Implantable cardioverter defibrillator treatment : benefits and pitfalls in the currently indicated population

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Chapter 7

Prediction of Non-Benefit from Implantable Cardioverter Defibrillator Treatment in Primary Prevention Patients with Ischemic Heart Disease

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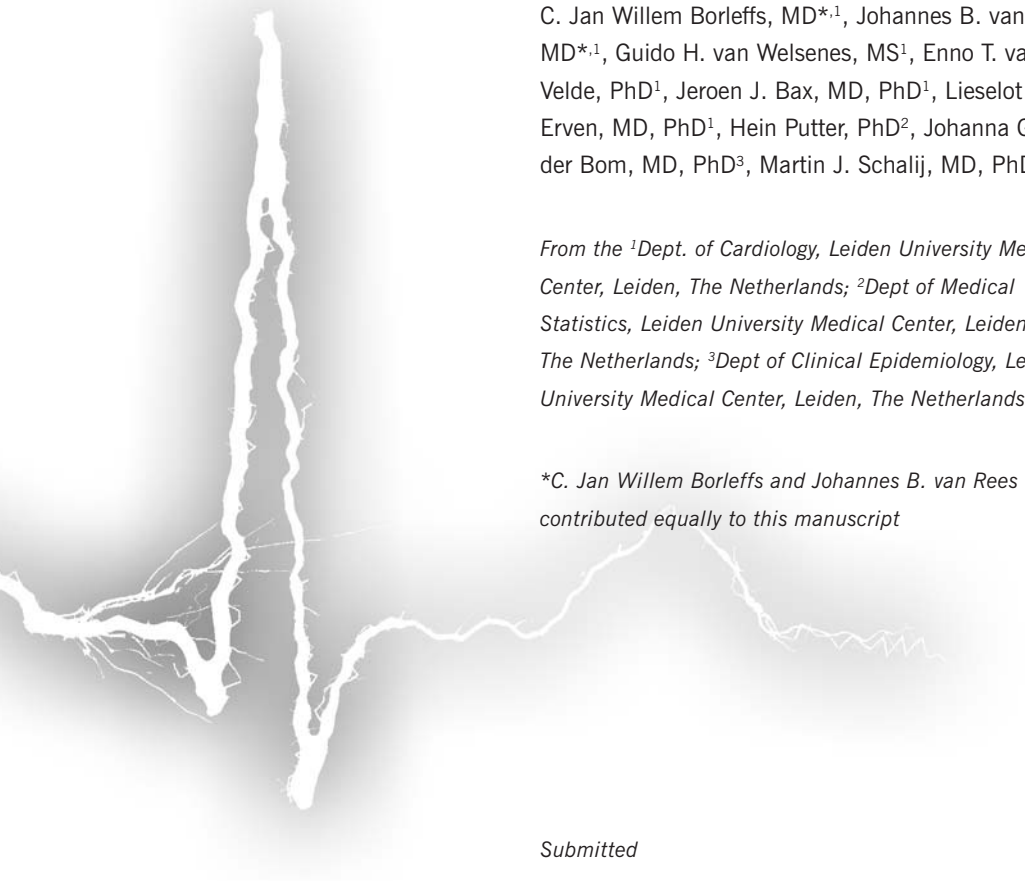


Submitted

Abstract

Context: Although the beneficial effect of implantable cardioverter defibrillator (ICD) therapy has been well established as primary prevention in a selected population at high risk for sudden arrhythmic death, a substantial part does not benefit from ICD treatment during long-term follow-up.

Objective: To assess the risk for non-benefit from ICD treatment in primary prevention ICD patients with ischemic heart disease

Design, setting and patients: Since 1996, all ICD recipients in the Leiden University Medical Center have been clinically assessed at implantation. For the current study, patients with ischemic heart disease and a primary indication for implantation have been included. During follow-up, all-cause mortality and device therapy (anti-tachycardia pacing or shock) were noted. Non-benefit was defined as death, prior to first appropriate ICD therapy. Out of baseline variables, a baseline risk score was constructed to estimate risk for non-benefit.

