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Clinical practice of defibrillator implantation after myocardial infarction: impact of implant time: results from the PreSCD II Registry†

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Aims Current guidelines recommend implantable cardioverter-defibrillator (ICD) therapy for primary prevention of sudden cardiac death in patients with the reduced left ventricular function (LVEF $\leq$30%) not earlier than 40 days after myocardial infarction (MI). The aim of the prospective Prevention of Sudden Cardiac Death II (PreSCD II) registry was to investigate the clinical practice of ICD therapy in post-MI patients and to assess the impact on survival.

Methods and results 10 612 consecutive patients (61 $\pm$ 12 years, 76% male) were enrolled 4 weeks or later after MI in 19 cardiac rehabilitation centres in Germany from December 2002 to May 2005. All patients with left ventricular ejection fraction (LVEF) $\leq$40% ($n = 952$) together with a randomly selected group of patients with preserved left ventricular function ($n = 1106$) were followed for 36 months. Cox proportional hazard models were used to correlate ICD implantation and survival with baseline characteristics. Of all patients studied, 75.9% were enrolled within 4–8 weeks, 10.7% more than 1 year after MI. Pre-specified Group 1 with an LVEF $\leq$30% consisted of 269 patients (2.5%), Group 2 with LVEF 31–40% of 727 patients (6.9%), and Group 3 with LVEF $>$40% of 1148 randomly selected patients from the cohort of 9616 patients with preserved LV function. After 36 months, only 142 patients (6.9%) had received an ICD; 82 (31.7%) of Group 1, 49 (7%) of Group 2, and 11 (1%) in Group 3. The ICD was implanted in 47% of all patients within 1 year after their index MI. Implantable cardioverter-defibrillator patients were predominantly characterized by low ejection fraction, but also by several other independent risk factors. Patients who received an ICD had an adjusted 44% lower mortality (hazard ratio 0.56, 95% confidence intervals 0.32–1.01; $P = 0.053$) than comparable patients without ICD therapy. All cause mortality of ICD recipients was significantly lower if the ICD was implanted later than 11 months after acute MI ($P < 0.001$).

Conclusions The PreSCD II registry demonstrated that the number of patients who develop a low LVEF ($\leq$30%) after acute MI is small. However, only few patients with guideline-based ICD indication received ICD therapy. All cause mortality was significantly reduced only if the ICD was implanted late ($>$11 months) after MI.

Keywords Myocardial infarction • Sudden cardiac death • ICD therapy • Primary prevention • Time of implantation

† The participating investigators and Cardiac Rehabilitation Centers are listed in the appendix.

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Introduction

Survivors of myocardial infarction (MI) have an increased risk of sudden cardiac death (SCD), particularly those with reduced left ventricular function (LVEF $\leq$35%).[1–3] Randomized trials have demonstrated that implantation of an implantable cardioverter-defibrillator (ICD) for secondary as well as primary prevention of SCD reduces all-cause mortality.[4–9]

The most important risk parameter for all-cause mortality—as well as sudden arrhythmic death—is reduced left ventricular ejection fraction (LVEF $\leq$35%).[10,11] In the MADIT II trial, ICD therapy led to a 31% reduction of all-cause mortality in patients with LVEF $\leq$30% and remote MI.[7] These findings are supported by the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) in patients with ischaemic- but also non-ischaemic cardiomyopathy and additional heart failure with LVEF $\leq$35%.[9,10] The benefit of ICD therapy increased with time of ICD implantation after the index MI.[12]

Although sudden death mortality was significantly reduced in the DINAMIT trial,[8] ICD implantation within $<$40 days after acute MI did not reduce all-cause mortality. The reason for the importance of the time interval after MI is still unclear. Therefore, current guidelines recommend ICD therapy for primary prevention of SCD in patients with acute MI not earlier than 40 days after MI.[13–16]

Since ~two-thirds of patients who survived a MI in Germany undergo 3–4 weeks of cardiac rehabilitation (CR) in a specialized inpatient centre,[17] the aim of the prospective Prevention of Sudden Cardiac Death II (PreSCD II) registry in post-MI patients was to investigate the clinical characteristics and the selected therapeutic approach, particularly the practice of ICD implantation, in patients after MI, and to assess their long-term outcome.

Methods

Study population

Prevention of Sudden Cardiac Death II, a prospective multicentre registry, enrolled 10 612 patients after survival of an acute MI in 19 CR centres throughout Germany from December 2002 to May 2005. All patients had given written informed consent for the follow-up investigation.

Patients were eligible for enrolment if they had survived an acute MI with or without revascularization procedures, percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG) more than 1 month prior to enrolment. Patients were excluded if they had already received an ICD, if they were scheduled for coronary artery bypass or valve surgery, or if they were LV assist system dependent.

Baseline characteristics including patient history and physical status were determined at enrolment. The first follow-up visit was performed by the patient's physician 4 months after enrolment into the registry. Further follow-up visits were scheduled after 8, 12, 24, and 36 months. Follow-up information was censored 3 years after end of enrolment, 30 June 2008. Occurrence of death and potential ICD implantation were retrieved from the patient's physician or hospitals involved in treatment of the PreSCD II registry patients.

Based on the assessment of LVEF at least 4 weeks after their index MI by biplane echocardiography at the CR centre, patients were assigned to three specified groups (*Figure 1*). Group 1 comprises 269 patients (2.5%) with LVEF $\leq$30%, Group 2 of 727 patients (6.9%) with LVEF between 31 and 40%, and Group 3 of 1148 patients who were randomly selected from 9616 patients (90.6%) with LVEF $>$40% of the initially enrolled patients. For the remaining 8468 patients, only baseline characteristics were assessed without further follow-up.

