Appropriate shocks and mortality in diabetic and vs. non-diabetic patients with prophylactic implantable cardioverter-defibrillators

Running title: Benefit of ICD therapy among diabetic patiens

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Abstract

Background: 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 diabetic vs. non-diabetic patients with implanted prophylactic cardioverter-defibrillator (ICD) included in the retrospective EU-CERT-ICD registry.

Methods and Results: A total of 3535 patients from 12 European EU-CERT-ICD centers with a mean age of 63.7±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. Endpoints were appropriate shock and all-cause mortality. Mean follow-up time was 3.2±2.3 years. Diabetes was associated with a lower risk of appropriate shocks (adjusted HR 0.77; 95% CI: 0.62-0.96, p=0.02). However, diabetic patients had significantly higher mortality (adjusted HR1.30; 95% CI: 1.11-1.53, p=0.001).

Conclusions: All-cause mortality is higher in diabetic than in non-diabetic patients with primary prophylactic ICDs. Subsequently, diabetic patients 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 diabetic patients with impaired left ventricular function.

Introduction

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 other risk parameters than LVEF for the purpose of identifying patients who would actually benefit from primary ICD therapy. Furthermore, the randomized DANISH ICD trial recently showed that patients with non-ischemic heart disease have a limited benefit from primary ICD therapy (5).

Diabetes mellitus (DM) increases the cardiovascular mortality among survivors of myocardial infarction (6). In an analysis of the CHARM study, DM was an independent predictor of mortality, including SCD, in patients with heart failure (7). In a series of post-infarction patients from Germany and Finland, SCD incidence was higher in type 2 DM than in non-diabetic patients. The SCD incidence was substantially increased among DM patients with an EF <35%, supporting the concept that a prophylactic implantable cardioverter defibrillator should be used in all DM patients with an EF <30–35% unless contraindicated (8).

These findings led to recommendations that DM patients should be routinely screened by echocardiography or some other method to measure the LVEF after acute myocardial infarction 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 DM in contemporary real life European primary prevention ICD population (EU-CERT-ICD retrospective study).

Methods

The EU-CERT-ICD project is funded by the European Community's 7th Framework Programme FP7/2007-2013 (grant agreement number 602299) . The prospective arm (clinicaltrials.gov NCT02064192) has enrolled 2327 patients with an indication for a primary prevention ICD implantation who will also undergo analysis of numerous candidate ECG 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. 2018. In this analysis, we only consider data from 12 out of 14 centers, since DM status was only available for those centers (10). Diabetes was diagnosed according to the WHO guidelines in all centers.

Data collection

The study design including twenty-three demographic, pre-defined device- and outcome-related variables, and the collection of 17 additional variables have been previously presented (including the supplementary online material) (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 pre-processed datasets to the coordinating clinical trial unit at the University Hospital of Basel, Switzerland. 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 standard deviations, categorical variables as frequencies. The primary endpoints 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±11.2 years) from 12 European hospitals where included. Figure 1 shows a flowchart to clarify data exclusions. Demographic details are presented in Table 1. The mean follow-up time was 1165 days (SD=850). We were able to collect mortality data from 3,509 patients of whom 990 had DM (28.2%) and data for appropriate shocks were available from 3,379 patients of whom 948 had DM (28.0%). Among diabetics, there were 233 deaths (233/990, 23.5%) and in non-diabetic patients 439 deaths (439/2,519, 17.4%). Appropriate shocks occurred in 110 DM (110/948, 11.6%) and in 352 non-DM patients (352/2,431, 14.5%). Detailed information on end-points and competing events are presented in Table 2.

Mortality

In the competing risk analyses, DM was significantly associated with increased risk of mortality (HR 1.42, 95%CI: 1.21-1.67, p< 0.001). In addition, increasing age, ischemic etiology of heart failure,

lower LVEF, NYHA class III or IV and male sex were significantly associated with mortality (Table 3). In the multivariate competing risk analyses adjusted with all significant co-variates, DM remained significantly associated with mortality (HR 1.30, 95%CI: 1.11-1.53, p= 0.001) as did all other variables which were significant in the univariate model (Table 4).

First appropriate shock

In the competing risk analyses, DM showed an associated with decreased risk for first appropriate shock (HR 0.81, 95%CI: 0.65-1.00, p= 0.047). 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 (Table 5). In the multivariate competing risk analyses adjusted with all significant co-variates, DM remained significant and had 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 which were significant in the univariate model (Table 6).

