Primary prevention of sudden cardiac death with implantable cardioverter-defibrillator therapy in arrhythmogenic right ventricular cardiomyopathy

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ABSTRACT

Background: Implantable cardioverter-defibrillator (ICD) therapy remains a corner stone of sudden cardiac death (SCD) prevention in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC).

Objective: We aimed to assess predictors of appropriate ICD therapies in ARVC patients who received ICD for primary prevention of SCD.

Methods: Study group comprised of 176 ARVC patients (70% male, age at ICD implant 41 [IQR 32-53] years) who were enrolled in the Nordic ARVC registry and received ICD for primary prevention of sudden death. Task Force 2010 diagnostic criteria, ECG characteristics and history of syncope or ventricular tachycardia (VT) were assessed as predictors of appropriate ICD therapies during median follow-up of 89 months.

Results: At baseline, 114 patients (65%) had a history of VT and 47 (27%) had syncope. Appropriate ICD therapy was detected in 104 patients (59%). ICD therapy was independently predicted by the history of syncope (HR 1.74, 95%CI 1.14 – 2.65, p=0.010), documented VT (HR 2.23, 95%CI 1.43 – 3.48, p<0.001) and age at ARVC diagnosis <40 years (HR 1.52, 95%CI 1.02 – 2.26, p=0.039). ICD recipients with family history of SCD before age of 35 years had lower risk of appropriate ICD therapies with HR=0.42, 95%CI 0.19 – 0.92, p=0.030 in the univariable analysis.

Conclusion: History of syncope, VT and young age at ARVC diagnosis were the most prominent clinical risk factors predicting appropriate ICD therapies in ARVC patients who received ICD for primary prevention of SCD. Our data did not identify family history of premature SCD as a risk factor for appropriate ICD therapy.

KEY WORDS: arrhythmogenic right ventricular cardiomyopathy; implantable cardioverter-defibrillator; sudden cardiac death prevention

Abbrevations:

ARVC	arrhythmogenic right ventricular cardiomyopathy
ATP	antitachicardia pacing
CI	confidence interval
CMR	cardiac magnetic resonance
ECG	electrocardiogram
HR	hazard ratio
ICD	implantable cardioverter-defibrillator
LGE	late gadolinium enhancement
NSVT	non-sustained ventricular tachycardia
SCD	sudden cardiac death
TF	Task Force
VT	ventricular tachycardia

INTRODUCTION

Increased awareness of arrhythmogenic right ventricular cardiomyopathy (ARVC) as a progressive inherited disease associated with the risk of sudden cardiac death (SCD) has lead to wide implementation of family screening strategies, including genetic screening, in clinical management guidelines[1] and revision of diagnostic criteria, which increased their sensitivity, in particular for establishing diagnosis in family members with less pronounced disease phenotype.[2] As a result, the number of patients with ARVC requiring risk stratification and decision whether to implant an implantable cardioverter-defibrillator for primary prevention of SCD is growing. While implantation of ICD in ARVC patients for secondary prevention of sudden death has become a standard practice and is based on a well-documented increased risk of recurrent life-threatening ventricular arrhythmias,[3-5] the literature regarding the indications for ICD implantation for primary prevention of SCD is limited.[6, 7] In addition, most prognostic data on ICD-treated ARVC patients comes from small to medium size studies performed before implementation of the modified ARVC criteria in 2010.[2] This leaves a significant uncertainty regarding this single most important decision that needs to be made for patients, who are now commonly diagnosed with ARVC at young age, often have few or no symptoms and will have many years of exposure to ICD therapy – and associated complications.

The objective of our study was to assess the predictors of ICD therapy in a large unselected cohort of patients with definite ARVC, who were diagnosed according to the 2010 Task Force criteria (TF2010) and received ICD implants for primary prevention of SCD. The patients were subsequently followed up at cardiogenetic clinics affiliated with university hospitals in Scandinavian countries participating in the Nordic ARVC Registry.[8] Two specific aims of the study were (1) to evaluate previously reported risk factors associated with appropriate ICD therapies and identify patients at the highest risk of ventricular arrhythmias and (2) identify

subgroups of patients with low risk of arrhythmias, in which ICD implantation for primary prevention may not be needed.

MATERIAL AND METHODS

The Nordic ARVC Registry (www.arvc.dk) was launched in June 2010 and included patients with ARVC previously diagnosed using 1994 TFC and followed through device follow-up clinics and dedicated cardio-genetics units affiliated with tertiary referral centers in Scandinavia. We have also prospectively recruited newly diagnosed patients with Definite ARVC according to 2010 Task Force criteria.[2]

In the registry, baseline clinical data (age, gender, previous cardiovascular disease, and diabetes) are collected, in addition to the data specific for ARVC diagnostic criteria as proposed in the original Task Force recommendations from 1994[9] and the updated task force criteria from 2010.[2] Data captured in the registry include family history of ARVC or sudden death, ARVC-related symptoms, imaging data from echocardiography and cardiac magnetic resonance (CMR), histology data from cardiac biopsies, electrocardiographic data including depolarization and repolarization abnormalities in the standard 12-leads resting ECG. Ventricular arrhythmia data included in the registry are reported either clinically as ECG-verified ventricular tachycardia or as captured by ICD device diagnostics. Historical information regarding VT prior to ARVC diagnosis or ICD implantation was retrieved from patients' medical records as assessed by a cardiology specialist, archived ECGs or ambulatory ECG monitoring reports.

Decision to implant ICD for primary prevention of SCD was guided by clinical guidance documents, which were in force at the time when patients underwent clinical evaluation,[10, 11] local practice and patient preferences. Clinical characteristics of the ICD study group were

compared with 63 patients with definite ARVC recruited during the same period but not treated with ICD (control group).

