

Usefulness of the MADIT-ICD Benefit Score in a S-ICD Patient Cohort

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Abstract

Background: The subcutaneous ICD (S-ICD) is used in an increasing number of patients for primary and secondary prevention of sudden cardiac death. Decision-making in primary prevention is not always trivial and many clinical scenarios are not reflected in current ICD guidelines. To help evaluating the patient's individual risk, a new score trying to predict the benefit of an ICD implantation for primary prevention, the MADIT-ICD benefit score, which tries to predict occurrence of ventricular arrhythmias and non-arrhythmic death, has been proposed. We therefore aimed at examining its usefulness in a large single centre register of S-ICD patients

Methods and results: All S-ICD patients with a primary preventive indication for ICD implantation from our large single centre database were included in the analysis (n=173). During a follow-up of 1227±978 days 27 patients developed sustained ventricular arrhythmias, while 6 patients died for non-arrhythmic reasons. Occurrence of ventricular arrhythmias could not sufficiently be predicted by the MADIT-ICD VT/VF score ($p=0.3$) in patients with (n=142, $p=0.19$) as well as patients without structural heart disease (n=31, $p=0.88$). However, there was a significant correlation for patients with ischemic cardiomyopathy (ICM) (n=29, $p=0.04$). Only one parameter (non-sustained ventricular tachycardia) was significantly associated with sustained ventricular arrhythmias ($p=0.02$). Of note, non-arrhythmic death could effectively be predicted by the proposed non-arrhythmic mortality score as part of the benefit score ($p=0.001$, $r=0.3$) also mainly driven by ICM patients. Age, diabetes mellitus, and a BMI <23 kg/m² were key predictors of non-arrhythmic death implemented in the score.

Conclusion: The MADIT-ICD benefit score adds a new option to evaluate expected benefit of ICD implantation for primary prevention. However, in our S-ICD cohort, the only group in which the score worked properly for prediction of sudden and non-sudden death were ICM patients, so that a larger validation in more heterogeneous cohorts is mandatory to claim general validity for this score in risk stratification for primary preventive ICD implantation.

Introduction

The subcutaneous ICD (S-ICD) (Boston Scientific, Natick, Massachusetts) is widely accepted as a valuable alternative to transvenous ICDs in a variety of clinical constellations requiring ICD therapy.¹⁻⁶ Quite recently the highly anticipated results of the PRAETORIAN trial have been published showing non-inferiority of the subcutaneous ICD compared to transvenous ICDs with regard to safety in a randomized controlled trial.⁷

The MADIT-ICD benefit score is a new score, which has recently been developed to predict the individual patient risk for a sudden cardiac death and/or appropriate ICD therapy on the one hand and a non-sudden death on the other hand.⁸ This may be of particular clinical importance as several recent studies have questioned the benefit of ICD therapy for primary prevention in the era of modern heart failure therapy.⁹⁻¹¹ One of the most important trials is the randomized controlled DANISH trial, in which patients

with a non-ischemic cardiomyopathy without an ICD had a non-inferior outcome in comparison to patients implanted with a ICD.¹²

The so-called MADIT-ICD benefit score was developed on the basis of study populations from the MADIT trials of about 4,500 ICD patients with a primary preventive indication for ICD implantation using a regression model identifying eight predictors of sudden death (male gender, age < 75 years, prior non-sustained VT, heart rate > 75 bpm, systolic blood pressure < 140 mmHg, ejection fraction < 25%, prior myocardial infarction and atrial arrhythmia) and seven predictors of non-sudden cardiac death in this cohort (age > 75 years, diabetes mellitus, body mass index < 23 kg/m², ejection fraction < 25%, heart failure NYHA class II or worse, missing cardiac resynchronization therapy and atrial arrhythmia). These two scores directly point out the risk for SCD (occurrence of VT/VF during follow-up) on the one and non-arrhythmic death on the other hand. In addition, the two scores were combined to a third personalized ICD benefit score ranging from 0–100 with values from 76–100 indicating the highest benefit, 26–75 an intermediate benefit and < 26 lowest benefit of ICD implantation for primary prevention. The score showed good validity in this cohort and could show a high predictive value for life threatening events. As these scores are based on a proof-of-principle study but claims to be suitable and useful for all kinds of patients with primary preventive ICD indication, we sought to examine the usefulness of the score for a cohort of primary preventive ICD patients. In order to evaluate the score's role for patients less likely to have an ischemic cardiomyopathy we chose a large consecutive group of subcutaneous ICD (S-ICD) implanted for primary prevention.

