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Incidence of appropriate implantable cardioverter-defibrillator therapy and mortality after implantable cardioverter-defibrillator generator replacement: results from a real-world nationwide cohort

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Aims The safety of omitting implantable cardioverter-defibrillator (ICD) generator replacement in patients with no prior appropriate therapy, comorbid conditions, and advanced age is unclear. The aim was to investigate incidence of appropriate ICD therapy after generator replacement.

Methods and results We identified patients implanted with a primary prevention ICD ($n = 4630$) from 2007 to 2016, who subsequently underwent an elective ICD generator replacement ($n = 670$) from the Danish Pacemaker and ICD Register. The data were linked to other databases and evaluated the outcomes of appropriate therapy and death. Predictors of ICD therapy were identified using multivariate Cox regression analyses. A total of 670 patients underwent elective ICD generator replacement. Of these, 197 (29.4%) patients had experienced appropriate therapy in their 1st generator period. During follow-up of 2.0 ± 1.6 years, 95 (14.2%) patients experienced appropriate therapy. Predictors of appropriate therapy in 2nd generator period was low initial left ventricular ejection fraction (≤25%) [hazard ratio (HR) 1.87, confidence interval (CI) 1.13–1.95] and appropriate therapy in 1st generator period (HR 3.95, CI 2.57–6.06). For patients with appropriate therapy in 1st generator period, 4-year incidence of appropriate therapy was 50.6% vs. 16.4% in those without ($P < 0.001$). Among patients >80 years with no prior appropriate therapy 8.8% of patients experienced appropriate therapy after replacement. Comorbidity burden and advanced age were associated with reduced device utilization after replacement and a high competing risk of death without preceding appropriate therapy.

Conclusion A significant residual risk of appropriate therapy in the 2nd generator was present even among patients with advanced age and with a full prior generator period without any appropriate ICD events.

Keywords Implantable cardioverter-defibrillator • Appropriate therapy • Ventricular arrhythmias • Mortality • Comorbidity • Generator

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What's new?

- There was a significant residual risk of appropriate implantable cardioverter-defibrillator (ICD) therapy in the 2nd generator life even among patients with advanced age and with a full prior generator period without any appropriate ICD events.
- Besides left ventricular ejection fraction and prior ICD therapy, comorbidity burden, advanced age, and high competing risk of non-cardiac death should be considered when deciding whether to replace ICDs.
- Non-cardiac comorbidities were significantly associated with mortality without prior appropriate therapy.
- In patients without appropriate therapy in the 1st generator period, up to 83% of the patients died without having utilized their device at any time (1st and 2nd generators).

Introduction

Clinical trials and practice have consistently shown that implantable cardioverter-defibrillators (ICDs), with or without cardiac resynchronization therapy (CRT), improve survival and reduce risk of sudden card

iac death (SCD) in patients with heart failure and markedly reduced systolic left ventricular function.[1] Primary prevention ICDs have now been implanted for more than 20 years. Consequently, many ICD recipients live to receive a 2nd or 3rd generator, which in many cases are scheduled routinely and without re-evaluation of the indication.

Two important clinical observations and issues are often debated among clinicians at time of generator replacement. First, some patients may not have experienced prior ventricular arrhythmias or received any ICD treatment at all during the 1st generator life period of 5–10 years. Which of these patients are still at a high arrhythmic risk of SCD at time of generator replacement and can generator replacement be omitted in the remaining patients with presumed low arrhythmic risk, high age, or expanding comorbidity burden?[2,3]

Second, patients, in particular those with CRT, who experience improvement or normalization of left ventricular ejection fraction (LVEF) have markedly reduced risk of arrhythmic sudden death, raising a question about the benefit of ICD at the time of generator replacement.[4] The latter was recently sought answered in smaller retrospective publications, where LVEF recovery at time of ICD replacement could not alone discriminate high- and low-risk patients for SCD.[5–9]

We set out to investigate patients who lived to receive a 2nd ICD generator to evaluate predictors and incidence of ventricular tachycardia or ventricular fibrillation as treated with appropriate ICD therapy prior to and after generator replacement along with time to death after replacement. The hypothesis was that patients without appropriate therapy in 1st generator period were at low risk for appropriate therapy in 2nd generator period, particularly among those with advanced age and high comorbidity burden, due to increasing competing risk of non-cardiac death.

Methods

All data on ICD and pacemaker implantations completed in Denmark have been prospectively collected in the Danish Pacemaker and ICD register (DPIR). In this study, we identified all first-time primary prevention ICD and CRT with defibrillator (CRT-D) implantations from the DPIR from 1 January 2007 to 31 December 2016. This register captures clinical data at implantation, i.e. indication, LVEF and New York Heart Association (NYHA) class, device type, lead type, and also data from follow-up, device related complications, time and indication for generator replacement, and appropriate device therapy as described previously.[10]

Figure 1 shows the selection of patients. Patients were excluded if they had hypertrophic cardiomyopathy, congenital heart disease, arrhythmogenic right ventricular cardiomyopathy, channelopathies, idiopathic ventricular fibrillation, or others not readily defined as clear ischaemic or non-ischaemic cardiomyopathy. Hereafter, we identified patients who received more than one generator. To make the cohort homogenous and clinically relevant from an elective operative approach, we excluded those where the reason for replacement was system or pocket infection, technical issues including device recalls, sense and pace failures, software issues and heart transplant. This constituted the final cohort with follow-up and baseline data defined and captured on the day of the generator replacement and follow-up to date of death, emigration, or end-of-study 31 December 2016.