Prospective follow-up information was available until May 2016 when data for the current analysis were retrieved. The vast majority of patients included in the current analysis was diagnosed with ARVC prior to implementation of the modified Task Force criteria in 2010 (Table 1), however patients had to fulfill the modified criteria for definite ARVC[2] in order to be included in the study.

Regional institutional ethics committees approved the study. In Denmark, registry studies do not require approval from an ethics committee, but approval was obtained from the Danish Data Protection Agency. The study complies with the Declaration of Helsinki.

STATISTICAL METHODS

Continuous data are presented as mean ± standard deviation or median [IQ range] as appropriate. Nominal data are presented as number (% of cases). Chi-squared or Fischer's exact test was used for comparison between categorical variables, and t-test was used for the comparison of continuous variables.

The endpoint was time to first appropriate ICD therapy defined as either anti-tachycardia pacing (ATP) or shock. Subjects who did not have any ICD therapy during follow-up were censored at the end of follow-up, at time of death, or heart transplantation. The Kaplan–Meier product-limit method was used to generate a survival curve indicating time to the first appropriate ICD therapy from the first ICD implantation date. Cox proportional hazard regression models were used to estimate the adjusted hazard ratios (HR) and their 95% confidence intervals (CI) of appropriate ICD therapy.

Univariable Cox regression analyses were performed for each component of the 2010 Task Force criteria, including imaging and ECG characteristics, gender, age at ARVC diagnosis,

and history of syncopal episodes or VT prior to ICD implantation. Clinical factors and ECG parameters associated with appropriate ICD therapies at the P-value <0.15 level in the univariable analyses were included in a stepwise regression analysis with backward elimination. A two-sided P-value of 0.05 was considered statistically significant.

The discriminative ability of the final multivariable model for the purpose of risk predication was evaluated using C-statistics.

RESULTS

Patient characteristics at baseline

Of the total number of 269 patients with definite ARVC recruited by May 2016, 203 had ICD implanted. Twenty-seven received ICD after aborted sudden cardiac death or defibrillation due to haemodynamically unstable VT. These patients were excluded from the analysis. The remaining 176 patients from 148 families, of whom 130 received ARVC diagnosis prior to the registry launch and 46 were prospectively recruited with newly diagnosed ARVC, constituted the study group of primary prevention ICD recipients.

Patient characteristics are presented in Table 1. Median age at ARVC diagnosis was 41 years and did not differ significantly between patients with and without ICD implant, however male gender was significantly overrepresented among patients treated with ICD. Patients treated with ICD more often had history of syncope and had documented VT prior to diagnosis. Few patients had family history of sudden cardiac death before 35 years of age in a first degree relative, which was overrepresented among the ICD-treated patients but no statistical difference between the groups could be observed. Left ventricular involvement assessed as reduced LV ejection fraction ≤40% was similarly uncommon in both groups. The vast majority of patients had mild or no functional limitation according to New York Heart

Association (NYHA class I or II).

All patients included in this study fulfilled diagnostic criteria required for definite diagnostic category by TF2010.[2] The vast majority of patients (75%) underwent CMR in addition to a conventional echocardiography, which was performed in all subjects. The use of CMR diagnostic modality did not differ between patients with and without ICD. In one third of patients fibrosis in the RV wall was detected using late gadolinium enhancement (LGE), which was observed equally common in both groups.

Very few patients underwent cardiac biopsy, which was performed on the right ventricular free wall in only 9 subjects (3.7%) and on the right ventricular septum in 59 (24%).

Less than a half of patients underwent invasive electrophysiological evaluation, which resulted in inducible sustained monomorphic or polymorphic VT in 46%, being insignificantly more common among patients who received ICD.

Signal-averaged ECG was performed in the vast majority and ventricular late potentials defined in accordance with the latest TF2010 showing abnormal values were found in 78% of tested patients without difference between the ICD-treated and not treated patients.

Repolarization abnormality defined as T-wave inversion extended to any of the inferior limb leads was common (40%) and more frequently observed among ICD recipients.

The ICD cohort consisted of 148 probands (affected individuals ascertained independently of family history of ARVC) and 28 family members with definite ARVC. Genetic evaluation was attempted in 115 probands (77%), of whom 77 (67%) were carriers of a disease-causing genetic variant. The vast majority of mutation-positive probands carried a mutation in the plakophillin-2 (PKP2) gene (65%), followed by the desmoglein-2 (DSG2) gene (19%) and the desmoplakin (DSP) gene (13%). No significant difference in regard to the proportion of mutation-positive probands was observed among patients with and without implanted ICDs.

In contrast to ICD patients, the majority of patients without implanted ICDs were asymptomatic at the time of diagnosis and underwent diagnostic work-up as a part of family

screening (55% vs 15%, p<0.001).

ICD therapies during follow up.

During a median follow up of 89 [IQR 58 - 146] months after ICD implantation, 18 patients underwent heart transplantation and five patients died (one of them within a month after heart transplantation). Of the remaining four deceased patients, the cause of death was non-cardiac in two and unknown in two. There were no deaths during follow up among patients not treated with ICD.

By the end of follow-up, 72 patients (41%) did not experience any appropriate ICD therapy. The first appropriate ICD therapy was delivered at a median of 15 [IQR 3.5 – 41] months after ICD implantation. Seventy-seven patients (44%) received ICD shock with or without ATP (5.8% per year) and remaining 27 patients (15%) received ATP only. Median age at first ICD therapy was 42 [IQR 32-53] years.

Inappropriate ICD shocks were seen in 13 patients and occurred with similar incidence among patients who received appropriate ICD therapy and those who did not (6.7% vs 8.3%, p=0.773).