Results: Nine-hundred patients (87% men, mean age 64 ± 10 years) were included in the analysis. During a median follow-up of 669 days (interquartile range, 363 to 1322 days), 150 patients (17%) died and 191 (21%) patients received appropriate device therapy. A total of 114 (13%) patients were considered the non-benefit group. Stratification for non-benefit resulted in risk categorization of patients as low, intermediate or high-risk. Advanced age was the strongest predictor of non-benefit. Five-year cumulative incidence for non-benefit ranged from 12% (95%CI 5–18%) in low-risk patients to 49% (95%CI 38–60%) in high-risk patients.

Conclusions: The risk of non-benefit can be predicted in primary prevention ICD patients with ischemic heart disease. The use of a baseline risk score facilitates patient-tailored risk estimation.

Introduction

Large randomized trials have demonstrated that implantable cardioverter defibrillator (ICD) treatment is the treatment of choice for patients with prior life-threatening arrhythmias (secondary prevention)[1-3] and for selected patients at high risk for sudden cardiac death, regardless of prior arrhythmia (primary prevention).[4-7] Since implementation of primary prevention in the international guidelines, implantation rates have increased drastically to an estimated 275000 devices in 2008.[8,9] However, with the inclusion of primary prevention in the currently ICD indicated population, rates of appropriate therapy for ventricular arrhythmias have decreased to 35% during long-term follow-up in the second Multicenter Automatic Defibrillator Implantation Trial (MADIT-II) compared to 64% in secondary prevention patients.[1,10] Furthermore, clinicians have expressed concern that the number of patients needed to treat with a primary prevention ICD might be too high and that the population, eligible for primary prevention ICD treatment, is of such magnitude that provision of ICD therapy will strain financial resources and the pool of trained personnel.[11] In addition, ICD therapy is associated with adverse events such as pocket related infections and inappropriate shocks.[12] The relatively low actual need for defibrillator therapy during follow-up, combined with the associated adverse events and the incapability to implant all indicated patients, urges for refinement of the current selection criteria for ICD treatment. Therefore, it would be of interest to identify a population, currently receiving ICD treatment, not benefiting from ICD therapy (i.e. death prior to appropriate ICD therapy).

Since 1996, all patients receiving an ICD at the Leiden University Medical Center have been assessed and followed up. This thoroughly screened cohort provided an opportunity to identify ICD recipients who do not benefit from ICD treatment and to assess whether baseline parameters influence the risk of non-benefit. Finally, a clinically applicable risk model is constructed to aid clinicians in individual risk estimations for primary prevention ICD patients with ischemic heart disease.

Methods

Patients and study protocol

Since 1996, all patients who received an ICD at the Leiden University Medical Center were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Center, Leiden, the Netherlands). Characteristics at baseline, data of the implant procedure and of all follow-up visits were recorded. For the current analysis, patients with a primary indication for defibrillator implantation and ischemic heart disease were selected.

It should be noted that, due to evolving guidelines, eligibility for ICD implantation in this population might have changed over time.[13,14] Nonetheless, in the majority of patients, indication for an ICD was made in the presence of a depressed left ventricular ejection fraction (LVEF) with or without non sustained ventricular tachycardia.[8,13] Ischemic heart disease was defined as the presence of significant coronary artery disease (a diameter stenosis of at least 50% in at least one coronary artery).[15,16] Exclusion criteria for the current analysis consisted of congenital structural or monogenetic heart disease (associated with an increased risk of sudden arrhythmic death).

Clinical variables

All tested variables were collected at device implantation and defined and categorized according to literature or common practice. Age was categorized as <65 years, 65–74 years and ≥75 years; a history of non sustained ventricular tachycardia was defined as a run of 3 to 30 ventricular ectopic beats at a rate >120 beats per minute;[6] renal clearance was estimated with the formula of Cockroft-Gault and categorized in normal or stage 1 renal failure (>90 ml/min), stage 2 renal failure (60-90 ml/min), or stage 3-5 renal failure (<60 ml/min);[17] QRS duration was categorized as <100 ms, 100-130 ms, or >130 ms; LVEF was categorized as ≤25% or >25%;[18] Heart failure symptoms were categorized as mild (New York Heart Association (NYHA) functional class I-II) or as severe (NYHA functional class III-IV);[19] atrial fibrillation was defined as a history of atrial fibrillation as documented on ECG; a history of smoking was defined if a patient had a positive answer when asked for past or present smoking;[20] and body mass index was categorized as <30 kg/m^2 or ≥30 kg/m.[21]