At discharge from the CR centre, ICD implantation was discussed with patients and their caring physicians if they had a guideline-based indication for ICD therapy. Performed or denied ICD implantation, together with the reason for refused ICD implantation, was carefully documented.

Statistical analysis

Statistical analyses of baseline data and ICD therapy

All further analyses were based on the subpopulation of patients with follow-up information. Arithmetic means, standard deviations, and absolute and relative frequencies were used for the description of the total registry population according to LVEF groups and according to ICD implantation and compared using Cochran–Armitage trend tests or polynomial contrast tests (LVEF groups) or χ^2 or Mann–Whitney *U* tests (ICD vs. no ICD). Isolated missing values were replaced by imputed values that were calculated using a likelihood-based algorithm. For a comprehensive analysis of the profile of patients who received an ICD at any time within 36 months of follow-up, multiple Cox proportional hazard models were applied since some observations were censored. Starting with a set of candidate baseline covariates including in particular time from index MI in three classes as an anticipated potential source of bias (*Table 1*), model search was performed by backward selection. For the finally selected variables, adjusted hazard ratios (HR) for ICD implantation are reported along with 95% confidence intervals (CI) and *P*-values.

Statistical analyses of mortality data in the follow-up

All registry patients with complete baseline information and at least one complete follow-up visit were analysed by LVEF classes (Groups 1–3) with respect to death from any cause using Kaplan–Meier techniques and log-rank test. Follow-up times started from enrolment. To evaluate the differences between ICD patients and comparable non-ICD patients, a Cox proportional hazard model was applied with ICD implantation as a time-dependent covariate and further time-independent covariates that were selected backwards from the same set of candidate baseline covariates as they were used for analysis of ICD implantations (*Table 2*). Results are presented as Forest plots based on estimated HR and their confidence limits. Additionally reported *P*-values are derived from Wald coefficient tests.

Three additional analyses were performed: (i) in a pre-specified analysis, the ICD effect was studied separately for Group 1 and Group 2, i.e. a group with sufficient evidence from randomized trials and a group with potential ICD implant recommendation. We tested whether the distinction between the ICD effect in Group 1 and Group 2 significantly improved the model by applying a likelihood ratio test.

(ii) Since recent trial results (DINAMIT,[8] IRIS[18] indicate that ICD implantation early after acute MI may not be as beneficial as compared with later ICD implantation, the ICD benefit was studied depending on the time from MI to ICD implantation in a *post hoc* analysis. Because no suggested cut-offs were available from the literature, we started with a search for informative cut-offs by likelihood-based optimization of model fit. We only accepted cut-offs that significantly improved model fit. We present the results of the best fitting model. In this model, the time-dependent covariate is split into three covariate

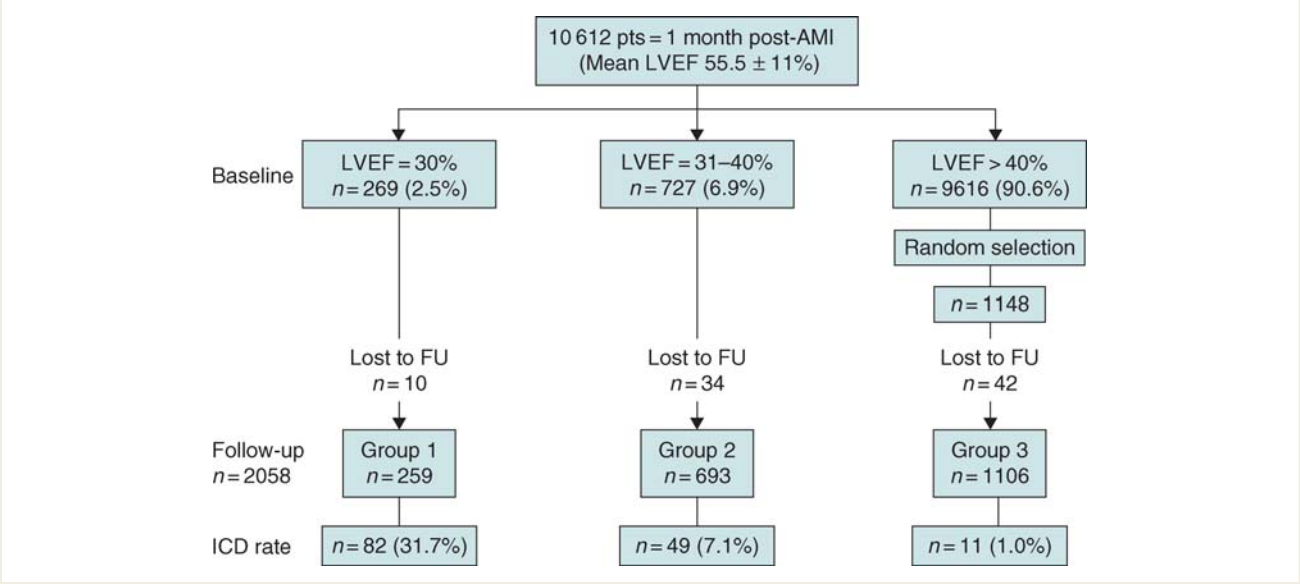

Figure 1 Flow chart of the PreSCD II registry.

according to whether the ICD implantation took place up to 3 months, between 4 and 11 months, or more than 11 months after inclusion to the registry.