Comorbidity and medications

Through encrypted access via the servers of Statistics Denmark to anonymized data from nationwide Danish registers we obtained and linked information on demographics (Civil Persons Register), medications (The Danish Register of Medicinal Products Statistics), and comorbidities (The Danish National Patient Register). Descriptions of the registers have previously been published and the registers have been continuously validated. Definitions on capture of comorbidities and medications as per baseline *Table 1* and non-cardiac comorbidities are provided in the Supplementary material online, *Table S1*.

Non-cardiac comorbidities were defined as dementia, cancer, liver disease, severe psychiatric disease, rheumatic disease, peripheral vascular disease, cerebrovascular disease/stroke, chronic obstructive pulmonary disease, chronic renal disease, and diabetes mellitus.

Outcomes

Appropriate ICD therapy was defined as anti-tachycardia pacing or shock for ventricular tachycardia or ventricular fibrillation as evaluated and recorded in the register by the treating physician and device technicians at interval clinic visits, relevant cardiac hospitalization, or remote follow-ups. Death and date of death were identified through the Danish Civil Person Register.

Device utilization after generator replacement was defined as the percentage distribution of patients who died without any appropriate ICD therapy and those who experienced appropriate ICD therapy.

Statistical analysis

Categorical variables are reported as number (%), and continuous variables are reported as mean ± standard deviation. Comparisons between groups were done with the χ^2 or Fisher's exact test for categorical variables where appropriate and Kruskal–Wallis test for continuous variables. For survival analysis we evaluated the outcome of appropriate therapy by use of cumulative incidence curves that account for competing risk of death and by method of Kaplan–Meier for the outcome of all-cause mortality. Univariate and multivariate Cox regression analyses were used to report risk factors associated with the outcomes of appropriate ICD therapy and to adjust for confounders of all-cause mortality. Hazard ratios (HRs), their 95% confidence intervals (CIs), and *P*-value are reported. A two-tailed *P*-value below 0.05 was considered significant. All analyses were performed through the use of encrypted and anonymized data using the servers of Statistics Denmark and SAS 9.4 statistical software

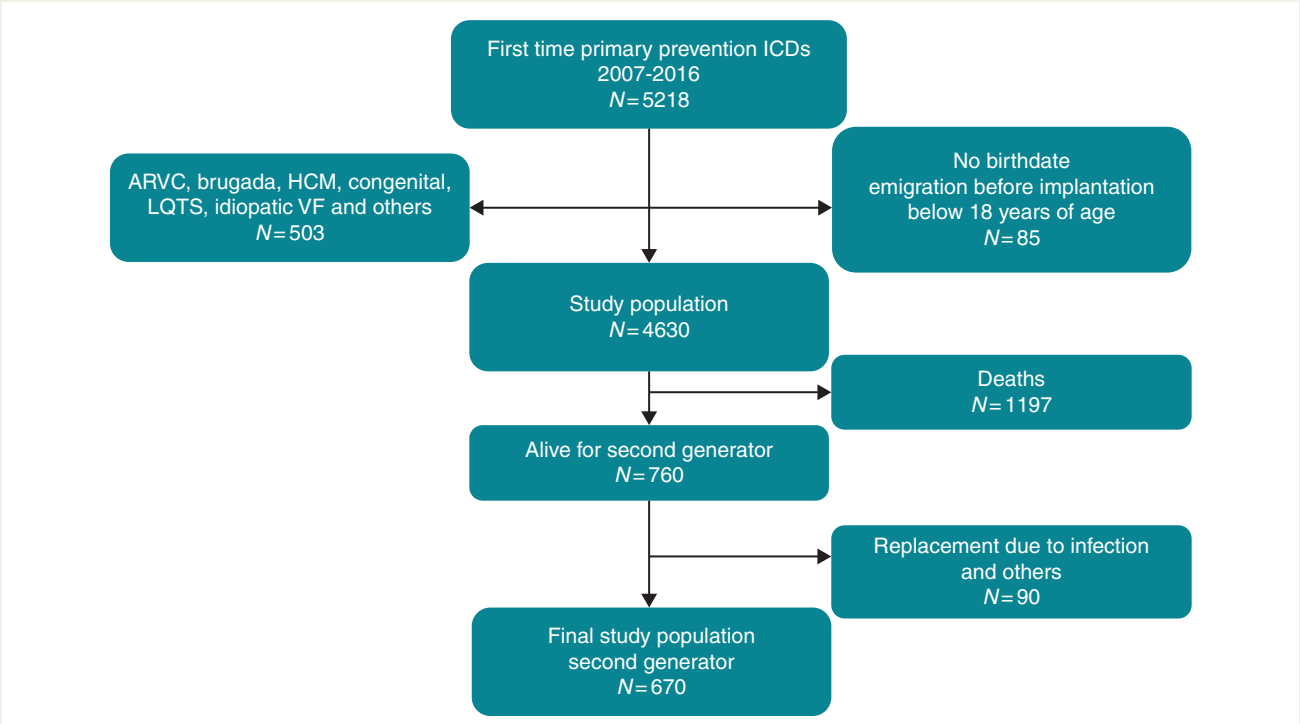

Figure 1 Flow chart outlining population inclusion and exclusion. ARVC, arrhythmogenic right ventricle cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LQTS, long QT syndrome; VF, ventricular fibrillation.