Device implantation

All ICD systems used were implanted in the pectoral region. Used systems were manufactured by Biotronik (Berlin, Germany), Medtronic (Minneapolis, MN, United States), Boston Scientific (Natick, MA, United States, formerly CPI, Guidant [St. Paul, MN, United States]) and St. Jude Medical/Ventritex (St. Paul, MN, United States).

Defibrillators were programmed as follows: a ventricular arrhythmia monitor zone was programmed in all patients (150-188 bpm). Ventricular arrhythmias faster than 188 bpm were initially attempted to be terminated with two bursts of anti-tachycardia pacing (ATP) and, after continuation of the arrhythmia, with defibrillator shocks. In the case of a ventricular arrhythmia faster than 210 bpm, device shocks were the initial therapy. Settings were adapted, only when clinically indicated.

Follow-up

All patients were seen at the implanting center. Follow-up started at the time of implantation and lasted until death or last date of data acquisition (February 2009). Devices were

interrogated every three to six months or more frequent when clinically indicated. Printouts of device interrogations were checked for delivered therapy, which was classified as appropriate when occurring in response to ventricular tachycardia or ventricular fibrillation. Furthermore, all-cause mortality was noted. Patients without data on the past six months were considered lost to follow-up. As previously reported, non-benefit from ICD treatment was defined as death from any cause, prior to appropriate ICD therapy (ATP or shock).[22,23]

Statistical analysis

Continuous data are expressed as mean with standard deviation (SD) or median with 25th and 75th percentile where appropriate. Dichotomous data are presented as numbers and percentages. Baseline characteristics in the non-benefit group and the remaining study population were compared with the chi-square test and unpaired Student's *t*-test as appropriate. All-cause mortality, appropriate therapy and non-benefit were analyzed by method of Kaplan-Meier and evaluated using the log rank test.[24] In the calculation of the cumulative incidence of non-benefit, appropriate therapy was considered a censoring event.

Baseline medication was excluded from risk score construction, since this clinician driven variable could bias the results and impede reproducibility. All other baseline variables were entered as categorical variables. Initially, the variables were entered in univariate logistic regression models, with non-benefit from ICD treatment as only outcome. Variables with a *P*-value <.10 were further analyzed in a multivariate logistic regression model, using backward stepwise selection until all variables in the model reached a *P*-value <.25. Based on the variables' regression coefficient in this multivariate model, a risk stratification score was constructed by giving a base regression coefficient the value of one point on the risk score and giving all variables the associating score, according to their multiplication of this base regression coefficient and rounding it off to the nearest whole or half number. Subsequently, the patient specific values for the predictors in the score were summed to obtain a score for each patient. After the determination of the individual patient risk score, cut-offs were determined for a population at low, intermediate and high risk of non-benefit from ICD treatment. These cut-offs were chosen to optimize the discriminative effect of the model without reducing the sizes of the groups. For internal validation and to assess the stability of variable selection, bootstrap with 1000 resamples was used.[25] All analyses were performed with SPSS for Windows, version 14.0 (SPSS, Chicago, IL).

Results

Patient characteristics

From 1996 to 2008, 935 patients with ischemic heart disease underwent ICD implantation for primary prevention. Thirty-five (3.7%) patients were lost to follow-up. Median follow-up of the remaining 900 patients was 669 days (interquartile range, 363-1322 days).

Baseline characteristics are provided in Table 1. The majority of patients (mean age 64±10 years) were male (87%), had a depressed LVEF (29±11%) and wide QRS (125±33 ms). Beta blockers were used by 63% of the patients, sotalol by 12% and ACE inhibitors or AT antagonists by 85%.