(iii) At the time when the statistical analysis was designed, time from index MI to inclusion was assumed to be a relevant confounder or effect modifier. We thus performed a series of sensitivity analyses where we used different categorizations of time from index MI, performed a restricted analysis within the subgroup of recent MIs (<8 weeks) and, in the complete population, tested interaction terms of time from MI to inclusion and ICD implantation time to study the robustness of the presented results to changes in the statistical approach.

Data were gathered and managed by a clinical research organization (IKKF, Munich, Germany), using internet-based electronic case record forms. All analyses were performed by the independent study statistician using SAS version 9.1.3.

Results

The PreSCD II registry enrolled 10 612 patients within 30 months, mean age was 61 ± 12 years, 75.8% of all patients were males. Earliest time of enrolment was 4 weeks after index MI, and 77.4% of the total cohort was enrolled within 8 weeks after MI. However, 10.7% of the patients who also underwent CR for reasons other than a recent MI had their MI more than 1 year prior to enrolment. Approximately 90% of all patients had been revascularized by percutaneous coronary intervention (74.3%) and/or coronary artery bypass grafting (24.7%). The vast majority of patients (n = 9616; 90.6%) had preserved LVEF >40%, whereas 727 patients (6.9%) had moderately impaired LV function (LVEF 31–40%), and only 269 patients (2.5%) had severely reduced LV function ≤30% (*Figure 1*).

Of the 2144 patients in the pre-specified three groups who were scheduled for a long-term follow-up, 86 patients (4%) were either lost to follow-up prior to the first follow-up visit 4 months after CR or refused a further follow-up. Therefore, a total of 2058 patients remained for 36 months long-term follow-up. These were 259 patients in Group 1 (LVEF ≤30%), 693 patients in Group 2 (LVEF 31–40%), and 1106 patients in Group 3 who were randomly selected from patients who had a more preserved LV function at the time of enrolment. Patients with low ejection fraction differ substantially from patients with better ejection fractions. They are more frequently male, older, have less weight and less recent MIs and are more severely ill in almost any regard. There was no difference of baseline medical treatment between the three groups [beta-blockers (94%), angiotensin-converting enzyme-inhibitors/angiotensin receptor blocker (93%), or statins 96%)]. Patient follow-up was scheduled for 36 months after discharge from CR. Baseline characteristics of the 2058 patients are presented by LVEF groups in *Table 1*.

Implantable cardioverter-defibrillator therapy

The clinical characteristics of patients with (*n* = 142) or without (*n* = 1916) ICD therapy are displayed in *Table 2*. Of the patients who received an ICD, 82 patients (58%) were in Group 1, 49 patients (34%) in Group 2, and 11patients (8%) in Group 3. Patients who were enrolled within 8 weeks after their acute index MI had relatively less ICD implantation rates (5.5%) than those 15% in patients who were enrolled but had a more remote MI event.

The PreSCD II registry predominantly enrolled patients early after their index MI, however, in the majority of cases, the ICD was not implanted within the early phase of MI. Patients enrolled within 8 weeks after MI received an ICD a mean of 307 days after acute MI, patients who had a remote MI at the time of enrolment a mean of 249 days after their MI. Of all 142 patients with ICD implants, 8% received the device within 8 weeks, 32% within 6 months, 47% within 12 months, and 59% within 24 months.

The result of a multivariate analysis of the impact of patient characteristics on ICD implantation is depicted in *Figure 2*.

Table 1 Patient characteristics of 2058 patients according to EF subgroups with a 36-months follow-up in the PreSCD II registry

	Group 1 LVEF≤30% ($n = 259$)	Group 2, LVEF 31–40% ($n = 693$)	Group 3, LVEF>40%, ($n = 1106$)	P_{Trend}
Male (%)	208 (80.31)	550 (79.37)	797 (72.06)	<0.001
Age mean ± SD (years)	65.2 (11.3)	63.9 (11.4)	60.8 (11.8)	<0.001
BMI				
BMI≤25 kg/m^2 (%)	115 (44.4)	245 (35.4)	297 (26.9)	<0.001
BMI>30 kg/m^2 (%)	40 (15.4)	168 (24.2)	272 (24.6)	0.011
Time from index MI				
≤8 weeks (%)	134 (51.7)	470 (67.8)	861 (77.9)	<0.001
8 weeks–1 year (%)	63 (24.3)	121 (17.5)	136 (12.3)	<0.001
>1 year (%)	62 (23.9)	102 (14.7)	109 (9.9)	<0.001
Multiple infarctions (%)	58 (22.4)	122 (17.6)	91 (8.23)	<0.001
Revascularization				
PCI (%)	153 (59.1)	450 (65.1)	826 (74.7)	<0.001
CABG (%)	119 (46.0)	262 (37.8)	255 (23.1)	<0.001
Patient history during acute MI				
Cardiac arrest (%)	16 (6.2)	26 (3.8)	23 (2.1)	<0.001
VT/VF (%)	12 (4.6)	12 (1.7)	14 (1.3)	0.002
Syncope (%)	20 (8.2)	21 (3.2)	23 (2.2)	<0.001
Pacemaker implantation (%)	16 (6.2)	26 (3.8)	17 (1.5)	<0.001
Co-morbidities				
Hypertension (%)	192 (74.1)	507 (73.2)	820 (74.1)	0.840
Diabetes mellitus (%)	97 (37.5)	212 (30.6)	268 (24.2)	<0.001
Renal failure (%)	38 (14.7)	69 (10.0)	60 (5.4)	<0.001
LV ejection fraction				
Mean LVEF ± SD (%)	26.3 (4.0)	37.2 (2.7)	57.9 (8.9)	<0.001
Heart failure				
NYHA I/II (%)	165 (63.7)	612 (88.3)	1089 (98.5)	<0.001
NYHA III/IV (%)	94 (36.3)	81 (11.7)	17 (1.5)	
ECG				
Sinus rhythm (%)	231 (89.2)	647 (93.4)	1074 (97.1)	<0.001
Atrial fibrillation (%)	28 (10.8)	46 (4.6)	32 (2.9)	<0.001
PQ interval. mean ± SD (ms)	172.4 (47.6)	156.3 (48.5)	158.2 (36.7)	<0.001
QRS duration >120 ms (%)	66 (26.8)	82 (12.1)	36 (3.3)	<0.001
Left bundle branch block (%)	77 (29.7)	83 (12.0)	32 (2.9)	<0.001
Non-sustained VT (%)	40 (17.5)	73 (12.8)	58 (6.6)	<0.001
Drug therapy				
Beta-blocker (%)	240 (92.7)	651 (93.9)	1051 (95.0)	0.110
ACE/ARB (%)	248 (95.8)	664 (95.8)	1009 (91.2)	<0.001
Statins (%)	244 (94.2)	665 (95.7)	1068 (96.6)	0.095
Antiarrhythmic drugs (III) (%)	34 (13.1)	50 (7.2)	33 (3.0)	<0.001