Materials And Methods

The study was conducted in accordance with the guidelines of the Declaration of Helsinki. As it was a solely retrospective study no additional vote from the local ethics committee was obtained. Patients were verbally informed about possibly being included in research projects anonymously when being treated in the University Hospital. No informed consent was obtained. Between June 2010 and January 2021, a total of 371 S-ICD systems were implanted at our institution. In the present single-centre retrospective study, we enrolled all patients (n = 173, 46.6%) with primary preventive indication for S-ICD implantation. Indication for ICD implantation was in accordance to current ESC guidelines. Patient characteristics are summarized in Table 1. Prior to implantation, S-ICD screening was performed with the automated screening tool. Patients were considered eligible for S-ICD implantation if there was at least one suitable vector. All patients were scheduled for an intraoperative defibrillation test. In case of an unsuccessful test, the shock vector was changed to reversed polarity, the shock energy was raised or, if necessary, system components were repositioned intraoperatively using fluoroscopy. For follow-up, patients were examined at six weeks after implantation and every three to six months subsequently. Adverse events were documented during regular follow-up in three to six months' intervals.

Data needed to determine VT/VF-score and non-arrhythmic death score were obtained from medical charts and history. For calculation of the individualized risk score the automated risk calculator provided

online under <https://is.gd/madit> on the website of the University of Rochester was used as described in the original manuscript.⁸

Data transformation and statistical analysis was performed using GraphPad PRISM 6.0 (San Diego, CA, USA) and the SPSS Statistics, version 20.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables are presented as mean and standard deviation (SD), while categorical data are expressed as frequencies. A p -value of $< .05$ was considered statistically significant.

Results

In total, we included 173 patients with S-ICD implanted for primary prevention. 124 patients were male (71.7%) with a mean age of 43.2 ± 16.0 years. The mean follow-up duration was about three and a half years (1227 ± 978 days (s. Table 1)). Dilated cardiomyopathy (24.3%), hypertrophic cardiomyopathy (21.4%), ischemic cardiomyopathy (17.3%) and electrical heart disease (15.6%) were the major indications for S-ICD implantation. Mean left ventricular ejection fraction was $44.9 \pm 16.1\%$.

In total, 27 (15.6%) patients received an appropriate ICD therapy during follow-up while 6 patients (3.5%) died during follow-up due to non-sudden causes, mostly due to heart failure or sepsis.

The mean VT/VF-score was 7.2 ± 1.8 ranging from 4–12 points, while mean score for non-arrhythmic mortality was 1.9 ± 1.8 ranging from 0–8 points. These scores resulted in a mean personalized benefit score of 59.5 ± 17.6 ranging from 20–87. In total, 59 patients were sorted to the high benefit group, 101 patients to the intermediate benefit group and 13 patients to the low benefit group, respectively.

Statistical analysis revealed no significant correlation between neither the benefit score ($p = 0.62$) nor the VT/VF score ($p = 0.3$) with the occurrence of appropriate therapies during follow-up. This finding was also confirmed when ordering the patients according to their respective subgroups (high/intermediate/low benefit) since there was no significant correlation in any of these groups. In absolute numbers, there were 8 shocks in 59 patients from the highest group (13.6%), 18 shocks in 101 patients from the intermediate group (17.8%) and 1 shock in 13 patients from the low risk group (7.7%). Differences did not reach statistical significance. Please see table 2 for a detailed description.

Furthermore, as the MADIT cohorts were used for validation and indeed consist of patients with structural heart diseases (SHD) we divided our cohort in patients with ($n = 142$) and without SHD ($n = 31$). For these subgroups statistical analysis revealed no predictive value of the VT/VF-Score (SHD $p = 0.19$; no SHD $p = 0.88$) nor the benefit score (SHD $p = 0.69$; no SHD $p = 0.74$) (for detailed information please see table 3).