Table 1. Baseline characteristics

	Ischemic (n=900)	Patients with missing data
Clinical parameters		
Male gender (%)	779 (87)	0
Age, mean (SD), years	64 (10)	0
median (interquartile range), years	66 (57-72)	
NYHA functional class		17 (2)
I	193 (21)	
II	352 (39)	
III	325 (36)	
IV	30 (3)	
History of nsVT (%)	221 (25)	0
Renal clearance, mean (SD), ml/min	78 (37)	53 (6)
QRS-duration, mean (SD), ms	125 (33)	10 (1)
LVEF, mean (SD), %	29 (11)	52 (6)
History of atrial fibrillation (%)	228 (25)	3 (0)
Diabetes (%)	227 (25)	36 (4)
History of smoking (%)	429 (48)	50 (6)
Body mass index, mean (SD), kg/m^2	27 (4)	54 (6)
Implantable cardioverter defibrillator		0
Single chamber (%)	40 (4)	
Dual chamber (%)	423 (47)	
Cardiac resynchronization therapy (%)	437 (49)	
Medication		0
Beta-blocker (%)	570 (63)	
Sotalol (%)	106 (12)	
ACE inhibitors / AT antagonist (%)	767 (85)	
Statins (%)	742 (82)	
Diuretics for CHF (%)	651 (72)	
Amiodarone (%)	126 (14)	

Abbreviations: ACE, angiotensin-converting enzyme; AT, angiotensin; LVEF, left ventricular ejection fraction; nsVT, non sustained ventricular tachycardia; NYHA, New York Heart Association.

Incidence of all-cause mortality and first appropriate ICD therapy

During follow-up, 150 patients (17%) died. Cumulative incidence of all-cause mortality in the study population was 7% (95%CI 6-9%) after one year, 19% (95%CI 16-23%) after three years and 27% (95%CI 22-31%) after five years. A total of 3638 episodes of ventricular arrhythmia, causing appropriate device therapy, were noted in 191 (21%) patients. These consisted of 3333 arrhythmia episodes being terminated by ATP in 128 (14%) patients and 298 episodes being terminated by ICD shocks in 100 (11%) patients. Cumulative incidence of first appropriate therapy in the study population was 12% (95%CI 10-15%) after one year, 26% (95%CI 22-30%) after three years and 39% (95%CI 34-44%) after five years follow-up. For first appropriate shock, the cumulative incidence was 6% (95%CI 4-8%) after one year, 13% (95%CI 10-16%) after three years and 21% (95%CI 16-26%) after five years.

Non-benefit from ICD treatment

During follow-up, 114 (13%) patients died without prior appropriate ICD treatment and were considered the non-benefit group. Cumulative incidence of death without prior ICD treatment was 7% (95%CI 6-8%) after one year, 18% (95%CI 15-22%) after three years and 24% (95%CI 21-27%) after 5 years.

Comparison of the non-benefit group with the remaining study population demonstrated that the non-benefit group was older, had higher NYHA functional class, worse renal function, longer QRS duration, lower LVEF, and more often a history of diabetes and smoking (Table 2). Subsequently, multivariate logistic modeling for the prediction of non-benefit from ICD treatment contained the following variables: (1) age (65-74 and ≥75 years), (2) diabetes, (3) LVEF ≤25%, (4) NYHA functional class III-IV and (5) a history of smoking. The strongest predictor of non-benefit from ICD treatment was age ≥75 years (odds ratio 2.95, 95%CI 1.7-5.1%) (Table 3). Bootstrap analysis demonstrated that age, diabetes, LVEF, NYHA and smoking were selected in 99, 99, 98 96, 97%, respectively.

For construction of the non-benefit prediction model, the following risk point cut-offs were used: (1) low risk (0-1.5 points); (2) intermediate risk (2-2.5 points); and (3) high risk (3-5.5 points). When extrapolated to the total study population, 371(41%) patients exhibited low risk of non-benefit, 323 (36%) patients intermediate risk and 206 (23%) patients high risk. Cumulative incidence of non-benefit after 5 years was 12% (95%CI 5-18%) in low risk patients, 22% (95%CI 12-32%) in intermediate risk patients and 49% (95%CI 38-60%) in high risk patients (Figure 1).

Table 2. Baseline characteristics of patients who do not benefit from ICD treatment versus the remaining study population.