VT/VF, ventricular tachycardia/ventricular fibrillation

According to the final model that contains only independent significant predictors, the physician's decision to implant an ICD was primarily influenced by the severity of left ventricular dysfunction. Patients in Group 1 had a 31-fold and in Group 2 a 6-fold probability compared with Group 3 to receive an ICD ($P <$ 0.001). Other factors favouring ICD implantation were multiple MI, increased resting heart rate, occurrence of non-sustained ventricular tachycardia, QRS duration >120 ms, syncope events, anti-arrhythmic drug treatment (mostly Class III anti-arrhythmic drugs), and an index MI of more than 1 year prior to enrolment into the PreSCD II registry. The likelihood of receiving an ICD was reduced with higher patient age.

All-cause mortality

Forty-one (2.0%) of 2058 patients available for mortality analysis were censored before Month 36 because of loss-to-follow-up,

Table 2 Characteristics of patients with and without ICD implantation

Variable	No ICD ($n = 1916$)	ICD ($n = 142$)	*P*-value
Male, *n* (%)	1436 (75.0)	119 (83.8)	0.018
Age, mean SD (years)	62.5 ± 11.8	60.3 ± 10.5	0.030
BMI			0.010
<25 kg/m^2 (%)	596 (31.1)	61 (43.0)	
≥30 kg/m^2 (%)	456 (23.8)	24 (16.9)	
Time from index MI			<0.001
≤8 weeks (%)	1385 (72.3)	80 (56.3)	
8 weeks–1 year (%)	299 (15.6)	21 (14.8)	
>1 year (%)	232 (12.1)	41 (28.9)	
Multiple MI (%)	233 (12.2)	38 (26.8)	<0.001
LV ejection fraction			<0.001
≤30 (%)	177 (9.2)	82 (57.8)	
31–40 (%)	644 (33.6)	49 (34.5)	
>40 (%)	1095 (57.2)	11 (7.8)	
NYHA Class			<0.001
II (%)	737 (38.5)	67 (47.2)	
III/IV (%)	147 (7.7)	45 (31.7)	
Co-morbidity			
Hypertension (%)	1422 (74.2)	97 (68.3)	0.122
Diabetes mellitus (%)	536 (28.0)	41 (28.9)	0.818
Renal failure (%)	148 (7.7)	19 (13.4)	0.017
Syncope (%)	55 (2.9)	14 (9.9)	<0.001
ECG			
QRS duration >120 ms (%)	161 (8.4)	42 (29.6)	<0.001
Atrial fibrillation (%)	97 (5.1)	9 (6.3)	0.507
Non-sustained VT	1707 (9.9)	32 (22.5)	<0.001
Drug therapy			
Beta-blocker (%)	1811 (94.5)	131 (92.3)	0.259
ACE/ARB (%)	1785 (93.2)	136 (95.8)	0.228
Statins (%)	1839 (96.0)	138 (97.2)	0.477
Antiarrhythmic drugs (III) (%)	97 (5.1)	20 (14.1)	<0.001

All values are *n* (%), if not specified otherwise. *P*-values refer to comparison between the subgroups with or without ICD therapy.
BMI, body mass index; MI, myocardial infarction; NYHA, New York Heart Association; ECG, electrocardiogram; VT, ventricular tachycardia; ACE, angiotensin-converting enzyme-inhibitor; ARB, angiotensin receptor blocker.

but still entered the analysis with reduced observation time. During a total observation time of 6353-patient years, 237 patients died (1 per 27 patient years, 11.5% of the follow-up population). Three-year all-cause mortality estimated from Kaplan–Meier curves was 4.6% in Group 3, 16.4% in Group 2, and 20.2% in Group 1. In the subgroup of patients with recent MI (enrolment ≤8 weeks), the corresponding mortalities were 4.4, 15.9, and 22.5% (*Figure 3*). In both analyses, group differences were significant.

