London, U.K.

<sup>7</sup>Medical Physiology, University Medical Center Utrecht, Utrecht, the Netherlands

<sup>8</sup>Medizinische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

<sup>9</sup>Semmelweis University Heart Center, Budapest, Hungary

<sup>10</sup>Medical University Lodz, Lodz, Poland

<sup>11</sup>Slovak Medical University and Institute of Cardiovascular Diseases, Bratislava, Slovakia

<sup>12</sup>Karolinska Institute, Stockholm, Sweden

<sup>13</sup>Division of Cardiology, University Hospital of Basel, Basel, Switzerland

Corresponding author: M. Juhani Juntila, [juhani.junttila@oulu.fi](mailto:juhani.junttila@oulu.fi)

Received 22 May 2019 and accepted 10 September 2019

Clinical trial reg. no. NCT02064192, [clinicaltrials.gov](http://clinicaltrials.gov)

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-1014/-/DC1>.

© 2019 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

showed that patients with nonischemic heart disease have a limited benefit from primary ICD therapy (5).

Diabetes increases the cardiovascular mortality among survivors of myocardial infarction (MI) (6). In an analysis of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study, diabetes was an independent predictor of mortality, including SCD, in patients with heart failure (7). In a series of postinfarction patients from Germany and Finland, SCD incidence was higher in patients with type 2 diabetes than in patients without diabetes. The SCD incidence was substantially increased among patients with diabetes with an ejection fraction (EF) <35%, supporting the concept that a prophylactic ICD should be used in all patients with diabetes with an EF <30–35%, unless contraindicated (8).

These findings led to recommendations that patients with diabetes should be routinely screened by echocardiography or some other method to measure the LVEF after acute MI or heart failure, in order to identify candidates for the primary prevention ICDs (9). We tested the validity of this concept in a large registry of combined data of primary ICD recipients from 12 centers in 11 European countries. We compared the incidence of appropriate ICD shocks and mortality in patients with and without diabetes in a contemporary real-life European primary prevention ICD population (European Comparative Effectiveness Research to Assess the Use of Primary Prophylactic Implantable Cardioverter Defibrillators [EU-CERT-ICD] retrospective study).

## RESEARCH DESIGN AND METHODS

The EU-CERT-ICD project is funded by the European Community's 7th Framework Program FP7/2007–2013 (grant agreement number 602299). The prospective arm (clinicaltrials.gov NCT02064192) has enrolled 2,327 patients with an indication for a primary prevention ICD implantation who will also undergo an analysis of numerous candidate electrocardiogram variables from 12-lead Holter recordings as potential markers for a higher risk of malignant arrhythmias. Our data stem from an associated work package 02 within

the project, a retrospective compilation of 14 locally existing registries of primary prevention ICD implantations between 2002 and 2014. The study design has already been described in Sticherling et al. (10). In this analysis, we only consider data from 12 out of 14 centers, since diabetes status was only available for those centers (10). Diabetes was diagnosed according to the World Health Organization guidelines in all centers.

### Data Collection

The study design, including 23 demographic, predefined device- and outcome-related variables and the collection of 17 additional variables, has been previously presented (10). All-cause mortality and appropriate ICD shock therapy were mandatory information from all centers. Appropriate ICD shock was considered as the best surrogate parameter for prevented SCD. Local investigators submitted their preprocessed data sets to the coordinating clinical trial unit at the University Hospital of Basel. Subsequently, the registries were merged into a single SecuTrial database (interActive Systems, Berlin, Germany). System-generated queries were thereafter addressed until the database was closed on 1 September 2015 and forwarded, for statistical analysis, to the University Medical Center in Göttingen, Germany.

### Statistics

Continuous variables are reported as means and SDs and categorical variables as frequencies. The primary end points were all-cause mortality and first appropriate ICD shock. Analyses were performed using a competing risk model stratified by study center, based on the proportional subdistribution model by Fine and Gray (11). The stratification by center accounts for between-center heterogeneity in the baseline risks. First, parameters were tested in a univariate model. All parameters with a significant effect in the univariate scenario, i.e.,  $P$  value <0.05, were included in a multivariable model. Missing values were very sparse; therefore, no imputation methods were applied. All analyses were done using SAS software version 9.4.