Predictors of appropriate ICD therapies

Patients who received ICD shock or ATP during follow-up were more likely to have ARVC diagnosed before 40 years of age, had a syncope history or documented VT before ICD implantation (Table 1). Of the 26 primary asymptomatic patients who were diagnosed with ARVC as a result of family screening and did not have any health concerns at baseline, the majority (n=19, 73%) did not receive any appropriate ICD therapy during follow-up (p<0.001).

Univariable Cox regression analysis was performed for all assessed disease manifestations and results of diagnostic work up and its results are summarized in Table 2. Five

characteristics predicted ICD therapies in the univariable analysis with p-value <0.05: being a proband, history of syncope and documented VT prior to ICD implantation, the lack of family history of sudden cardiac death before age of 35 years and ventricular repolarization abnormality fulfilling major repolarization criteria by TF 2010. An additional three characteristics passed the p<0.15 threshold for inclusion in the multivariable analysis (age at ICD implant <40 years, structural abnormality fulfilling TF 2010 major imaging criterion and repolarization abnormality fulfilling TF 2010 major repolarization criterion). T-wave inversion extending beyond the precordial leads V1-V3 was more common among patients who received appropriate ICD therapies (45% vs 28%, p=0.027), however it was not a significant predictor in the univariable analysis.

Multivariable analysis was performed with inclusion of all ARVC phenotype characteristics that demonstrated p <0.15 in the univariable analysis: (1) age at diagnosis under 40 years, (2) history of syncope, (3) history of any VT, (4) family history of SCD before 35 years in 1st degree family member, (5) major repolarization abnormality and (6) major right ventricular structural abnormality (Table 3). History of VT, syncope and young age at diagnosis remained the three independent predictors of appropriate ICD therapies (Figure 1).

Figure 2 demonstrates Kaplan-Meier curve analysis of the time to any appropriate ICD therapy (left) or appropriate ICD shocks (right) depending on the presence of the three independent risk factors (below).

Compared to patients who did not have either of them, those with 1 risk factor had borderline significant risk increase while those with 2 or 3 risk factors had significantly five- to sevenfold increased risk depending on the endpoint (Table 4). Regardless of the endpoint (any appropriate ICD therapy or appropriate ICD shocks only) a significant risk increase was observed between patients with 2 vs. 1 risk factors while no further risk increase was seen when patients with 3 risk factors were compared with those with 2 (Table 4).

Delivery of inappropriate ICD shocks during follow-up was not related to the risk factors

associated with appropriate ICD therapies (log rank p=0.804).

The multivariable model had a C-statistics of 0.63.

Patients without risk factors

Low-risk patients without any of the three independent risk factors (history of VT, syncope or the age at ARVC diagnosis) were compared with definite ARVC patients without implanted ICD. In both groups the majority of patients were diagnosed through family screening and were asymptomatic at baseline (60% vs. 56% in the control group, p=1.0), however low-risk patients who had ICD implanted more often had family history of SCD among their first degree relatives (20% vs. 1.6%, p=0.021), positive ventricular late potentials (100% vs 69%, p=0.028) and reduced LVEF ≤40% (14% vs 4.9%, p=0.232). Otherwise, no difference was observed between the groups in regard to other diseases manifestations, including major imaging criteria (80% vs 64%, p=0.361), major repolarization criteria (47% vs 65%, p=0.241), VT inducibility (22% vs 32%, p=0.714) or LGE at cardiac MRI (30% vs 28%, p=1.0).

DISCUSSION

Main findings

Our findings are based on the largest reported international cohort of patients with definite ARVC diagnosed according to TF 2010 who received ICD implants for primary prevention of SCD, which is twice the size of the recently reported cohort.[7] Even though a number of disease characteristics, including ventricular repolarization abnormality and advanced right ventricular structural abnormalities demonstrated association with appropriate ICD therapies in univariate analyses, only young age at the time of ARVC diagnosis and the symptoms (syncope or any ECG-documented VT) reported prior to ICD implantation remained

significant predictors of the outcome. The presence of these risk factors, however, did not affect occurrence of inappropriate ICD shocks, which was reported equally common among patients with and without risk factors in nearly 7% of patients during follow-up. Importantly, our data do not support the use of family history of premature SCD in a first degree relative as a risk factor associated with ventricular arrhythmias during follow-up.

Clinical characteristics of primary prevention ICD recipients in Scandinavia

Our findings need to be interpreted in the context of clinical characteristics of primary prevention ICD recipients, which demonstrate significant variability in the literature and may affect the results of analyses yielding different clinical characteristics as independent predictors of arrhythmic outcomes. Our results dealing with primary SCD prevention in ICD recipients with definite ARVC enrolled in the Nordic ARVC Registry can be compared with two earlier reported primary prevention cohorts[6, 7] and the most recent report from the North American multidisciplinary study of ARVC, which included 56 patients (52%) who received ICD for primary prevention indication[12] (Table 5).

In general, the international cohort reported in 2010 and diagnosed according to the Task Force 1994 criteria[6] appeared to have the most distinct phenotype with vast majority of patients expressing advanced right ventricular structural abnormalities, T-wave inversion in right precordial leads V_1-V_3 and family history of SCD. In that regard, the Scandinavian ARVC patients are more similar to the Johns Hopkins cohort,[7] which was diagnosed by TF 2010 and therefore also includes patients with less severe disease manifestations. The prevalence of syncope history among primary prevention ICD recipients in our group was remarkably similar to the findings in two most recently reported cohorts,[7, 12] while the prevalence of non-sustained VT was lowest in the North American multidisciplinary study.[12] While being similar in regard to the ECG phenotype of the disease, ICD treated patients in the

Nordic ARVC registry were older at ICD implantation (42 vs. 32 years), more often were men (65% vs 46%), and had less family members enrolled in the study (16% vs 36%) than reported by Bhonsale et al.[7] Notably, three of four patients in the Nordic ARVC registry had advanced structural right ventricular abnormality giving rise to major imaging criterion by TF 2010, which is compared to only 29% in the Johns Hopkins cohort and 71% in the North American registry. Differences in the patient characteristics and more severe disease phenotype observed in patients recruited in the Nordic ARVC registry may explain the observed differences in clinical characteristics identified as risk factors for appropriate ICD therapies.