Cox regression modelling identified seven baseline covariates for survival. Severely or moderately reduced EF, higher age, low body mass index (BMI), renal failure, higher New York Heart Association (NYHA) class, and multiple MI were associated with an increased mortality (*Figure 4*).

Patients who received an ICD had a non-significant adjusted 44% reduction (HR 0.56, 95% CI 0.32–1.01; $P = 0.053$) of all-cause mortality compared with those with comparable baseline characteristics, but without ICD. Hazard ratio was 0.53 in Group 1 and 0.74 in Group 2. However, the distinction between Group 1 and Group 2 did not significantly improve the preceding model ($P = 0.542$).

The *post hoc* analysis of date of MI to ICD implantation time identified two cut-offs that improved the model significantly ($P < 0.001$): 90 days and 330 days. These cut-offs separate a time of 3 months of ICD implant after MI which demonstrates a non-significantly higher mortality than comparable patients who did not receive an ICD (HR 2.1, 95% CI 0.95–4.65; $P = 0.068$), a time period of 4–11 months after MI where ICD patients revealed a non-significant moderate reduction of mortality (HR 0.72, 95% CI 0.29–1.78; $P = 0.469$), and a subgroup of patients with ICD implantation more than 11 months after their index MI with a significantly reduced mortality (HR 0.14, 95% CI 0.03–0.56; $P = 0.006$; *Figure 4*). The analysis was robust if the number of covariates for adjustment was increased, in particular, if time from index MI to inclusion that was eliminated during the model search procedure was added again. For sensitivity analysis, the analysis was repeated in Group 1 only as well as in patients included within 8 weeks only. The time trend was the same, but due to the smaller number of ICD implantations and events, the CI were wider than in the analysis of the total follow-up population. There were no significant differences between groups with respect to time trend. If interaction terms of time from index MI to inclusion or of LVEF groups with ICD implantation times were tentatively added to the model, none of them was found to be significant, indicating that the presented results are robust with respect to changes in the patient selection or model assumptions.

Discussion

The PreSCD II registry demonstrated three important findings: first, the vast majority of the patients sent to CR centres had preserved left ventricular function. Only 9.7% of all patients had an ejection fraction of <40%. Secondly, <one-third of patients fulfilling the criteria for guideline-based ICD therapy received the device within 3 years after enrolment. Decision criteria for ICD implantation were in line with current ICD therapy recommendations. Thirdly, although the rate of ICD implantations was low within the follow-up of 36 months, a meaningful benefit with regard to all-cause mortality could only be demonstrated if ICD implantation was performed relatively late after acute MI, but not early after acute MI.

The registry included a large cohort of post-MI patients predominantly referred to CR centres within 4–8 weeks after an acute MI (9512 patients) and additional 1100 patients (10.7% of the total patient cohort) who were admitted for inpatient CR, although their index MI occurred more than 1 year prior to CR. Despite this relatively early enrolment, 68% of the PreSCD II patients received their ICD more than 6 months after MI. Hence, in this registry, ICD implantations occurred over a wide range of time