When further dividing in patients with ischemic (ICM) and non-ischemic cardiomyopathy (NICM), however, there was a significant predictive value of the VT/VF-Score for appropriate ICD interventions ($p = 0.04$), but not for the benefit score ($p = 0.45$) in ICM patients. For NICM patients, there was no significant predictive value for both scores (VT/VF-score: $p = 0.55$, benefit score: $p = 0.86$).

While the benefit score did not significantly predict non-arrhythmic death as well ($p = 0.25$), the non-arrhythmic death score indeed did ($p = 0.0001$, $r = 0.3$).

This results was also driven by ICM patients ($p < 0.001$) while there was no significant correlation in NICM patients ($p = 0.18$). In the group of patients, no patient died during follow-up, so that no statistical analysis regarding this outcome could be performed.

To identify the predictive value of the factors implemented in the score, we performed a regression analysis with either appropriate therapy or non-arrhythmic death as dependant variable.

Concerning the prediction of appropriate therapy, only the presence of prior non-sustained VT had a significant impact ($p = 0.02$), none of the other factors reached true or borderline statistical significance (for detailed information please see table 2).

Taking a look at the different risk groups, there were only two factors in the intermediate risk group significantly associated with appropriate therapy – NYHA II or worse and high heart rate, which did not play a role in the main analysis (NYHA II: $p = 0.5$, heart rate > 75 bpm: $p = 0.72$ in the main analysis, respectively).

For the prediction of non-arrhythmic mortality, the analysis revealed three factors significantly associated with the occurrence of non-arrhythmic death. These factors were an age < 75 years, which had a strong negative correlation with non-arrhythmic death ($p = 0.0001$), the presence of diabetes mellitus ($p = 0.01$) and a BMI < 23 kg/m² ($p = 0.005$). The relevance of these factors could be confirmed in every of the three subgroups.

Discussion

In our large S-ICD patient cohort with an ICD implanted for primary prevention, the MADIT-ICD benefit score was not useful for prediction of the occurrence of VT/VF and appropriate therapies. However, patients at risk for non-arrhythmic death and low benefit of ICD implantation could be effectively identified using the Non-arrhythmic Mortality Score.

These findings may be explained by several reasons. First and probably most importantly, our S-ICD collective differs significantly from the patient population in which the benefit score was developed and validated. Our study cohort was younger, included more patients with hypertrophic cardiomyopathies and channelopathies and far less patients with ischemic cardiomyopathy.^{8,13-16}

For instance, a low blood pressure $< 140/90$ mmHg is a key risk factor for the occurrence of VT/VF in the benefit score. However, in our patient collective only 16 of 173 patients had a blood pressure below this threshold. All other patients received 2 points on the VT/VF score, so that it has to be assumed that in younger patient cohorts including more patients without ischemic cardiomyopathy and its classical risk factors such as arterial hypertension, the arrhythmogenic risk is considerably overestimated.

However, we also performed subgroup analysis and could show that the VT/VF-Score and the MADIT ICD benefit score did not predict ventricular arrhythmias in patients with structural heart diseases from our patient cohorts as well.

In addition to that, it has to be underlined, that although the patient cohorts might be different, the authors who developed the MADIT-ICD benefit score have suggested that it is suitable and valid for the risk and benefit assessment of all patients being evaluated for a primary preventive ICD. As our data give a hint that this might not be the case, either the target patient population has to be adjusted or larger validation cohorts of patients with heart diseases including electrical heart diseases in young patients as well have to be used to validate and/or improve the score.

Furthermore, other patient characteristics and risk factors such as chronic renal failure as a strong predictor of non-arrhythmic death^{11,17}, a positive family history for sudden cardiac death which could be especially important in young patients with genetically determined cardiomyopathy^{18,19} and oncological diseases as a mortality-influencing factor being a major risk factor for non-arrhythmic death have not been considered.