(SAS Institute Inc., Cary, NC, USA). The study was approved by the Danish Data Protection Agency and the DPIR. In Denmark, register-based research does not require approval from the ethics committee.

Results

Study population

From 2007 to 2016, we identified 4630 patients with ischaemic or non-ischaemic cardiomyopathy who received a first-time ICD for primary prevention. Of these patients, a total of 1197 (25.9%) died and a cohort of 670 (14.5%) patients received a 2nd generator (first replacement) (*Figure 1*). Among the 670 patients who received a generator replacement, patient and device characteristics and medications are shown in *Table 1*. The majority of patients had ischaemic cardiomyopathy (76.9%) as the cause of heart failure. The mean age at first implantation was 64.3 ± 9.7 years and at generator replacement it was 69.3 ± 9.7 years with a mean time to replacement of 5.0 ± 2.0 years. The mean follow-up after generator replacement was 2.0 ± 1.6 years.

Stratifying the cohort on whether or not they had received an appropriate ICD therapy during the 1st generator period, we found significantly more male patients in the prior appropriate ICD therapy group (88.8% vs. 75.1%). A total of 50% of the ICDs implanted were CRT-Ds with a higher frequency among patients with a prior appropriate ICD therapy (62.2% vs. 44.8%). The mean LVEF at initial implant was 24.4 ± 7.2% with no difference between the groups. The comorbidities and medications can be seen in *Table 1*. The frequency of patients with prior myocardial infarction and atrial fibrillation differed between the groups and the frequency of amiodarone treatment was significantly higher among those who had experienced appropriate ICD therapy in the 1st generator period (32.5% vs. 8.5%). The reason for generator replacement was end of battery life in 64.8% of the cases and upgrades/downgrades in 24.6% of the cases and 10.6% of patient requests or unknown reasons.

Predictors of appropriate implantable cardioverter-defibrillator therapy after generator replacement

Using univariate and multivariate Cox regression analysis, we found two factors independently and significantly associated with increased risk of appropriate ICD therapy after generator replacement (*Table 2*). The factor with strongest association was appropriate ICD therapy in the 1st generator period (HR 3.95, CI 2.57–6.06), while very low LVEF (≤25%) at initial implant also was significantly associated (HR 1.87, CI 1.13–1.95).

Risk of appropriate implantable cardioverter-defibrillator therapy prior to and after generator replacement

At the time of generator replacement, 197 (29.4%) of the patients had experienced at least one appropriate ICD therapy in the 1st generator period. During a mean follow-up of 2.0 ± 1.6 years after generator replacement a total of 95 (14.2%) patients experienced appropriate ICD therapy. In *Figure 2*, the cumulative incidence of

Table 1 Baseline patient and device characteristics at time of generator replacement stratified by prior vs. no prior appropriate ICD therapy in first generator period for primary prevention ICD patients

Variables	Overall (*N* = 670)	No prior appropriate ICD therapy (*N* = 473) (70.6%)	Prior appropriate ICD therapy (*N* = 197) (29.4%)	*P*-value
Age (years)	69.3 ± 9.7	69.6 ± 9.8	68.6 ± 9.7	0.148
Age ≥80 years	73 (10.9%)	57 (12.1%)	16 (8.1%)	0.137
Age at initial implant (years)	64.3 ± 9.7	64.8 ± 9.7	63.1 ± 9.4	0.018
Male sex	530 (79.1%)	355 (75.1%)	175 (88.8%)	<0.001
CRT-D	335 (50.0%)	212 (44.8%)	123 (62.2%)	<0.001
Types of cardiomyopathy				
Ischaemic	515 (76.9%)	361 (76.3%)	154 (78.2%)	0.605
Non-ischaemic	155 (23.1%)	112 (23.7%)	43 (21.8%)	0.605
LVEF at initial implant	24.4 ± 7.2	24.7 ± 7.1	23.7 ± 7.6	0.080
LVEF at replacement (*n* = 133)	23.9 ± 7.5	24.5 ± 8.1	23.0 ± 6.6	0.384
NYHA initial implant (*n* = 637)	2.4 ± 0.6	2.4 ± 0.6	2.3 ± 0.6	0.167
NYHA at replacement (*n* = 120)	2.8 ± 0.6	2.8 ± 0.6	2.7 ± 0.6	0.584
Comorbidities				
Atrial fibrillation	216 (32.0%)	136 (28.8%)	80 (40.6%)	0.003
Diabetes	196 (29.3%)	149 (31.5%)	47 (23.9%)	0.048
COPD	137 (20.5%)	103 (21.8%)	34 (17.3%)	0.187
Chronic kidney disease	79 (11.8%)	56 (11.8%)	23 (11.7%)	0.952
Previous MI	430 (64.2%)	292 (61.7%)	138 (70.1%)	0.041
Revascularized total—PCI or CABG	429 (64.0%)	297 (62.8%)	132 (67.0%)	0.300
CABG	181 (27.0%)	120 (25.4%)	61 (31.0%)	0.137
Medications				
Beta blocker	620 (92.5%)	439 (92.8%)	181 (91.9%)	0.675
ACEi or ARB	571 (85.2%)	405 (85.6%)	166 (84.3%)	0.651
CCB	63 (9.4%)	45 (9.5%)	18 (9.1%)	0.879
Digoxin	138 (20.6%)	90 (19.0%)	48 (24.4%)	0.120
Amiodarone	104 (15.5%)	40 (8.5%)	64 (32.5%)	<0.001
Statins	528 (78.8%)	378 (79.9%)	150 (76.1%)	0.276
Diuretics	572 (85.4%)	402 (85.0%)	170 (86.3%)	0.663
Reason for replacement				
EOL	434 (64.8%)	316 (66.8%)	118 (55.9%)	0.092
Upgrade/downgrade[a]	165 (24.6%)	100 (21.1%)	65 (33.0%)	0.002
Patient request	37 (5.5%)	28 (5.9%)	9 (4.6%)	0.580
Unknown	34 (5.1%)	29 (6.1%)	5 (2.5%)	0.055
Mean time to replacement (years)	5.0 ± 2.0	4.8 ± 2.0	5.5 ± 1.9	<0.001