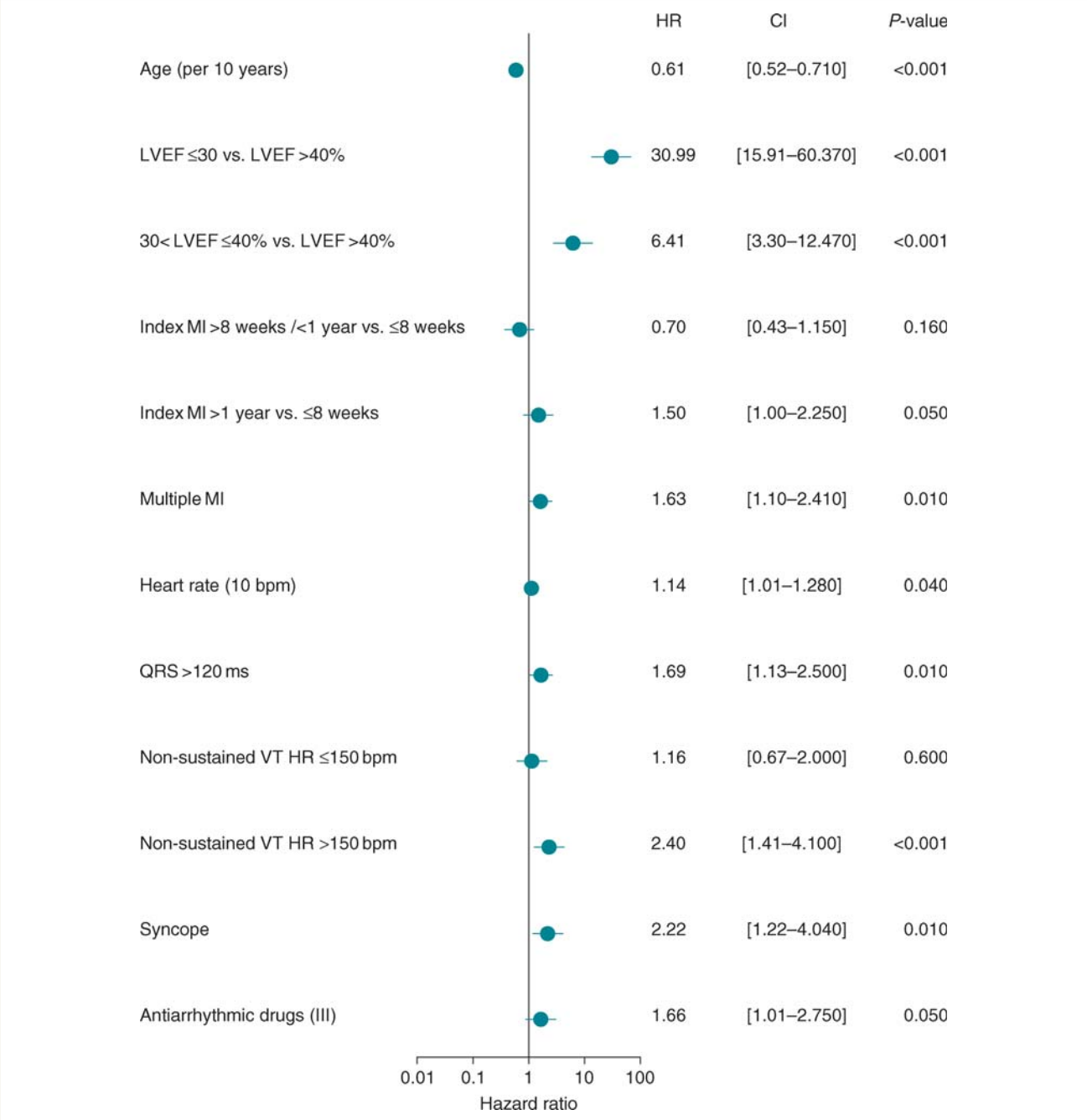

Figure 2 Effect of various patient and treatment characteristics on the probability of ICD implantation during 36-month follow-up of 2058 patients (hazard ratios).

intervals from study entry as well as from most recent MI, thus covering a range that links the patients enrolled in the IRIS[18] and DINAMIT[8] trial with the MADIT-II[7] cohort. The majority of the patients were enrolled later than those studied in the DINAMIT or IRIS trial—however, PreSCD II evaluated patients earlier than in MADIT II since in this trial only 12% of the patients were recruited within the first 6 months post-MI. This way, we can for the first time directly compare these populations in one database with a sufficient number of patients that fill the gap between the trials.

Compared with previous studies of patients after acute MI, the proportion of patients with severely reduced LVEF in the PreSCD II registry was smaller than expected. During the thrombolysis era of MI, 20% of all patients showed severely reduced ventricular function with an LVEF $\leq$30% after MI. Due to more often applied coronary revascularization, particularly with acute PCI more patients survive with preserved ventricular function.[19,20] In recent studies with primary PCI in acute MI patients revealed a severely reduced LVEF ($<$30%) in $<$5%.[20,21] Approximately 75% of the PreSCD II patients had PCI and/or CABG (25%).

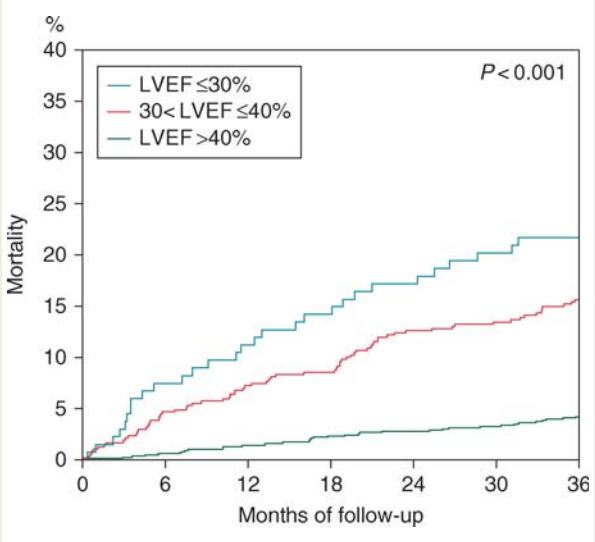

Figure 3 Kaplan–Meier estimate of all-cause mortality in the 36-months follow-up, divided by LVEF groups, restricted to recent myocardial infarctions (≤8 weeks at inclusion). The *P*-value results from a log-rank test.

Decision criteria for implantable cardioverter-defibrillator therapy

More than two-thirds of high-risk patients (LVEF ≤30%) eligible for ICD implantation did not receive ICD therapy after risk assessment during CR (*Figure 1*), although this variable had the greatest impact on the decision-making process of ICD implantation. Poor adherence to current ICD guidelines has been reported.[22,23] Several reasons may explain our findings.

When the PreSCD II registry was started in 2002, 9 months after the MADIT II results were published, guidelines recommended ICD implantation as a 'Class II a' indication.[13,15] This has changed since 2005 after the SCD-HeFT and DINAMIT trials had been published.[14,16] DINAMIT demonstrated that ICD implantation within 40 days after an acute MI in patients with LVEF ≤35% does not reduce all-cause mortality, although sudden arrhythmic death was significantly diminished.[8,16] Current recommendations exclude ICD implantation within this time frame after MI.[16] *Post hoc* analyses of MADIT II data indicate that the highest ICD benefit may be achieved in the chronic phase of MI e.g. more than 18 months after MI.[24] The rate of ICD implantation in the PreSCD II registry was significantly higher in patients with a remote MI (≥365 days).

Reasons for not implanting an ICD during the follow-up time of the registry in patients with severely reduced LV function were assessed. Denial of patients (29.2%) to receive an ICD or reluctance of their physicians to recommend ICD therapy (34.7%) was the main argument for not implanting an ICD, followed by patient's poor physical condition, short-life expectancy and advanced age (29.2%).