Syncope as predictor of ventricular arrhythmias in ARVC

While syncope is now generally recognized as a risk factor for ventricular arrhythmias, and adverse outcome in patients with ARVC and as such is listed among the risk factors that may motivate ICD implantation (class IIb indication, level of evidence C[11]), it is important to acknowledge that the data supporting this recommendation come mostly from the primary prevention study on patients diagnosed by TF1994[6] while a number of secondary prevention studies[4, 5, 13, 14] or the single primary prevention study based on TF2010 diagnostic criteria[7] did not support syncope as a predictor of appropriate ICD therapy. It is likely that in the secondary prevention cohorts the history of aborted cardiac arrest or haemodynamically unstable VT identifies a patient category with the highest arrhythmic risk so that any further risk stratification based on the syncope symptom is not longer possible. This does not explain, however, the differences between our study and the findings by Bhonsale et al., which despite similar syncope prevalence at baseline did not report any predictive value of syncope in a slightly less symptomatic cohort, in which appropriate ICD therapy was reported in 52% of patients compared to 59% in our cohort. The North American ARVC registry reported increased risk of events in patients with syncope, which however did not appear as an

independent risk factor in the multivariate analysis.[12]

The prevalence of syncope history among ICD carriers in our study was three times higher than in patients who did not receive ICD, which indicates that syncope was treated as a factor that likely played a role for the decision to implant ICD in our cohort. Even though demonstrating lower hazard ratio than earlier reported,[6] it is notable that in our primary prevention cohort syncope performs as a strong independent predictor of ventricular arrhythmias in ICD carriers, thus in the present and largest to date material supporting the role of syncope as a major risk indicator for the choice of primary prevention strategy as suggested in the recent consensus document by the ARVC task force.[15]

History of ventricular tachycardia as a risk indicator

Haemodynamically unstable VT is a straightforward indication for ICD implantation and according to the most recent recommendations it is a Class I evidence level C indicaton.[11] Patients who were resuscitated from cardiac arrest or with haemodynamically unstable VT prior to ICD implantation were considered in need of ICD for secondary prevention of SCD and thus not included in our study, which was focused on the primary prevention scenario.

Previously published data in support of non-sustained VT (NSVT) as a risk marker for ICD therapy give a mixed picture. Although most of studies report NSVT as a predictor of appropriate ICD therapies un univariate analyses,[4, 6, 14] this was not supported by all[13] and only one earlier study devoted to the primary prevention indication found it to be an independent predictor of appropriate ICD therapies in a multivariable analysis.[7] In our study, not all historical information on VT documented in medical records may have been supported by ECG documentation but only noted by a cardiologist, which precludes independent validation of VT anamnesis. While understanding that this may have potentially included arrhythmias of uncertain duration and broad-QRS tachycardias that may not necessarily have

ventricular origin, we have chosen to apply this broader definition of historical VT, acknowledging the limitation that clear-cut delineation of NSVT vs. haemodynamically stable sustained VT prior to ICD implantation may be difficult. Sustained haemodynamically stable VT is generally considered a high-risk indicator and ICD is recommended with a Class IIa (Level C) indication[11] and assessed as a Class I indication in the recent consensus document endorsed by an international ARVC task force.[15] Even though we excluded all patients who underwent cardioversion for haemodynamically unstable VTs prior to ICD implantation from the analysis, we cannot completely rule out that some patients with reported anamnestic VT in our study may have had sustained haemodynamically stable VT that did not require cardioversion in the past. However, the prevalence of anamnestic VT in our cohort (65%) is similar to the one reported in the primary prevention cohort from Johns Hopkins for NSVT (53%)[7] and given the general similarities between our cohorts we believe that our findings on the predictive value of VT history is comparable with earlier reported.[7]

Our findings of historical VT as a strong risk indicator of appropriate ICD therapies is in full agreement with previous reports in the context of the primary prevention of SCD in ARVC regardless of the extent of the disease phenotype[6, 7] and support its use as a major risk factor indicating the presence of a substrate for ventricular arrhythmias which should motivate implantation of ICD.

Young age at time of ARVC disease manifestation

It has been observed that arrhythmic manifestations of ARVC are linked to the phenotypic expression of the disease otherwise[16] and its progression to the overt phenotype, which can be assessed as the age of ARVC diagnosis. Studies performed on ICD primary prevention cohorts of ARVC patients have consistently reported that younger age at time of diagnosis or enrollment was associated with ventricular arrhythmias during follow-up,[6, 7, 12, 14] even though

age was not shown to be a predictor of outcome in the recently reported cohort with high proportion of less symptomatic family members.[7] Corrado et al. reported young age at diagnosis as an independent outcome predictor in a mixed population of ARVC patients that to a large extent consisted of secondary prevention ICD carriers[3] and as a univariate predictor in the primary prevention cohort.[6] Young age at presentation was the only predictor of appropriate ICD therapies for fast VT in the North American registry.[12]

Our findings from a large cohort of primary prevention ICD carriers with high endpoint rate of appropriate ICD therapies is in line with these previous observations and support the use of age at disease presentation as a risk marker of arrhythmic events during follow-up with a risk estimate similar to the one for history of syncope.