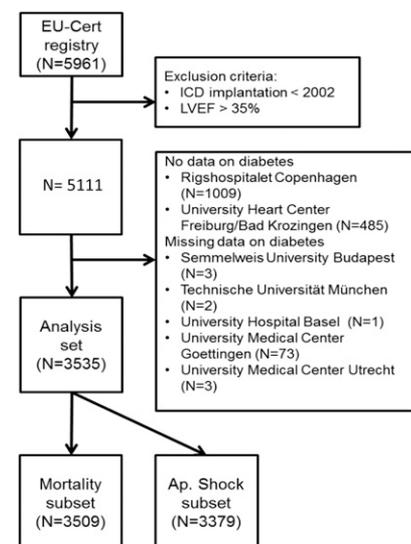
## RESULTS

### Baseline Characteristics

For this analysis,  $n = 3,535$  patients (82.2% male, mean age  $63.7 \pm 11.2$  years) from 12 European hospitals were included. Figure 1 shows a flowchart to clarify data exclusions. Demographic details are presented in Table 1. The mean follow-up time was 1,165 days (SD = 850). We were able to collect mortality data from 3,509 patients, of whom 990 had diabetes (28.2%), and data for appropriate shocks were available from 3,379 patients, of whom 948 had diabetes (28.0%). Among patients with diabetes, there were 233 deaths (233 of 990, 23.5%), and in patients without diabetes 439 deaths (439 of 2,519, 17.4%). Appropriate shocks occurred in 110 patients with diabetes (110 of 948, 11.6%) and in 352 patients without diabetes (352 of 2,431, 14.5%).

### Mortality

In the competing risk analyses, diabetes was significantly associated with increased risk of mortality (hazard ratio [HR] 1.42 [95% CI 1.21–1.67],  $P < 0.001$ ) (Fig. 2). In addition, increasing age, ischemic etiology of heart failure, lower LVEF, New York Heart Association (NYHA) class III or IV, and male sex were significantly associated with mortality. In the multivariate competing risk analyses adjusted with all significant covariates, diabetes remained significantly



**Figure 1**—Flowchart on patient exclusion and subset generation. Ap. shock, appropriate shock.

**Table 1—Baseline characteristics**

Overall (n = 3,535)	Without diabetes (n = 2,540)	With diabetes (n = 995)
Sex		
Female/male	469 (18.5)/2,071(81.5)	160 (16.1)/835(83.9)
Age, years (mean ± SD)	62.9 ± 11.7	65.7 ± 9.4
BMI (mean ± SD)	26.4 ± 4.4	29.1 ± 5.2
LVEF, % (mean ± SD)	25.3 ± 6.1	25.7 ± 6.0
Etiology		
Ischemic	1,501 (59.1)	753 (75.7)
Nonischemic	1,039 (40.9)	242 (24.3)
ICD type		
ICD	1,488 (58.6)	547 (55.0)
CRT-D	1,052 (41.4)	448 (45.0)
NYHA		
Class I or II	1,091 (43.0)	318 (32)
Class III or IV	1,449 (57.0)	677 (68.0)

Data are presented as n (%), unless otherwise indicated. CRT-D, cardiac resynchronization therapy pacemaker with defibrillator.

associated with mortality (HR 1.30 [95% CI 1.11–1.53], *P* = 0.001), as did all other variables that were significant in the univariate model (Table 2).

**First Appropriate Shock**

In the competing risk analyses, diabetes showed an association with decreased risk for first appropriate shock (HR 0.81 [95% CI 0.65–1.00], *P* = 0.047) (Fig. 2). Of the other variables associated with increased mortality, ischemic etiology of heart failure, lower LVEF, and male sex were significantly associated with increased risk for first appropriate shock. In the multivariate competing risk analyses adjusted with all significant covariates, diabetes remained significant and had an even stronger association with decreased risk for first