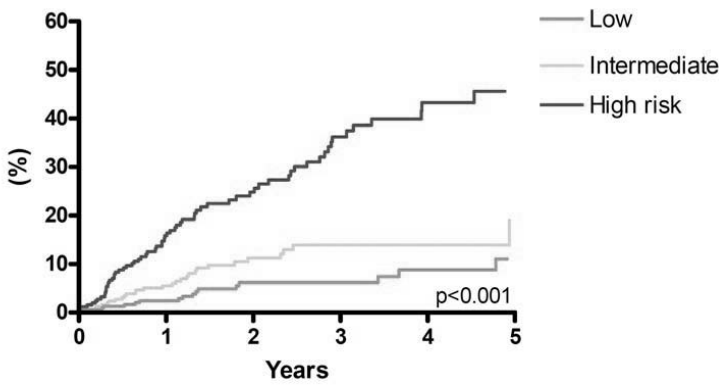
	Non-benefit group (n=114)	Remaining group (n=786)	*P*-value
Clinical parameters			
Male gender (%)	102 (90)	677 (86)	.33
Age			< .001
< 65 years (%)	41 (36)	386 (49)	
65 - 74 years (%)	40 (35)	286 (36)	
≥ 75 years (%)	33 (29)	114 (15)	
NYHA functional class			< .001
I or II (%)	45 (39)	500 (64)	
III or IV (%)	69 (61)	286 (36)	
History of nsVT (%)	25 (22)	196 (25)	.49
Renal failure			< .001
Stage 1 (> 90ml/min) (%)	15 (13)	262 (33)	
Stage 2 (60 – 90 ml/min) (%)	23 (20)	311 (40)	
Stage 3 (< 60 ml/min) (%)	76 (67)	213 (27)	
QRS-duration			.01
< 100 ms (%)	15 (13)	163 (21)	
100-130 ms (%)	42 (37)	344 (44)	
>130 ms (%)	57 (50)	279 (35)	
LVEF ≤ 25% (%)	66 (58)	280 (36)	< .001
History of atrial fibrillation (%)	35 (31)	193 (25)	.10
Diabetes (%)	46 (40)	181 (23)	< .001
History of smoking (%)	65 (57)	364 (46)	.03
Body mass index ≥ 30 kg/m^2 (%)	18 (16)	144 (18)	.31
Implantable cardioverter defibrillator			.003
Single chamber (%)	2 (5)	38 (2)	
Dual chamber (%)	40 (49)	383 (35)	
Cardiac resynchronization therapy (%)	72 (46)	365 (63)	

Abbreviations: LVEF, left ventricular ejection fraction; nsVT, non sustained ventricular tachycardia; NYHA, New York Heart Association.

Table 3. Multivariate logistic regression model and corresponding risk score for non-benefit from ICD treatment

	Regression coefficient	Odds ratio (95% CI)	*P*-value	Score
Age			< .001	
65 – 74 years	.26	1.30 (.81 – 2.10)	.28	.5
≥ 75 years	1.08	2.95 (1.69 – 5.14)	< .001	2
LVEF ≤ 25%	.76	2.13 (1.40 – 3.24)	< .001	1.5
Diabetes	.72	2.05 (1.33 – 3.15)	.001	1
NYHA functional class III-IV	.64	1.89 (1.23 – 2.90)	.003	1
History of smoking	.65	1.91 (1.25 – 2.94)	.004	1

Abbreviations: CI, confidence interval; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.



Patients at risk						
Low	317	225	138	95	57	33
Intermediate	325	206	118	64	39	17
High	258	155	93	60	34	19

Figure 1. Risk stratification for non-benefit. Kaplan-Meier curve for non-benefit in patients with low, intermediate or high risk