Other risk factors from previous studies

A number of other risk factors have been proposed as predictors of arrhythmic events in the earlier studies and listed in the recent consensus document by the international ARVC Task Force.[15] We were able to test a number of them, including male gender, repolarization abnormalities with T-wave inversions in the inferior leads and extended T-wave inversions in the precordial leads, advanced right ventricular structural abnormalities, VT inducibility during invasive electrophysiological studies and left ventricular involvement/dysfunction. None of these factors turned out as an independent predictor of arrhythmic outcome. However, extended repolarization abnormality in precordial leads giving rise to major repolarization criterion and advanced right ventricular abnormality meeting major imaging criterion by TF2010 were significant univariable predictors of appropriate ICD therapies in line with previous studies.

Proband or family member – Implications for the low risk group

Ascertainment of ARVC diagnosis in a patient identified through family screening results in a situation where risk assessment needs to be done in an individual, who will often present with mild disease manifestations, which would nevertheless be sufficient for establishing definite ARVC diagnosis. It is therefore not surprising that disease phenotype in family members is consistently reported to be less distinct compared with probands[6, 7] and that having a proband status *per se* indicate a greater risk of arrhythmic endpoints.[7, 17] Primary indication asymptomatic ICD patients with definite ARVC in our cohort, i.e. those who were diagnosed through a dedicated family screening procedure without any symptoms, which would motivate contact with health care otherwise, appeared to be at very low risk for development of ventricular arrhythmias in agreement with earlier data.[18]

Some controversy exists in regard to the history of SCD in a family member, especially when it occurred at young age. While listed among the possible risk factors for SCD as "family history of premature sudden death" by the SCD prevention guidelines,[11] it has very little support in the literature and did not appear among the risk factors assessed in the primary prevention studies mentioned earlier.[6, 7] In our material, the prevalence of family history of SCD before 35 years of age was two times higher among patients who never experienced appropriate ICD therapies, which resulted in the HR=0.42 (p=0.019) in the univariable analysis. Clear overrepresentation of patients with family history of SCD among asymptomatic ICD carriers is likely to reflect the risk stratification strategy that led to ICD implantation, which considered family history of SCD as an important risk indicator regardless of other diagnostic findings. From a patient-physician relationship perspective, it is also understandable that belonging to a family with ARVC and having a close relative dying suddenly can shift physician and patient preferences towards ICD implantation upon confirmation of the ARVC diagnosis.

Implications for the primary prevention ICD implantation

Our findings based on the appropriate ICD therapy endpoint cannot be considered as an equivalent of prevented SCD. One way to overcome this limitation, at least in part, could be to perform a separate analysis of ICD therapies for fast VTs, which has been reported by others[7, 12] Though the rate of VT treated by ICD has not been captured in our registry, the endpoint limited to appropriate shocks only, which does not include ATP that successfully treated VT and thus comes closer to estimates of prevented SCD, was tested with similar risk estimates for the same three risk factors,.

Though demonstrating a step-wise risk increase related to the presence of one or two risk factors, no further risk increase could be observed in patients beyond that point. Thus patients with 2 or more risk factors in our cohort represent a high-risk group with risk estimates being in the range of 6 to 7 depending on the ICD therapy endpoint compared to the low-risk group and factor two increase risk of ICD therapies in medium-risk patients.

Overall the model's ability to discriminate between patients experiencing an outcome and those that do not was moderate with a C-statistics of 0.63.

While the use of ICD therapies overestimate the life-saving efficacy of ICD therapy, the lack of ICD therapies can be considered as freedom from life-threatening arrhythmias and be used for identification of the low-risk group of patients who would not benefit from ICD implantation, especially in the view of expected long-lasting therapy and the risk of complications not related to the arrhythmia risk profile. Our data further support earlier observations that family members, and primary asymptomatic family members in particular, are at low risk of arrhythmic events.[7, 18] No fatalities were observed among the low-risk ICD recipients in our study during the long-term follow-up.

LIMITATIONS

Though the Nordic ARVC registry cohort presented in this study consists of ICD recipients consecutively enrolled in the participating sites, it consists of patients who were under clinical follow-up by the register launch in June 2010 and those who were prospectively enrolled with newly diagnosed ARVC since then, which may be considered a limitation of the study. However, the main endpoint of the study, i.e. delivery of ICD therapies, is governed by strict documentation requirements in the participating countries, which supports the validity of the study endpoint. We have also compared clinical characteristics of patients who were diagnosed with ARVC before and after 2010 and found no difference in the extent of the diagnostic work-up including genetic evaluation, invasive EP study and CMR. Apart from more frequent observation of a history of syncope (80% vs 59%, p=0.012) and positive LGE at cardiac MRI (51% vs 28%, p=0.014) ICD recipients diagnosed after 2010 did not differ in clinical characteristics from those who were under follow-up at the registry initiation.

CONCLUSION

Our data based on the large contemporary cohort of patients with definite ARVC treated with ICD implantation for primary prevention of SCD further supports the use of history of syncope, VT and young age at disease diagnosis as the major risk factors predicting appropriate ICD therapies. Low-risk patients who did not have any of the three risk factors have low risk of ventricular arrhythmias, which was not different from the risk of clinical VT documented in ARVC patients who did not receive ICD implant and showed good prognosis during long-term follow-up. Family history of SCD at young age in a first degree relative does not increase the risk of arrhythmic events in primary prevention ICD recipients.

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CLINICAL PERSPECTIVES

The principles of primary prevention of sudden cardiac death in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) have largely been based on recommendations derived from observational studies and limited data exist in regard to contemporary ARVC diagnosed according to the Task Force criteria revised in 2010. Data from a large contemporary cohort of patients with definite ARVC from Nordic countries identified major clinical risk factors that independently predict appropriate ICD therapies: history of syncope, ventricular tachycardia and early disease manifestations defined as age at diagnosis under 40 years. Patients with two or more risk factors appear to have strong rationale for recommending prophylactic ICD therapy.