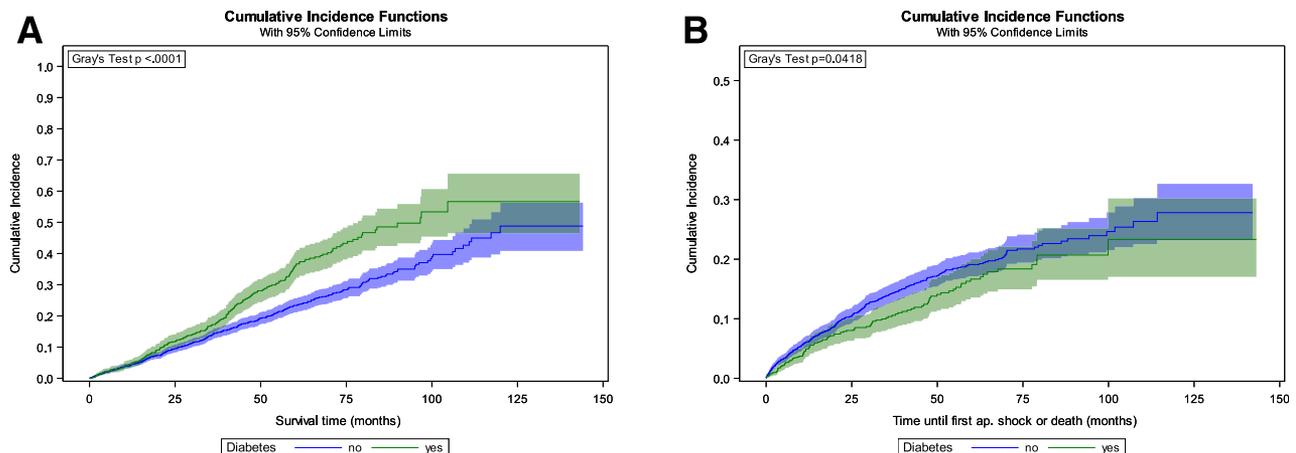
appropriate shock (HR 0.77 [95% CI 0.62–0.96], *P* = 0.017), as did all other variables that were significant in the univariate model (Table 2).

**CONCLUSIONS**

In this study, we present results from a large, “real-life,” multicenter retrospective registry on the association of diabetes with mortality and appropriate shocks among patients with primary prevention ICDs. As in previous studies, diabetes was strongly associated with increased mortality, but, most interestingly, diabetes was also associated with a decreased cumulative incidence of first appropriate ICD shock.

In a recent meta-analysis of the Multicenter Automatic Defibrillator Implantation Trial I and II (MADIT-I, MADIT-II)

and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), there was no significant reduction of mortality in the ICD treatment arm among patients with diabetes (12). From these data, it seems that among patients with diabetes with LVEF <35%, ICD therapy may not be effective. One of the major reasons for this is the increased comorbidity-related mortality (i.e., competing non-arrhythmic mortality) among patients with diabetes, because there was a significant reduction in survival benefit in interaction analysis among patients with diabetes. In the aforementioned meta-analysis, no significant differences between patients with and without diabetes could be found in regards to appropriate shocks. In our present study, we could confirm the significant excess of mortality among ICD patients with diabetes compared with patients without diabetes. Importantly, we could also demonstrate, in competing risk analysis, that patients with diabetes had a significantly lower incidence of appropriate shocks compared with patients without diabetes. This result was independent of etiology of heart failure and LVEF. In our previous study among post-MI patients, subjects with diabetes with impaired LVEF (<35%) had a very poor prognosis compared with subjects without diabetes. On the other hand, subjects with diabetes with LVEF >35% had an incidence of SCD similar to subjects without diabetes with LVEF <35%, suggesting that among post-MI patients with diabetes, the



**Figure 2—**Cumulative incidence of death (A) and first appropriate (ap.) shock (B) for patients with and without diabetes in competing interest analyses.