Categorical variables are listed as *n* (%). Continuous variables are listed as mean ± standard deviation.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy with defibrillator; EOL, end of life; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.
[a]Upgrades from ICD to CRT-D was performed in 144 of 165 patients (87%).

appropriate ICD therapy is shown stratified by appropriate ICD therapy in the 1st generator period. The cumulative incidence was 4.3% vs. 20.3% at 1 year, 7.4% vs. 27.8% at 2 years, and 16.4% vs. 50.6% at 4 years (log-rank *P*-value for all comparisons <0.001), respectively for those without vs. those with prior appropriate therapy during the 1st generator period.

Using the predictive univariate table and a clinical perspective we aimed to identify specific low-risk patients. However, we found a significant residual risk of appropriate ICD therapy after generator replacement, i.e. among patients with no prior appropriate ICD therapy and an initial LVEF > 25% then 8 out of 165 (4.9%) patients experience appropriate therapy anyway (*Figure 3*). When we investigated the influence of advanced age, we similarly found a considerable residual risk. Among patients older than 80 years without prior appropriate ICD therapy, 5 out of 57 (8.8%) patients experienced appropriate ICD therapy after generator replacement. However,

Table 2 Univariate and multivariate analyses of predictors of first appropriate ICD therapy after generator replacement

	Univariate			Multivariate		
Variables	**Hazard ratio**	**95% CI**	***P*-value**	**Hazard ratio**	**95% CI**	***P*-value**
Advanced age ≥80 years	0.77	0.34–1.77	0.543			
Appropriate therapy in first generator period	4.03	2.67–6.08	<0.001	3.95	2.57–6.06	<0.001
Male sex	1.48	0.85–2.57	0.166			
Ischaemic CM	1.00	0.61–1.64	0.994			
LVEF ≤25%	1.69	1.04–2.75	0.034	1.87	1.13–1.95	0.014
CRT-D	0.70	0.46–1.06	0.089			
Atrial fibrillation	1.19	0.78–1.81	0.421			
Previous MI	1.10	0.71–1.69	0.676			
Hospitalization for HF in last year	1.60	0.96–2.67	0.074			

The multivariate analysis was adjusted for the variables presented in the table (univariate).
CI, confidence interval; CM, cardiomyopathy; CRT-D, cardiac resynchronization therapy with defibrillator; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