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FIGURE LEGENDS:

Figure 1: Kaplan-Meier survival curve analysis of the impact of history of syncope (left) ventricular tachycardia (middle), or age at ARVC diagnosis under 40 years (right) on the time to appropriate ICD therapy.

Figure 2: Kaplan-Meier curve analysis of the relationship between the number of risk factors (history of syncope, VT or age at ARVC diagnosis under 40 years) on the time to appropriate ICD therapy (left) or appropriate ICD shocks (right). See Table 5 for details of Cox regression analysis and comparison between the groups.

Table 1. Clinical characteristics of patients with definite ARVC (TF2010) who received ICD for primary prevention of sudden cardiac death in the Nordic ARVC Registry

	All patients n=176	**ICD therapy** n=104	**No ICD therapy** n=72	
Male, n (%)	123 (70)	73 (70)	50 (69)	1.000
Probands	148 (84)	93 (89)	55 (76)	0.035
ARVC diagnosis after 2010	46 (26)	21 (20)	25 (35)	0.037
Medical history				
Age at ICD implant, years (median [IQR])	41 [32-53]	39 [31-50]	44 [34-55]	0.092
Age at ARVC diagnosis, years (median [IQR])	40 [30-53]	38 [29-50]	43 [33-53]	0.081
Age at ARVC diagnosis <40	86 (49)	58 (56)	28 (39)	0.032
SCD in a 1st degree relative <35 yr	17 (10)	7 (6.7)	10 (14)	0.127
Syncope history	47 (27)	34 (33)	13 (18)	0.038
NYHA I-II	163 (93)	95 (91)	68 (94)	0.350
NYHA III	13 (7)	9 (9)	4 (6)	
Imaging:				
TF 2010 Imaging criterion major	131 (74)	80 (77)	51 (71)	0.384
TF 2010 Imaging criterion minor	11 (6.3)	6 (5.8)	5 (6.9)	0.761
LVEF, %	59 [50-60]	57 [52-60]	60 [50-60]	0.686
LVEF≤40%	13 (7.8)	7 (7.1)	6 (8.8)	0.772
Cardiac MRI performed	127 (72)	79 (76)	48 (67)	0.231
LGE-positive	44 (35)	28 (35)	16 (33)	0.849
Histology:				
TF 2010 Tissue criterion major	6 (3.4)	5 (4.8)	1 (1.4)	0.403
TF 2010 Tissue criterion minor	0	0	0	N/A
Electrocardiography:				
TF 2010 Repolarization criterion major	95 (54)	62 (60)	33 (46)	0.091
TF 2010 Repolarization criterion minor	21 (12)	13 (13)	8 (11)	0.818
TF 2010 Depolarization criterion major	16 (9.1)	9 (8.7)	7 (9.7)	0.797
TF 2010 Depolarization criterion minor	96 (55)	59 (57)	37 (51)	0.539
Ventricular late potentials (n=128)	104 (81)	66 (87)	38 (73)	0.065
T-wave inversion inferior	81 (46)	51 (49)	30 (42)	0.359
Documented arrhythmia:				
Documented VT	114 (65)	76 (73)	38 (53)	0.007
Invasive EP Study performed	82 (47)	51 (49)	31 (43)	0.447
Inducible sustained VT/VF	39 (48)	28 (27)	11 (15)	0.112
Family history and genetics				
TF 2010 Family history criterion major	109 (62)	66 (64)	43 (60)	0.638
TF 2010 Family history criterion minor	10 (5.7)	5 (4.8)	5 (6.9)	0.742
Genetic evaluation performed in probands	115 (77)	75 (72)	40 (55)	0.161
Desmosomal mutations in probands	77 (67)	54 (72)	23 (58)	0.146
Antiarrhythmic drugs at ICD implantation				
Beta-blockers	47 (27)	29 (28)	18 (25)	0.731
Amiodarone	17 (9.5)	13 (13)	4 (6)	0.193
Sotalol	24 (14)	15 (14)	9 (13)	0.825

Table 2: Univariable analysis of predictors of appropriate ICD therapies in the primary prevention ARVC cohort

	Univariable Cox regression			
	HR	**95% Confidence interval**		**p-value**
Proband status	2.79	1.47	5.29	0.002
Male	0.97	0.64	1.48	0.891
Age at ARVC diagnosis <40 years	1.44	0.98	2.12	0.066
SCD in a 1st degree relative <35 yr	0.42	0.19	0.92	0.030
Syncope history	1.64	1.09	2.48	0.019
NYHA III	1.11	0.56	2.20	0.768
Imaging:				
TF 2010 Imaging criterion major	1.53	0.96	2.43	0.072
TF 2010 Imaging criterion minor	0.97	0.42	2.21	0.941
LVEF. %	1.01	0.99	1.03	0.432
LGE-positive	0.86	0.69	1.08	0.193
Electrocardiography:				
TF 2010 Repolarization criterion major	1.54	1.04	2.28	0.032
TF 2010 Repolarization criterion minor	0.95	0.53	1.71	0.868
TF 2010 Depolarization criterion major	0.86	0.43	1.71	0.672
TF 2010 Depolarization criterion minor	1.11	0.75	1.63	0.607
Ventricular late potentials (n=128)	1.05	0.78	1.43	0.739
T-wave inversion inferior	1.11	0.75	1.63	0.605
Documented arrhythmia:				
Documented VT before ICD implant	1.92	1.24	2.98	0.003
Inducible sustained VT/VF (n=82. 47%)	1.53	0.87	2.68	0.137
TF 2010 Family history criterion major	0.83	0.56	1.25	0.384
TF 2010 Family history criterion minor	1.40	0.57	3.46	0.463
Desmosomal mutation-positive	1.03	0.79	1.36	0.817