**Table 2—Significant risk variables in multivariable competing risk analyses for death and appropriate shock**

	Variable	<i>P</i> value	HR	95% CI
Death	Age	<b>&lt;0.0001</b>	1.035	1.026 1.044
	Diabetes (yes vs. no)	<b>0.0014</b>	1.300	1.107 1.528
	Etiology (ischemic vs. nonischemic)	<b>0.0128</b>	1.262	1.051 1.515
	LVEF	<b>&lt;0.0001</b>	0.962	0.950 0.975
	NYHA (class I or II vs. III or IV)	<b>&lt;0.0001</b>	0.676	0.563 0.813
	Sex (male vs. female)	<b>0.0122</b>	1.356	1.069 1.720
Appropriate shock	Diabetes (yes vs. no)	<b>0.0172</b>	0.770	0.621 0.955
	Etiology (ischemic vs. nonischemic)	<b>0.0034</b>	1.374	1.111 1.700
	LVEF	<b>0.0012</b>	0.976	0.962 0.991
	Sex (male vs. female)	<b>0.0009</b>	1.665	1.232 2.250

First ordered variable as reference. *P* value <0.05 in boldface type.

distribution of primary prevention ICDs might be reconsidered (8).

Our data suggest that patients with DM with primary prevention ICDs might not benefit from the device because of significant competing risk mortality and also because of a lower incidence of the device treatment, even though the rate of SCD among patients with diabetes is higher according to multiple previous studies (6,8,13,14). According to several reports, the incidence of pulseless electrical activity and asystole as primary rhythm of sudden cardiac arrest has increased in the last decades (15,16). This has been speculated to be the result of an increased number of heart failure patients in the community. In fact, one study in the Danish National Registry showed that out-of-hospital cardiac arrest subjects with diabetes had significantly less shockable rhythm at first contact with the paramedics (17). Therefore, one possible explanation would be that among heart failure patients with diabetes, the initial rhythm causing sudden death would be different than ventricular tachyarrhythmia, which would be treatable by the device. In other words, the level of the cardiac disease among heart failure patients with diabetes may lead to an increased possibility of SCD by a mechanism other than ventricular tachyarrhythmias.

The results of this study suggest that for patients with diabetes, left ventricular (LV) systolic function might not play the same key role in patient selection for primary prevention ICD in the future. Possibly other risk-stratifying methods, such as identification of excess myocardial fibrosis with cardiac MRI, could be more efficient. In different ICD patient

populations, a clear correlation exists between the degree of LV fibrosis and appropriate shocks (18–20).

#### Limitations

The current study is retrospective, and direct conclusions should be drawn with caution. Another limitation is the appropriate shock end point. For the EU-CERT-ICD retrospective data set, we did not have a uniform programming regimen for ICDs across the centers. Therefore, some appropriate shocks could have been administered for arrhythmias that might have not resulted in SCD. The EU-CERT-ICD prospective study has gathered a large prospective population with unified ICD programming, and results of the coming analyses from the prospective population will ultimately clarify the incidence of appropriate shocks among patients with diabetes. Additionally, in the current study population, we do not have information on the mode of death (i.e., SCD or non-SCD), which would be important in further evaluating the association of diabetes and mortality. However, increased risk for SCD among patients with diabetes, including patients with impaired LV function, has been described in several prior studies (6,8,13,14). Furthermore, the increased SCD risk among patients with diabetes with LVEF <35% was evident in our large post-MI population study ( $n = 3,276$ ) where patients with diabetes had a threefold higher risk for SCD compared with patients without diabetes with LV dysfunction (8).

#### Conclusion

Patients with diabetes with LVEF <35% have an increased mortality despite

implantation of an ICD, and they also have less appropriate shocks from the ICD, suggesting a limitation of the potential of prophylactic ICD therapy to improve survival in this patient group. Patients with diabetes are in need of new risk stratification models in addition to LV systolic function when prophylactic ICD therapy is considered in order to identify the subjects who would benefit from the device. Future prospective studies are needed to confirm these findings.

**Funding.** The EU-CERT-ICD project is funded by the European Community's 7th Framework Programme FP7/2007–2013 (grant agreement number 602299).