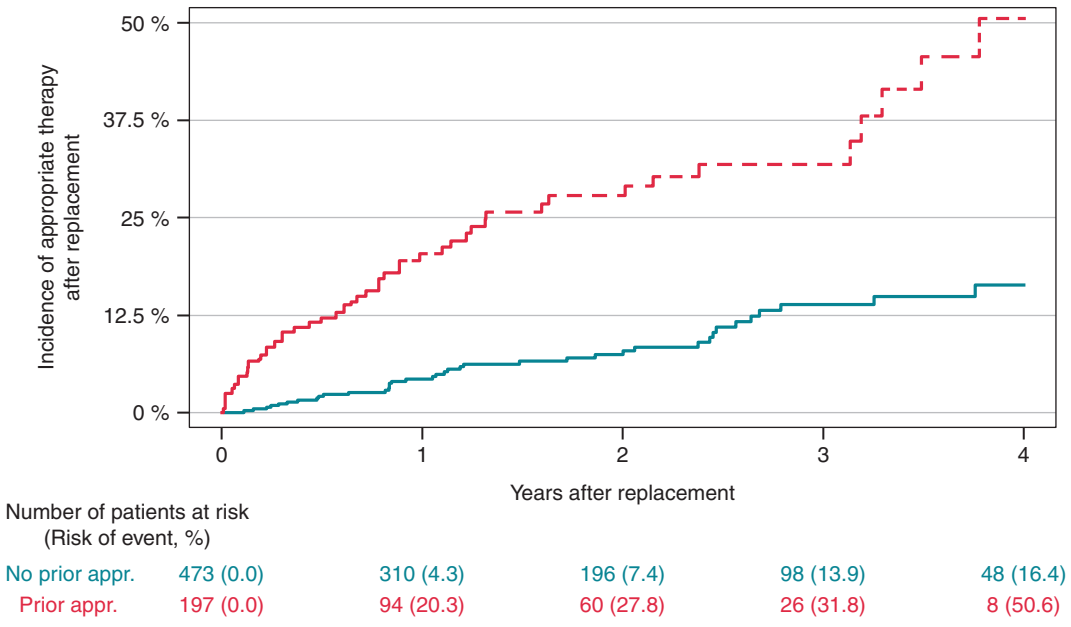

Figure 2 Appropriate ICD therapy after generator replacement. Cumulative incidence graph. Incidence of appropriate ICD therapy after generator replacement stratified by appropriate ICD therapy in the first generator period. ICD, implantable cardioverter-defibrillator.

when evaluating very small groups of patients such as those above the age of 80, with initial implant LVEF >25% and no prior appropriate therapy zero patients out of 17 (0%) had an appropriate ICD therapy but with a mean follow-up specifically for these patients of only 1.33 ± 0.98 years. Patients at particular high risk of an appropriate ICD therapy after generator replacement were patients with LVEF ≤25% at the initial implant who had experienced appropriate ICD therapy in the 1st generator period; 38 out of 138 (27.5%) (*Figure 3*).

Mortality after generator replacement and influence of non-cardiac comorbidity burden

A total of 170 (25.4%) deaths occurred during follow-up of which 130 (76.5%) did not receive any appropriate ICD therapy before death after generator replacement. A total of 93 (54.7% of deaths) patients who survived to generator replacement died without ever having an appropriate therapy in *any* of the generator periods. A total

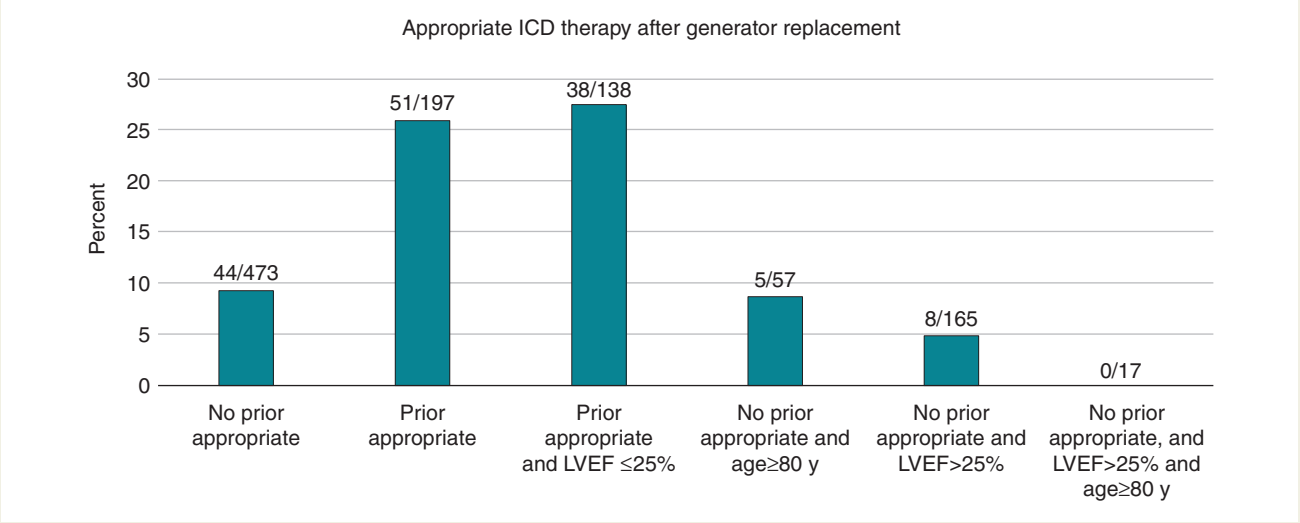

Figure 3 Appropriate ICD therapy after generator replacement. Bar graph showing percentages of patients with appropriate ICD therapy after generator replacement according to clinical status at time of replacement. ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction.

Table 3 Multivariate adjusted Cox regression analyses of the outcome of all-cause mortality and appropriate therapy by increasing non-cardiac comorbidity burden

	All-cause mortality					Appropriate therapy				
Non-cardiac comorbidities	**Events/patients**	**Rate**	**Hazard ratio**	**95% CI**	***P*-value**	**Events/ patients**	**Rate**	**Hazard ratio**	**95% CI**	***P*-value**
0	33/234	14.1%	Ref			40/234	17.1%	Ref		
1	72/267	27.0%	1.95	1.27–2.99	0.002	34/267	12.7%	0.99	0.61–1.60	0.952
2	28/97	28.9%	2.77	1.65–4.66	<0.001	13/97	13.7%	1.12	0.59–2.15	0.724
≥3	37/72	51.4%	5.27	3.19–8.70	<0.001	8/72	11.1%	1.15	0.52–2.57	0.725

Adjusted for appropriate ICD therapy in first generator, age, sex, ischaemic cardiomyopathy, treatment with CRT, atrial fibrillation, previous myocardial infarction, left ventricular ejection fraction ≤25%, hospitalization for heart failure within recent year.
CI, confidence interval; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator.