Table 3: Multivariable analysis of appropriate ICD therapy predictors in the primary prevention ARVC cohort (adjusted for the presence of major repolarization abnormality and major imaging criterion by TF2010 and history of sudden cardiac death in 1st degree relatives)

	Multivariable Cox regression			
	HR	**95% Confidence interval**		**p-value**
Endpoint: Any appropriate ICD therapy				
Syncope history	1.74	1.14	2.65	0.010
Documented VT before ICD implant	2.23	1.43	3.48	<0.001
Age at ARVC diagnosis < 40 years	1.52	1.02	2.26	0.039
Endpoint: Any appropriate ICD shock				
Syncope history	1.84	1.15	2.97	0.012
Documented VT before ICD implant	1.93	1.16	3.23	0.012
Age at ARVC diagnosis < 40 years	1.78	1.12	2.81	0.014

Table 4. Risk estimates of appropriate ICD therapies associated with the presence of independent risk factors: history of VT, syncope or age at ICD implant <40 years.

	Multivariable Cox regression			
	HR	**95% Confidence interval**		**p-value**
Endpoint: Any appropriate ICD therapy				
1 risk factor vs 0 risk factors	3.10	0.96	10.03	0.058
2 risk factors vs 1 risk factor	**2.33**	**1.54**	**3.52**	**<0.001**
3 risk factors vs 2 risk factors	0.73	0.34	1.56	0.418
2-3 risk factors vs 1 risk factors	**2.22**	**1.49**	**3.30**	**<0.001**
2 risk factors vs 0 risk factors	**7.26**	**2.26**	**23.36**	**0.001**
3 risk factors vs 0 risk factors	**5.30**	**1.40**	**20.00**	**0.014**
2-3 risk factors vs 0 risk factors	**6.95**	**2.17**	**22.23**	**0.001**
Endpoint: Any appropriate ICD shock				
1 risk factor vs 0 risk factors	2.99	0.71	12.54	0.135
2 risk factors vs 1 risk factor	**2.13**	**1.31**	**3.44**	**0.002**
3 risk factors vs 2 risk factors	1.12	0.50	2.52	0.778
2-3 risk factors vs 1 risk factor	2.16	1.35	3.44	0.001
2 risk factors vs 0 risk factors	**6.39**	**1.54**	**26.51**	**0.011**
3 risk factors vs 0 risk factors	**7.09**	**1.47**	**34.14**	**0.015**
2-3 risk factors vs 0 risk factors	**6.49**	**1.57**	**26.77**	**0.010**

Table 5. Clinical characteristics of ARVC patients from contemporary primary prevention cohorts

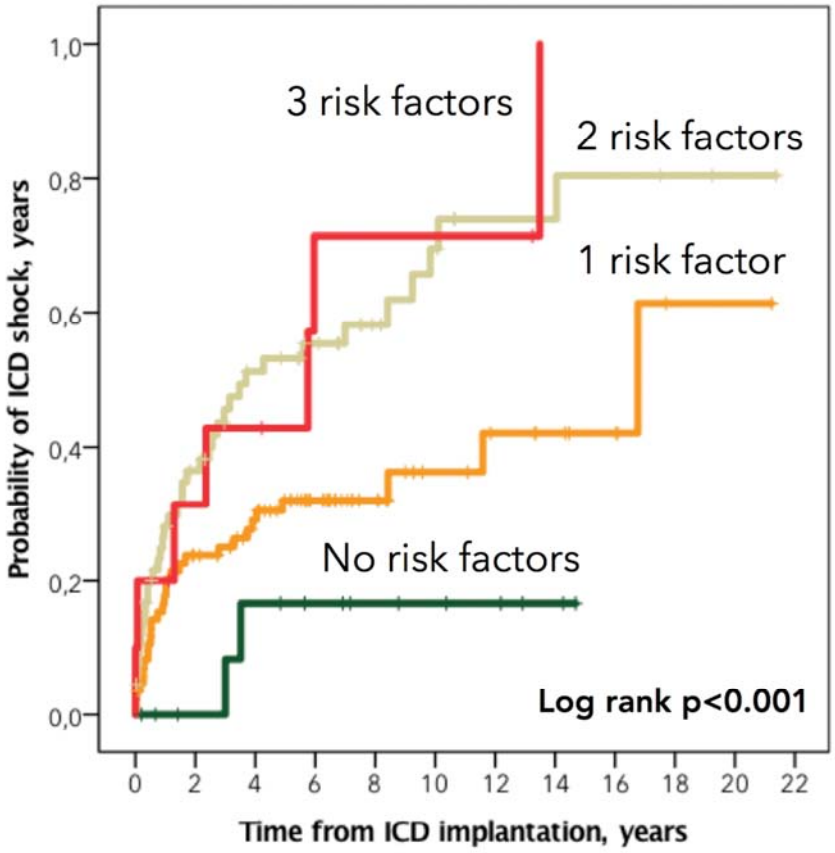
	Corrado 2010[6]	Bhonsale 2011[7]	Link 2014[12]	Nordic ARVC Registry
Number	106	84, 83% 1° prevention	108 52% 1° prevention	176
Diagnostic criteria	TF1994	TF2010	TF2010	TF2010
Age, years	35.6±18	31.9±11.9	40±14	42.3±15
Male gender	67%	46%	60%	65%
Follow-up duration	58±35	57±40	29±18	103±63
History of syncope	39**%**	27%	25%†	27%
History of NSVT	53%	49%	16%	65%
VT inducibility, % of performed EPS	60%	56%	15%†	48%
Family History of SCD	46%	17%	17%‡	10%
Ventricular late potentials on SAECG	62%	74%	62%	81%
Right precordial T-wave inversion (V_1-V_3)	82%	68%	76%	54%
Major RV abnormality	92%	29%	71%‡	74%
LV dysfunction	14%	25%	13%‡	31%*