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

**Author Contributions.** M.J.J. collected the patient population and wrote the manuscript. A.P. collected data and reviewed and edited the manuscript. T.V.K. and M.A.V. analyzed data and reviewed and edited the manuscript. T.F. and M.H. performed statistical analyses and reviewed and edited the manuscript. R.W., L.B., B.V., G.S., B.M., A.L., M.S., and F.B. collected the patient population and reviewed and edited the manuscript. M.M. analyzed data, reviewed grammar, and reviewed and edited the manuscript. M.Z. collected the patient population, supervised the project and funding, and reviewed and edited the manuscript. H.V.H. and C.S. supervised and collected the patient population and reviewed and edited the manuscript. T.F. and M.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Prior Presentation.** This study was presented in poster form at the 2018 European Society of Cardiology Congress, Munich, Germany, 25–29 August 2018, and the Heart Rhythm Society's 39th Annual Scientific Sessions, Boston, MA, 9–12 May 2018.

#### References

1. Yancy CW, Jessup M, Bozkurt B, et al.; WRITING COMMITTEE MEMBERS; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013;128:e240–e327
2. Moss AJ, Hall WJ, Cannom DS, et al.; Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;335:1933–1940
3. Moss AJ, Zareba W, Hall WJ, et al.; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction

- and reduced ejection fraction. *N Engl J Med* 2002; 346:877–883
4. Bardy GH, Lee KL, Mark DB, et al.; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure [published correction appears in *N Engl J Med* 2005;352:2146]. *N Engl J Med* 2005;352:225–237
  5. Køber L, Thune JJ, Nielsen JC, et al.; DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;375:1221–1230
  6. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med* 1998;339:229–234
  7. MacDonald MR, Petrie MC, Varyani F, et al.; CHARM Investigators. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) programme. *Eur Heart J* 2008;29:1377–1385
  8. Junttila MJ, Barthel P, Myerburg RJ, et al. Sudden cardiac death after myocardial infarction in patients with type 2 diabetes. *Heart Rhythm* 2010;7:1396–1403
  9. Rydén L, Grant PJ, Anker SD, et al.; Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); Document Reviewers. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the task force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2013;34:3035–3087
  10. Sticherling C, Arendacka B, Svendsen JH, et al.; EU-CERT-ICD Investigators. Sex differences in outcomes of primary prevention implantable cardioverter-defibrillator therapy: combined registry data from eleven European countries. *Europace* 2018;20:963–970
  11. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509
  12. Sharma A, Al-Khatib SM, Ezekowitz JA, et al. Implantable cardioverter-defibrillators in heart failure patients with reduced ejection fraction and diabetes. *Eur J Heart Fail* 2018;20:1031–1038
  13. Jouven X, Lemaître RN, Rea TD, Sotoodehnia N, Empana J-P, Siscovick DS. Diabetes, glucose level, and risk of sudden cardiac death. *Eur Heart J* 2005;26:2142–2147
  14. Junttila MJ, Kiviniemi AM, Lepojärvi ES, et al. Type 2 diabetes and coronary artery disease: preserved ejection fraction and sudden cardiac death. *Heart Rhythm* 2018;15:1450–1456
  15. Bunch TJ, White RD, Friedman PA, Kottke TE, Wu LA, Packer DL. Trends in treated ventricular fibrillation out-of-hospital cardiac arrest: a 17-year population-based study. *Heart Rhythm* 2004;1:255–259
  16. Kuisma M, Repo J, Alaspää A. The incidence of out-of-hospital ventricular fibrillation in Helsinki, Finland, from 1994 to 1999. *Lancet* 2001; 358:473–474
  17. Mohr GH, Søndergaard KB, Pallisgaard JL, et al. Survival of patients with and without diabetes following out-of-hospital cardiac arrest: a nationwide Danish study. *Eur Heart J Acute Cardiovasc Care*. 11 January 2019 [Epub ahead of print]. DOI: 10.1177/2048872618823349.
  18. Chimura M, Kiuchi K, Okajima K, et al. Distribution of ventricular fibrosis associated with life-threatening ventricular tachyarrhythmias in patients with nonischemic dilated cardiomyopathy. *J Cardiovasc Electrophysiol* 2015;26:1239–1246
  19. Gulati A, Jabbour A, Ismail TF, et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. *JAMA* 2013;309:896–908
  20. Mordi I, Jhund PS, Gardner RS, et al. LGE and NT-proBNP identify low risk of death or arrhythmic events in patients with primary prevention ICDs. *JACC Cardiovasc Imaging* 2014;7: 561–569