of 62 (27.0%) of the patients died within the first year after replacement. Non-cardiac comorbidities were significantly associated with mortality and mortality without prior appropriate therapy in a stepwise manner (*Table 3* and *Figure 4*). High all-cause mortality rates were found showing 1-, 2-, and 4-year mortality of 36%, 56%, and 73%, respectively among those with ≥3 non-cardiac comorbidities. We found that the cumulative number of non-cardiac comorbidities (i.e. burden) highly influenced and reduced the 'device utilization'. *Figure 5* shows estimated device utilization among those who died or received appropriate therapy in the 2nd generator period stratified by appropriate ICD therapy in the 1st generator period. It shows a significant association between increasing burden of non-cardiac comorbidities and decreasing device utilization. In patients without appropriate therapy in the 1st generator period, up to 83% of the patients died without having utilized their device at any time (1st and 2nd generators). In contrast, among patients with appropriate ICD therapy in the 1st generator period and low non-cardiac comorbidity burden, up to 73% received at least one appropriate ICD therapy prior to death in the 2nd generator period.

When we performed sensitivity analyses excluding patients with less than 1-year follow-up we did not see a significant change of results in terms of prediction of appropriate therapy variables and the influence of appropriate therapy in the 1st generator period. The risk estimates were similar with wider CIs. Among all patients receiving an appropriate therapy, only 6% were affected in the first year. In contrast, 27% of the patients died within the first year.

Discussion

We present prospectively recorded data from a nationwide contemporary cohort of ICD patients implanted for primary prevention who survived to receive their 2nd generator. Our primary findings were a significant residual risk of appropriate ICD therapy in the 2nd

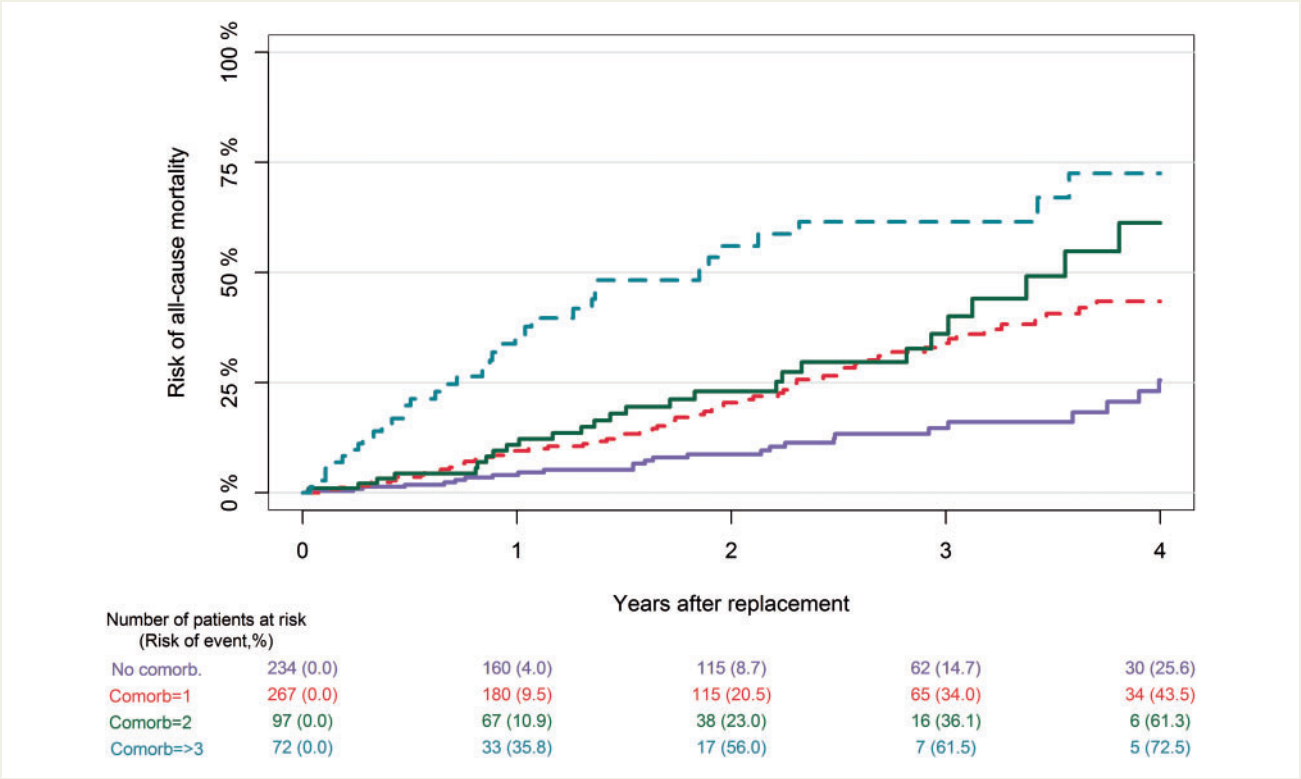

Figure 4 All-cause mortality after generator replacement. Kaplan–Meier graph. Incidence of all-cause mortality after generator replacement stratified by non-cardiac comorbidity burden at time of generator replacement.