Discussion

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

In a recent meta-analysis of MADIT I, II and SCD-HeFT there was no significant reduction of mortality in the ICD treatment arm among DM patients (12). From these data, it seems that among diabetic patients with LVEF under 35%, ICD-therapy may not be effective. One of the major reasons for this is the increased co-morbidity related mortality (i.e. competing non-arrhythmic mortality) among DM patients since there was a significant reduction in survival benefit in interaction analysis among DM patients. In the aforementioned meta-analysis, no significant differences between DM and non-DM patients could be found in regards to appropriate shocks. In our present study, we could confirm the significant excess of mortality among DM ICD patients compared to non-DM patients. Importantly, we could also demonstrate, in competing risk analysis, that DM patients had a significantly lower incidence of appropriate shocks compared to non-DM patients. This result was independent of etiology of heart failure and LVEF. In our previous study among post-MI patients, DM subjects with impaired LVEF (under 35%) had a very poor prognosis compared to non-DM subjects. On the other hand, DM subjects with LVEF over 35% had similar incidence of SCD than non-DM subjects with LVEF under 35% suggesting that among DM post-MI patients the distribution of primary prevention ICDs might be reconsidered (8).

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

The results of this study suggests that for DM patients, 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 endpoint. For the EU-CERT-ICD retrospective dataset we did not have a uniform programming regime for ICDs across the centers. Therefore, some appropriate

shocks could have been administrated for arrhythmias which 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 diabetic patients. Additionally, in the current study population, we do not have information on the mode of death i.e. sudden cardiac death and non-sudden cardiac death which would be important in further evaluating the association of diabetes and mortality. However, increased risk for SCD among diabetic patients, including patients with impaired LV function has been described in several prior studies (6,8,13-14). Furthermore, the increased SCD risk among diabetic patients with LVEF under 35% was evident in our large post MI population study (n=3,276) where diabetic patients had three fold higher risk for SCD compared to non-diabetic patients with LV dysfunction (8).

Conclusion

Diabetic patients with LVEF under 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. Diabetic patients are in the 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.

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Table 1. Baseline characteristics.

Overall (n=3535)	**Non-diabetic (n=2540)**	**Diabetic (n=995)**
Sex		
Female/Male	469 (18.5%)/2071(81.5%)	160 (16.1%)/835(83.9%)
Age (mean±SD, years)	62.9±11.7	65.7±9.4
BMI (mean±SD)	26.4±4.4	29.1±5.2
LVEF (%)	25.3±6.1	25.7±6.0
Etiology		
ischemic	1501 (59.1%)	753 (75.7%)
non-ischemic	1039 (40.9%)	242 (24.3%)
ICD type		
ICD	1488 (58.6%)	547 (55.0%)
CRT-D	1052 (41.4%)	448 (45.0%)
NYHA		
Class I or II	1091 (43.0%)	318 (32%)
Class III or IV	1449 (57.0%)	677 (68.0%)

SD= standard deviation, BMI= body mass index, LVEF= left ventricular ejection fraction,

ICD= implantable cardioverter defibrillator, CRT-D= cardiac resyncronization therapy pacemaker with defibrillator, NYHA= New York Heart Association functional class

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

	Variable	**p-value**	**Hazard ratio**	**95%-Confidence interval**	
Death	Age	**<.0001**	1.035	1.026	1.044
	Diabetes (yes vs. no)	**0.0014**	1.300	1.107	1.528
	Etiology (ischemic vs. non-ischemic)	**0.0128**	1.262	1.051	1.515
	LVEF	**<.0001**	0.962	0.950	0.975
	NYHA (Class I or II vs. III or IV)	**<.0001**	0.676	0.563	0.813
	Sex (male vs. female)	**0.0122**	1.356	1.069	1.720
App. shock	Diabetes (yes vs. no)	**0.0172**	0.770	0.621	0.955
	Etiology (ischemic vs. non-ischemic)	**0.0034**	1.374	1.111	1.700
	LVEF	**0.0012**	0.976	0.962	0.991
	Sex (male vs. female)	**0.0009**	1.665	1.232	2.250

First ordered variable as reference. P-value < 0.05 written in bold. App.shock= appropriate shock

FIGURE LEGENDS

Figure 1. Flowchart on patient exclusion and subset generation.

Figure 2. Cumulative incidence of death (A) and first appropriate shock (B) for diabetic and non-diabetic patients in competing interest analyses.