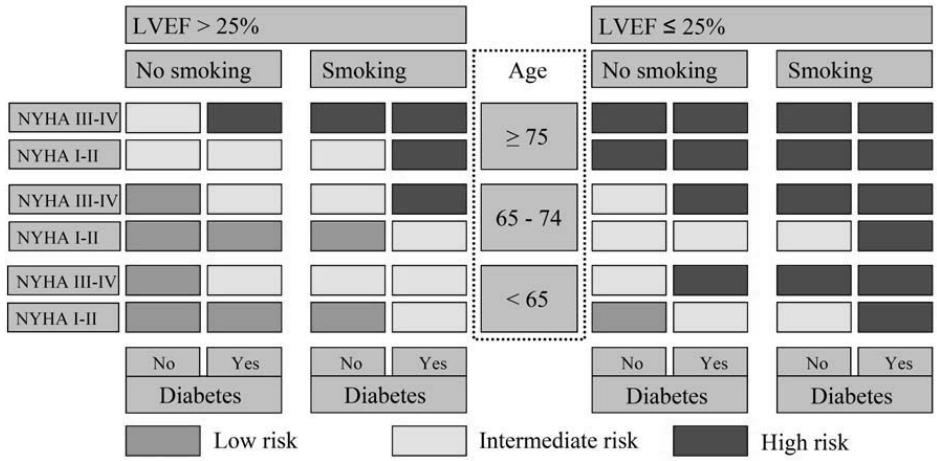
Comment

In the current study on the identification of primary prevention ICD patients with ischemic heart disease who do not benefit from ICD treatment, the findings can be summarized as follows: 1) Five-year cumulative incidence was 27% for all-cause mortality and 39% for first appropriate ICD therapy; 2) Five-year cumulative incidence of non-benefit was 24%; 3) Strongest predictor of non-benefit was advanced age; 4) Almost 50% of high risk patients did not benefit from ICD treatment after five years follow-up.

The current study adds to current literature in that it is the first to propose a risk model for the estimation of non-benefit in primary prevention ICD patients with ischemic heart disease.

Risk model application

When using the proposed risk score, patients with ischemic heart disease, considered for primary prevention ICD treatment, could be stratified as follows: 1) assess the patient's characteristics for the presence of variables, influencing risk for non-benefit; 2) use the scorecard to determine patient's risk as low, intermediate or high-risk for non-benefit from device treatment (Figure 2).



Abbreviations: LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Figure 2. Scorecard for risk of non-benefit from ICD treatment. By using patient's characteristics, the risk for non-benefit can be determined as low (green), intermediate (yellow) or high (red).

Drawbacks of ICD treatment

Large randomized trials have sufficiently shown the beneficial effect of ICDs in a large population at risk for sudden cardiac death and with the inclusion of primary prevention ICD treatment in the current international guidelines, worldwide implantation rates have increased 20-fold over the last 15 years.[9,14] Nevertheless, the utilization of ICD treatment does have a few serious drawbacks. Firstly, even when pursuing maximized patient safety, approximately 6% of ICD patients experience severe device-related adverse events.[26] Furthermore, currently the most debated issue in the validation of ICD treatment is the relatively low occurrence of ventricular arrhythmia, causing the need for defibrillator backup.[27] In the first trial on secondary prevention, ICD shocks occurred in over 60% of patients and follow-up studies clearly demonstrated the need for ICD treatment in this population.[1,16] However, more recent large trials on the value of primary prevention ICD treatment demonstrate significantly lower incidences of appropriate device therapy ranging from 21% during 46 months follow-up in the Sudden Cardiac Death in Heart Failure Trial to 35% during a mean 20 months follow-up in the MADIT-II.[4,10] These data are comparable to a rate of 21% during a median 22 months follow-up, as observed in the current study and emphasis the relatively low actual need for defibrillator backup. This issue, in combination with the mentioned drawbacks, urges for baseline risk stratification in the population currently indicated for primary prevention ICD treatment.