On the contrary, published data demonstrate that particularly patients with the combination of severely reduced LV function, older age, and more risk parameters including impaired renal function have significant benefit from ICD therapy.[10,11,25,26] Recent *post hoc* analyses have shown that post-MI patients with non-sustained ventricular tachycardia (VT), previous syncope, or prolonged QRS duration carry a very high risk of SCD.[27–31] With the exception of age, these risk parameters were also used for decision-making for ICD implantation in PreSCD II. Variables like multiple MI, QRS duration >120 ms, non-sustained VT, or syncope doubled the probability of ICD implantation.

Impact on mortality

Risk factors for increased mortality identified in our registry population by backward selection are well in line with observations in trials and other registries.[3,19,25,26,31–35] While increasing age, a severely or moderately reduced LVEF, high NYHA class, multiple MI, a QRS duration >150 ms, and renal failure go along with a two-fold increased mortality risk, ICD therapy showed a meaningfully diminished reduction of all-cause mortality in the registry cohort.

The overall adjusted HR for ICD therapy in PreSCD II was 0.56, and 0.53 in the subgroup of patients with LVEF ≤30%. However, the registry data failed to show a significant difference between patients with or without ICD implantation. A possible explanation may be the limited amount of ICD observation time due to the low ICD implantation rate. Although it is tempting to discuss the small difference between ICD effects in patients with LVEF ≤30% and LVEF 31–40%, it would be statistically incorrect because of the limited power of this analysis. The ICD benefit difference, however, was strong enough to allow a conclusion similar to those from other ICD trials after MI. According to our analysis, late ICD implantation ≥11 months after acute MI was beneficial concerning all-cause mortality, whereas ICD implantation within the first 3 months after MI may even be detrimental. Implantable cardioverter-defibrillator implantation between 4 and 10 months after MI did not demonstrate a clear advantage. The time shift in the benefit of ICD therapy was still present if the analysis was restricted to patients with LVEF ≤30%, or if other sets of covariates were applied. This robust result from 'real-life data' complements the observations from randomized trials. For the first time, the PreSCD II registry allows an empirical determination of potential cut-offs from a database that covers a broad range of possible time points for implantation.

Limitations

Several limitations have to be considered when interpreting the presented results. Prevention of Sudden Cardiac Death II is a registry and not a randomized clinical trial. A hidden bias and limited assessment of covariates may have confounded the comparisons. Particularly, bias by indication is a potential scenario since we may have failed to control all criteria which may have influenced the decision to implant ICDs. Although more than 10 000 post-MI patients were originally enrolled, the hypothesized number of ~600 patients with severely reduced LV function was not met, and the ICD implantation rate was less than expected. This resulted in a reduced power compared with well-accepted ICD trials. However, the power was sufficient to demonstrate the effect of known risk parameters and the importance of the time frame of ICD implantation. Another limitation of the