In contrast, e.g. a BMI < 23 kg/m² a priori does not seem not to be a suitable parameter for evaluating the risk of VT/VF in a young woman with long QT syndrome while it is certainly helpful in an older patient cohort indicating cachexia and multimorbidity.²⁰ Surprisingly, despite the young mean age, the BMI was also a significant predictor of non-arrhythmic death in our cohort underlining the potential role of this parameter.

The only parameter used in the VT/VF score consistently being associated with VT/VF in all risk groups was non-sustained VT (nsVT), which is in line with previous research.^{3,21} Therefore, nsVT as a precursor of later sustained VT may justify more intensified monitoring or even decision pro ICD implantation also in patients with LV-EF > 35% if the patients have other risk factors such as extensive late gadolinium enhancement in cardiac MRI or a positive family history for sudden cardiac death.

Regarding age, there is evidence that although cardiovascular morbidity and mortality is increasing over time, patients often do not benefit from ICD implantation for primary prevention. Bilchick et al. could show in a very large patient cohort of about 100.000 patients with heart failure that about one quarter of patients having been implanted with an ICD did not have any survival benefit from ICD implantation with older age being one of the main predictors of not profiting.^{22,23} This result is probably explained by other comorbidities competing with arrhythmic mortality in older patients.²⁴ This relationship of sudden to non-sudden death decreasing with age was already published by Kahn et al. in 2004.²⁵

Furthermore, there are possibly additional risk factors not represented in the benefit score. For instance, advanced renal disease or even chronic haemodialysis in a patient collective is associated with a very high morbidity and mortality. Evidence for a missing reduction of mortality by ICD implantation for primary prevention in this patient cohort has been initially collected from small cohorts²⁶ but massively

been strengthened by the ICD2-trial, a randomized controlled trial, in 2017.¹¹ Therefore, it might be worth looking at a possible influence of renal function on benefit score in future pieces of research as advanced renal failure could be a relevant risk factor for non-sudden cardiac death.²⁷

Limitations

This study has many limitations mainly caused by its retrospective nature. Furthermore, it has to be underlined that follow-up was not equally long for all patients. Patients were not scheduled for further investigations in our institution if they preferred an outpatient aftercare closer to their homes. However, we regularly received information from the outpatient cardiologists if problems occurred. In addition to that, the MADIT-ICD benefit score is a novel tool which is not evaluated in many different populations, so that this study is just a first step to test it in a younger patient cohort with a large variety of underlying cardiomyopathies rather than a classical ischemic cardiomyopathy cohort.

Conclusion

All in all, the recently developed MADIT-ICD benefit score does not seem to be helpful in evaluating the risk of sudden cardiac death in every primary prevention population. One of its major advantages is the fact that it is possible to calculate it with just a few easily available information. However, in our population it did not help predicting appropriate ICD therapies. The score did only work for the subgroup of ICM patients, probably reflecting the surplus of ICM patients in the MADIT patient cohorts. Hence, some of the parameters influencing the score result (blood pressure, heart rate, BMI, age < 75 years) were very different from the validation cohorts, so that it might be necessary to further advance the score by examining additional different patient cohorts or adopt the score with different parameters for different populations. The option of having another tool to evaluate the risk-benefit-relation is indeed very attractive so that a further development of the score is desirable.

Declarations

Conflict of interest

KW, FR, JK, PSL, LE and GF received travel cost support and research grants from Boston Scientific. BR, JW and CE are or have been supported by a fellowship sponsored by Boston Scientific.

References

1. Bögeholz, N. *et al.* Spotlight on S-ICD™ therapy: 10 years of clinical experience and innovation. *Europace***21**, 1001–1012 (2019).
2. Burke, M. C. *et al.* 1-Year Prospective Evaluation of Clinical Outcomes and Shocks: The Subcutaneous ICD Post Approval Study. *JACC Clin Electrophysiol***6**, 1537–1550 (2020).