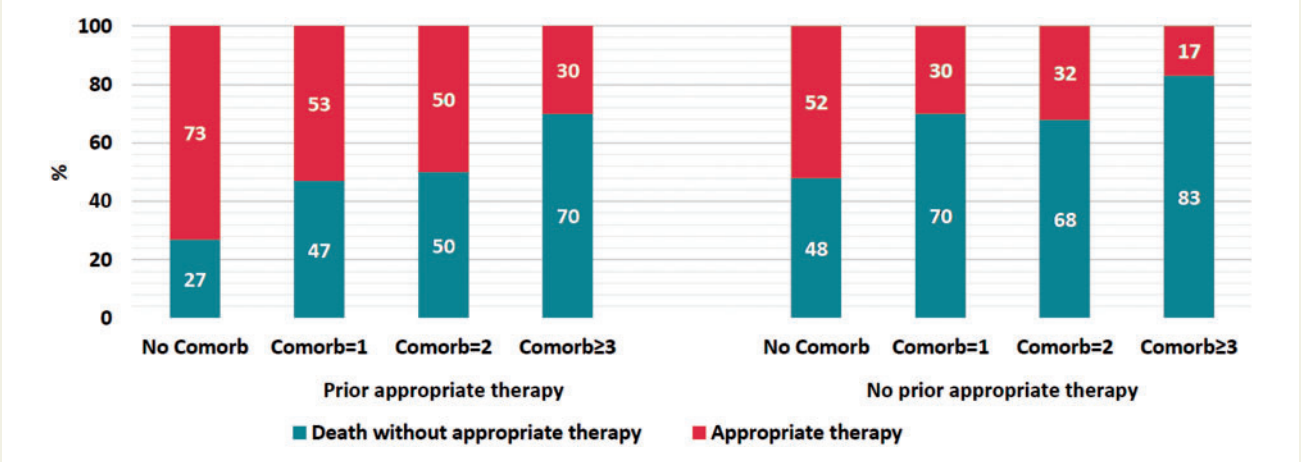

Figure 5 Device utilization. Bar graph showing the percentage of patients who either died without appropriate ICD therapy (black) or experienced appropriate ICD therapy (green) after generator replacement stratified by appropriate ICD therapy in the first generator period (i.e. prior appropriate therapy) and grouped by non-cardiac comorbidity burden. ICD, implantable cardioverter-defibrillator.

generator life, during which history of appropriate ICD therapy in the 1st generator period and low LVEF at initial implant were highly predictive of appropriate ICD therapy in the 2nd generator period. We were not able to identify a subgroup of patients with an obvious very low risk of appropriate therapy. We found that non-cardiac comorbidity burden was associated with reduced appropriate device utilization prior to death.

No randomized studies exist on the benefit of generator replacement on SCD and no studies have evaluated cost benefit. Discussions on benefits and risks of generator replacement in

primary prevention ICD patients should consider appropriate ICD therapy delivered by the 1st generator, LVEF at time of replacement, influence of comorbidity burden, and the competing risk of death in patients with advanced age.

Compared with patients undergoing their 1st ICD implantation (in trials and in real-life), those who receive replacement are generally older with shorter life expectancy, have more non-cardiac comorbidities and more advanced cardiac disease. On the other hand, those who were too sick with a high mortality risk have already died in the 1st generator period and in a sense those who receive a 2nd generator are a healthy survivor group *per se*. Here, we discuss the influence of LVEF, prior ventricular arrhythmias and the influence of comorbidities and advanced age. Unfortunately, in the present study, we only had information on LVEF at the time of generator replacement in a minority of the patients.

Low LVEF is a well-known risk factor for appropriate therapy. Several retrospective smaller studies have reported on appropriate ICD therapy after generator replacement in cohorts of both primary and secondary prevention or primary alone ICDs with improved LVEF (number of patients included ranging from 93 to 1421).[5,7,8,11–13] One retrospective study by Kini *et al*. found that among 231 patients undergoing primary prevention ICD (and CRT-D) generator replacement from 2006 to 2013, 26% of the patients no longer had ICD indication on the basis of LVEF improvement to ≥40% without any appropriate therapy in the 1st generator period. On an average of 3.5 years of follow-up the annual rate of appropriate ICD therapy was 10.7% vs. 2.3% in those with and without continuous ICD indication. Similarly, Witt *et al*.[8] recently retrospectively investigated a mixed cohort of primary and secondary prevention ICDs (and CRT-Ds) in the period 2001–2011 and found that 25% had LVEF >35% at time of generator replacement. In the primary prevention ICD patients without prior ICD therapy those with improvement in LVEF had significantly lower 1-year incidence of appropriate therapy (2.6%) than those with no improvement (7.0%). Importantly, this study included secondary prevention ICD patients ($n = 654$) and replacements due to infection and malfunctions ($n = 262$). Patients which in most cases may not be representative for the elective clinical decision-making of whether or not to replace an ICD, since the majority of these patients require replacement anyway. Lower risk of appropriate therapy in patients with LVEF recovery has also been shown in primary prevention ICD and CRT-D patients who did not undergo replacement but had paired LVEF assessments at implantation and at a later time in follow-up.[4,9,14] In aggregate, all studies report some degree of residual ventricular tachyarrhythmia triggering device therapy among patients with LVEF recovery to more than 35%. Complete LVEF recovery >50% was however associated with a very low risk of ventricular tachyarrhythmias faster than 200 b.p.m. or appropriate shock among CRT-D patients in a sub-study of MADIT-CRT.[4] In addition to the myocardial substrate, scar involvement and LVEF estimation at the time of generator replacement the presence or absence of appropriate ICD therapies in the first battery life is important.