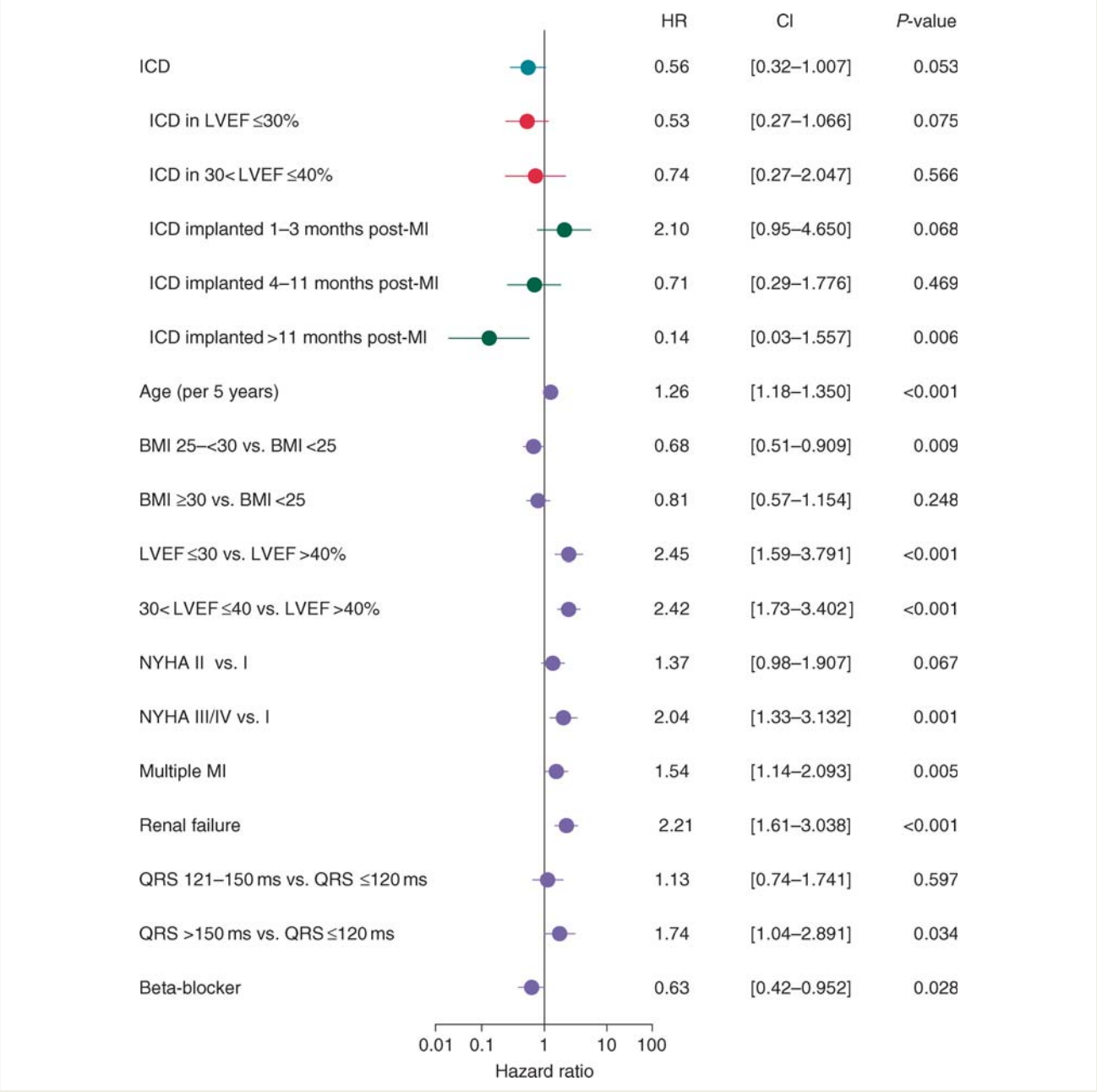

Figure 4 Effect of various patient and treatment characteristics on mortality during 36-month follow-up of 2058 patients.

PreSCD II registry is the lack of completeness of data acquisition, particularly the unknown mode of death of the registry patients during the follow-up time. No information was available about a potential improvement of left ventricular function during follow-up which may have influenced the decision not to implant an ICD.

It needs to be emphasized that the analysis of ICD implantation time represents a *post hoc* analysis. The selection of cut-offs had to be done data driven, resulting in an optimistic bias of unknown size. The results of our analyses are not solid enough to deduce any clinically meaningful recommendations concerning ICD implantation.[8,12,17] However, there were no substantial changes of the results in several sensitivity analyses with different methods of statistical control of potential sources of bias or within selected subgroups. Thus, based on our results, it seems justified to ask for more evidence on the dependency of the ICD benefit in mortality reduction on device implantation time, in particular, in the early phase up to 1 year after an acute MI.

Conclusion

The portion of post-MI patients admitted to CR centres with reduced left ventricular function who are eligible for ICD implantation was low in this registry. Less than one-third of high-risk post-MI patients received ICD therapy although they were

recommended in the guidelines for ICD therapy. However, Cox regression analysis on 3-years follow-up data of the PreSCD II registry demonstrates that the decision to implement ICD therapy into clinical practice was based on parameters that have been associated with a higher risk of all-cause mortality. Within 3 years of follow-up, the overall mortality of all enrolled patients was non-significantly lower with ICD therapy, although in a *post hoc* analysis a significant reduction of mortality over time could be observed depending on the time interval between index MI and ICD implantation.

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Conflict of interest: none declared.

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Appendix: The participating investigators and Cardiac Rehabilitation Centres are listed in the appendix

Centres: Klinik am See, Ruedersdorf, R.R., W.K. ($n = 2046$); Klinik Schwabenland, Isny-Neutrauchburg, Dr Boesch ($n = 1324$); Gollwitz-Meier-Klinik, Bad Oeynhausen, Dr R. Bertram ($n = 994$); Klinik Martinusquelle, Bad Lippspringe, Dr T. Ylinen ($n = 762$); Klinik Reha-Zentrum Bad Dueben, Dr Seifert ($n = 727$); Klinik Hoehenried, Bernried, Dr H.-P. Einwang ($n = 635$); Klinik der LVA Hessen, Bad Nauheim, Dr Thomas Kloster, ($n = 603$); KMG Klinik Silbermuehle, Plau am See, Dr F. Rohn ($n = 584$); Klinik Bad Gottleuba, Dr Ch. Altmann, ($n = 538$); Bayerwald-Klinik, Cham, Dr J. Straschewski ($n = 416$), Reha-Zentrum Spreewald, Burg, W.K., ($n = 406$); Klinik am Rennsteig, Tabarz, PD Dr A. Lauten ($n = 355$); Fachklinik Rhein-Ruhr, Essen, Dr St. Gronemeyer ($n = 313$); Klinik Koenigsfeld, Ennepetal, P. Krznaric ($n = 306$); Klinik Augustinum Ammermuehle, Rottenbuch, Dr H. Seidel ($n = 281$); Fachklinik Fuerstenhof, Bad Wildungen, H.-P. Terwersten ($n = 268$); Klinik Bergfried, Saalfeld, Dr G. Grohmann ($n = 230$); Frankenklinik, Bad Neustadt an der Saale, PD Dr K. Schroeder ($n = 89$); Rehabilitationszentrum Tatzmannsdorf, Dr H. Laimer ($n = 68$).

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Further we state: (i) the paper is not under consideration elsewhere; (ii) none of the paper's contents have been previously published; (iii) all authors have read and approved the manuscript; and (iv) the full disclosure of any potential relationship with industry (see 'Relationship with Industry Policy') is as follows: The registry was conducted in co-operation with the German Society of Cardiology (DGK) and the German Society for Prevention and Rehabilitation (DGPR) and was supported by a grant from Boston Scientific Medizintechnik GmbH, Germany. H.V. has received an unrestricted research grant and lecture fees from Boston Scientific. H.U.K. has received research grants and speaker fees from Boston Scientific. M.B. has received consultancy fees by Biotronik and Boston Scientific and speaker fees by Biotronik, Boston Scientific, Medtronic and Sorin. S.T. and K.C. are employees of Boston Scientific Corporation.

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