3. Willy, K. *et al.* Performance of the entirely subcutaneous ICD in borderline indications. *Clin Res Cardio***109**, 694–699 (2020).
4. Willy, K. *et al.* The role of entirely subcutaneous ICD™ systems in patients with dilated cardiomyopathy. *J Cardio***75**, 567–570 (2020).
5. Willy, K. *et al.* Outcome differences and device performance of the subcutaneous ICD in patients with and without structural heart disease. *Clin Res Cardio***109**, 755–760 (2020).
6. Willy, K. *et al.* The entirely subcutaneous ICD™ system in patients with congenital heart disease: experience from a large single-centre analysis. *Europace***21**, 1537–1542 (2019).
7. Knops, R. E. *et al.* Subcutaneous or Transvenous Defibrillator Therapy. *N Engl J Med***383**, 526–536 (2020).
8. Younis, A. *et al.* Predicted benefit of an implantable cardioverter-defibrillator: the MADIT-ICD benefit score. *Eur Heart J* (2021) doi:10.1093/eurheartj/ehaa1057.
9. Hohnloser, S. H. *et al.* Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med***351**, 2481–2488 (2004).
10. Colquitt, J. L. *et al.* Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: systematic review and economic evaluation. *Health Technol Assess***18**, 1–560 (2014).
11. Jukema, J. W. *et al.* Prophylactic Use of Implantable Cardioverter-Defibrillators in the Prevention of Sudden Cardiac Death in Dialysis Patients. *Circulation***139**, 2628–2638 (2019).
12. Køber, L. *et al.* Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. *N Engl J Med***375**, 1221–1230 (2016).
13. Moss, A. J. *et al.* Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med***346**, 877–883 (2002).
14. Moss, A. J. *et al.* Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med***361**, 1329–1338 (2009).
15. Moss, A. J. *et al.* Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med***367**, 2275–2283 (2012).
16. Zareba, W. *et al.* Ranolazine in High-Risk Patients With Implanted Cardioverter-Defibrillators: The RAID Trial. *J Am Coll Cardio***72**, 636–645 (2018).

17. Di Lullo, L. *et al.* Chronic kidney disease and cardiovascular complications. *Heart Fail Rev***20**, 259–272 (2015).
18. Webster, G. *et al.* Cardiac Evaluation of Children With a Family History of Sudden Death. *J Am Coll Cardio***74**, 759–770 (2019).
19. Norrish, G. *et al.* Risk factors for sudden cardiac death in childhood hypertrophic cardiomyopathy: A systematic review and meta-analysis. *Eur J Prev Cardio***24**, 1220–1230 (2017).
20. Kenchaiah, S. *et al.* Body mass index and prognosis in patients with chronic heart failure: insights from the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) program. *Circulation***116**, 627–636 (2007).
21. de Sousa, M. R., Morillo, C. A., Rabelo, F. T., Nogueira Filho, A. M. & Ribeiro, A. L. P. Non-sustained ventricular tachycardia as a predictor of sudden cardiac death in patients with left ventricular dysfunction: a meta-analysis. *Eur J Heart Fail***10**, 1007–1014 (2008).
22. Bilchick, K. C. *et al.* Seattle Heart Failure and Proportional Risk Models Predict Benefit From Implantable Cardioverter-Defibrillators. *J Am Coll Cardio***69**, 2606–2618 (2017).
23. Scheurlen, C. *et al.* ICD therapy in the elderly: a retrospective single-center analysis of mortality. *Herzschr Elektrophys* (2021) doi:10.1007/s00399-021-00742-x.
24. Pellegrini, C. N. *et al.* Impact of advanced age on survival in patients with implantable cardioverter defibrillators. *Europace***10**, 1296–1301 (2008).
25. Krahn, A. D., Connolly, S. J., Roberts, R. S., Gent, M., & ATMA Investigators. Diminishing proportional risk of sudden death with advancing age: implications for prevention of sudden death. *Am Heart J***147**, 837–840 (2004).
26. Pun, P. H. *et al.* Primary prevention implantable cardioverter defibrillators in end-stage kidney disease patients on dialysis: a matched cohort study. *Nephrol Dial Transplant***30**, 829–835 (2015).
27. Go, A. S., Chertow, G. M., Fan, D., McCulloch, C. E. & Hsu, C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med***351**, 1296–1305 (2004).

Tables

Due to technical limitations, table 1-3 is only available as a download in the Supplemental Files section.

Supplementary Files

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- [Table13.pdf](#)