The largest report is from the Latitude Registry where 24 203 ICD patients on remote monitoring (not a clinical database) had generator replacement. They found that the cumulative incidence of ICD shocks was significantly lower among those without appropriate therapy in the 1st generator period, however not negligible (9.2% vs. 24.3%).[15] In a small study of 154 primary prevention ICD patients at time of generator replacement it was found that 14% of the patients experienced appropriate therapy after an uneventful 1st generator period.[16] Similarly, Yap *et al*.[3] found a 3-year incidence of appropriate therapy of 13.7% among 206 primary prevention ICD patients after generator replacements with uneventful 1st generator period.

Our findings confirm that approximately two-thirds undergo generator replacement with no prior appropriate therapy and experience an annual rate of appropriate ICD therapy of approximately 5%, while those who have experienced appropriate therapy in the 1st period have an annual rate of 10–20%. Collectively, the findings support a lower risk of appropriate therapy with improved LVEF and no prior appropriate therapy but a residual annual rate of appropriate therapy of 2–5% despite these conditions. The rate of SCD in the general population of approximately the same age has been estimated to be 0.8–1.0%/year.[17] Although rate of SCD increases with age, the proportion of deaths that are sudden is much larger in the younger age groups. Improved medical therapy, early revascularization and management of heart failure has furthermore significantly reduced the rate of SCD.[18,19] Inarguably, the rate of appropriate ICD therapies does however not translate into rate of aborted SCD. Since many of appropriate therapies are unnecessary and the ventricular arrhythmias could have been self-limiting without intervention from the device; thus, one appropriate therapy does not equal one saved life.[20]

One quarter of the patients died during follow-up reflecting the high age and comorbidity burden at time of generator replacement which is comparable to before mentioned studies.[8] Previous studies have shown reduced efficacy of the ICD associated with increased comorbidity and the ratio of non-arrhythmic death to SCD increases among patients with advanced age.[21] Our data are supportive of this and suggest that non-arrhythmic death increases markedly, while utilization of the ICD after generator replacement decreases markedly to a very low level with increasing non-cardiac comorbidity burden and age.

If risk stratification tools existed to discriminate between patients at high and low risk of future appropriate ICD therapy at time of generator replacement, issues including inappropriate shocks and complication risks of ICD replacement could be more carefully discussed with patients prior to replacement with estimates of benefits and risks. Indeed, questions still remain about how to proceed in patients who reach end of battery life in the categories of advanced age, those with many non-cardiac comorbidities, where no appropriate ICD therapy has even been delivered, and in particular in those where LVEF improved. Al-Khatib *et al*.[22] suggested an algorithm for CRT-D replacement where downgrade from CRT-D to CRT with pacemaker could be advised after counselling the patients of pros and cons among those who had no prior ICD therapy and who had normalized the LVEF to ≥45%. The algorithm was based on a meta-analysis[9] investigating the risk of ventricular arrhythmias after CRT-D implantation, where this cut-off of LVEF appeared to be associated with markedly low risk of ventricular arrhythmias. This meta-analysis was conducted on six retrospective studies involving 1740 patients.

To summarize, future clinical trials should randomize ICD replacement vs. no replacement at the time of battery depletion if LVEF > 35% and no appropriate therapy has been yielded. Until clinical trials are available, physicians should consider factors of advanced age, non-cardiac comorbidity burden, LVEF recovery, and in

particular ICD therapy in the 1st generator period in order to guide the optimal shared decision-making with the patient.

Limitations

The results from this study are based on data from a prospective registry but were retrospectively analysed and is hypothesis generating. The reported associations may be prone to unmeasured confounding. Our data on LVEF at generator replacement are only available on 133 patients and therefore analysis specifically on LVEF improvement has been omitted. Appropriate therapy may be underreported and misinterpreted by the physician and technician reporting the data to the DPIR. Use of appropriate adjudication by a core lab or expert committee would have increased the likelihood of correct interpretation. In the DPIR we do not have information on ICD therapy programming or changes in programming. The patients in the current analysis are all patients who undergo elective generator change as scheduled and planned by the implanting physicians. It is unknown whether some of these patients were selected due to a perceived higher risk for later appropriate therapy. Furthermore, patients with deteriorated clinical conditions that were not candidates for generator change are also not included. These two points could represent possible selection-bias. Lastly, we included elective upgrades to CRT-D at time of generator change in the present analysis, which may cause some confounding since these patients are not readily comparable to ICD only patients.

Conclusion

In this nationwide real-life cohort of primary prevention ICD patients, we observed a significant residual risk of appropriate ICD therapy in their 2nd generator life even among patients with advanced age and with a full prior generator period without any appropriate ICD events. Besides LVEF and prior ICD therapy, comorbidity burden, advanced age, and high competing risk of non-cardiac death should be considered when deciding whether to replace ICDs.

Supplementary material

Supplementary material is available at *Europace* online.

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