Risk factors

In recent literature, several subgroup analyses of the MADIT-II focused on the identification of patients who were most likely to receive appropriate device therapy. These analyses mentioned interim hospitalization for heart failure or a coronary artery event, no beta-blocker usage, current smoking, NYHA class >II, renal dysfunction, high body mass index and digitalis use as factors increasing the risk of ventricular arrhythmia during follow-up.[20,28,29] Interestingly, these baseline predictors for ICD therapy were similar to baseline variables associated with an increased risk for mortality.[28,30] Consequently, the patients with the highest risk of receiving potentially life-saving appropriate device therapy have the worst prognosis, regardless of the implanted device. This paradox makes the findings in literature difficult to interpret. Therefore, a different approach to assess ICD efficacy was necessary. Koller and co-workers combined appropriate ICD therapy with all-cause mortality and defined non-benefit from ICD treatment as death prior to appropriate therapy, instead of focusing on patients with the lowest occurrence of ICD therapy. They demonstrated that usage of diuretics for heart failure – which was considered a surrogate of advanced heart failure – compared with nonuse was found to be the only significant predictor of non-benefit from ICD treatment. The current analysis demonstrated that besides advanced heart failure, a history of smoking, diabetes and higher age were also associated with non-benefit from ICD treatment. Differences between the study by Koller et al and the current analysis might be explained by the limited set of variables, smaller population size and heterogeneity (e.g. primary and secondary prevention ICD patients) of the study population assessed in the analysis of Koller and co-workers.[23]

Goldenberg et al demonstrated in a risk analysis of MADIT-II that benefit from ICD treatment is following a U-shaped pattern with evident benefit for patients with intermediate risk of all-cause mortality and little benefit in low and high-risk patients.[31] This principle implies two non-benefiting groups at both ends of this efficacy curve. One group comprises patients with major comorbidities, in whom the risk of non-arrhythmic mortality exceeds the risk of arrhythmic (sudden) death. The other group consists of relatively healthy ICD patients who exhibit very low risk for life-threatening ventricular arrhythmia. It should be noted that, according to the observed risk factors, the current risk stratification identified the first mentioned group of non-benefit ICD patients with high risk of non-arrhythmic mortality. To identify the other group (i.e. with low-risk for ventricular arrhythmia) a different approach is desirable. Hallstrom and co-authors focused on predictors of recurrent arrhythmia in a subgroup analysis of the Antiarrhythmics versus Implantable Cardioverter Defibrillator Trial as secondary prevention of sudden cardiac death and identified, based on sextiles of the hazard distribution, a subgroup for which ICDs did not render survival advantage over amiodarone.[22] Indeed, they reported on a 'healthy' subgroup, presenting with an isolated episode of ventricular fibrillation, few comorbidities and moderate preserved LVEF, which was not likely to benefit from ICD treatment over amiodarone.

Concisely, for further prospective research to refine the current selection criteria for ICD treatment of sudden cardiac death one should be aware of the U-shaped pattern of ICD efficacy.

Usage of risk model in clinical practice

As mentioned earlier, refinement of the current selection criteria for primary prevention patients with ischemic heart disease is essential. The current study provides a model to predict the individual risk for non-benefit, which may assist physicians in the decision-making process whether or not to prophylactically implant an ICD. It is however important to realize that patients at high-risk for non-benefit do not per se receive no appropriate ICD therapy at all. Some of the parameters that were associated with high risk of non-benefit were interestingly also identified as predictors of all-cause mortality, sudden cardiac death or appropriate therapy, like advanced age, depressed ejection fraction and smoking.[28,31,32] This paradox could be explained with the short life-expectancy of this very sick group of patients. Consequently, even if an ICD terminates a life-threatening arrhythmia, non-benefit patients are still likely to die within a short period of time from other causes than sudden cardiac death. Thus, despite the fact that ICD therapy is not uncommon is this subset of patients, the survival advantage of prophylactic ICD implantation is limited.

Limitations

This was a non-randomized prospective observational study, performed to predict the non-benefit risk in primary prevention ICD patients with ischemic heart disease outside the setting of a clinical trial. Since patients were collected over a long period of time, evolving guidelines could have created a heterogeneous population. Additionally, the proposed risk score does not take clinician driven variables (medication) or follow-up acquired variables (hospitalizations, adverse events) in account since this could lead to a decrease in baseline applicability and reproducibility. Finally, the constructed risk score requires validation.

Conclusion

A significant number of primary prevention ICD patients with ischemic heart disease does not benefit from ICD treatment during long-term follow-up. The use of a baseline risk score can facilitate patient-tailored risk estimation of the non-benefit (death, prior to first appropriate ICD therapy).

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