* % of patients with LVEF<55% as in Bhonsale et al.[7] and Corrado et al.[6]

† % of patients without primary prevention indication

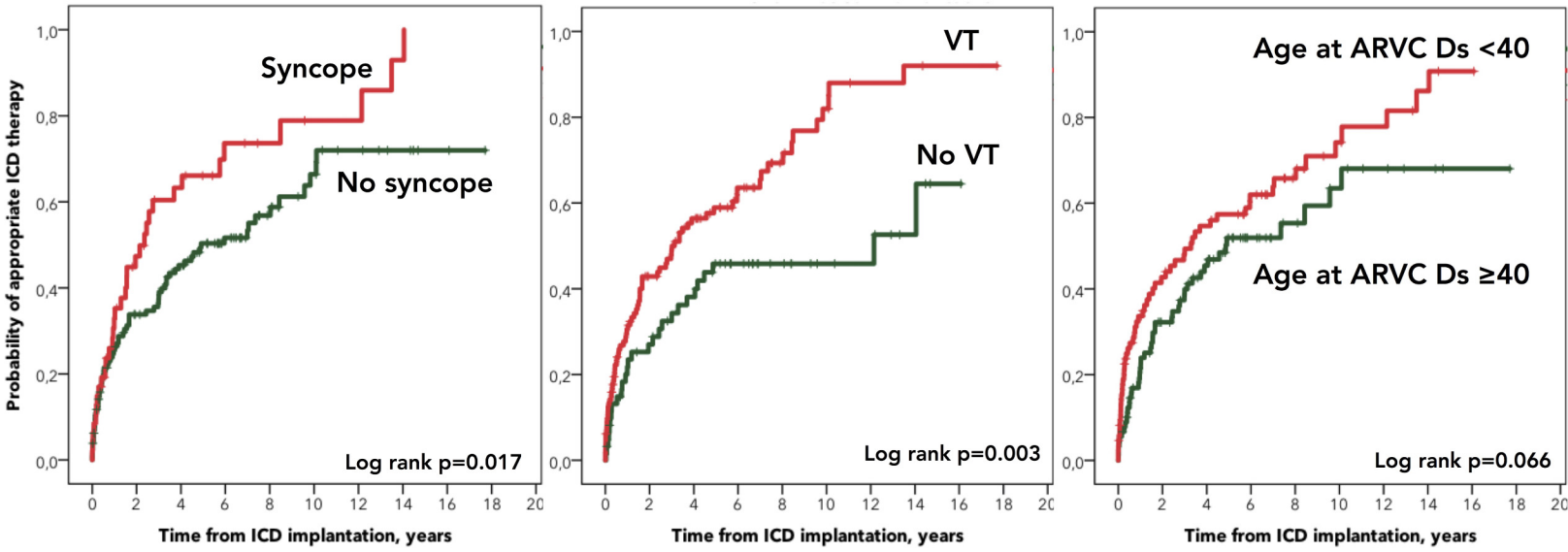
‡ data not published, provided by North American multidisciplinary ARVC study team.

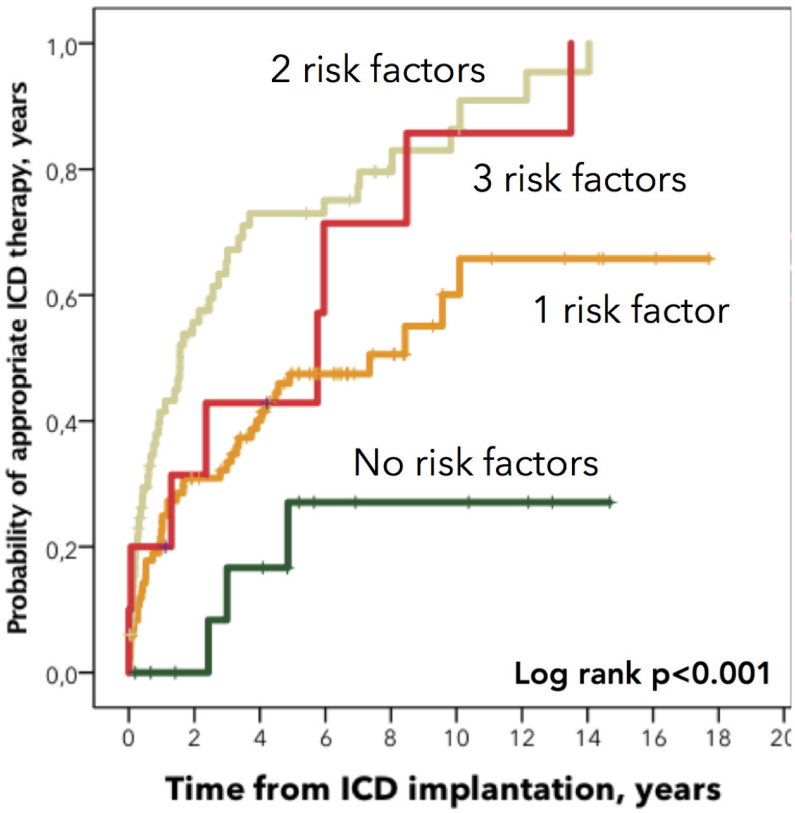
CENTRAL ILLUSTRATION:

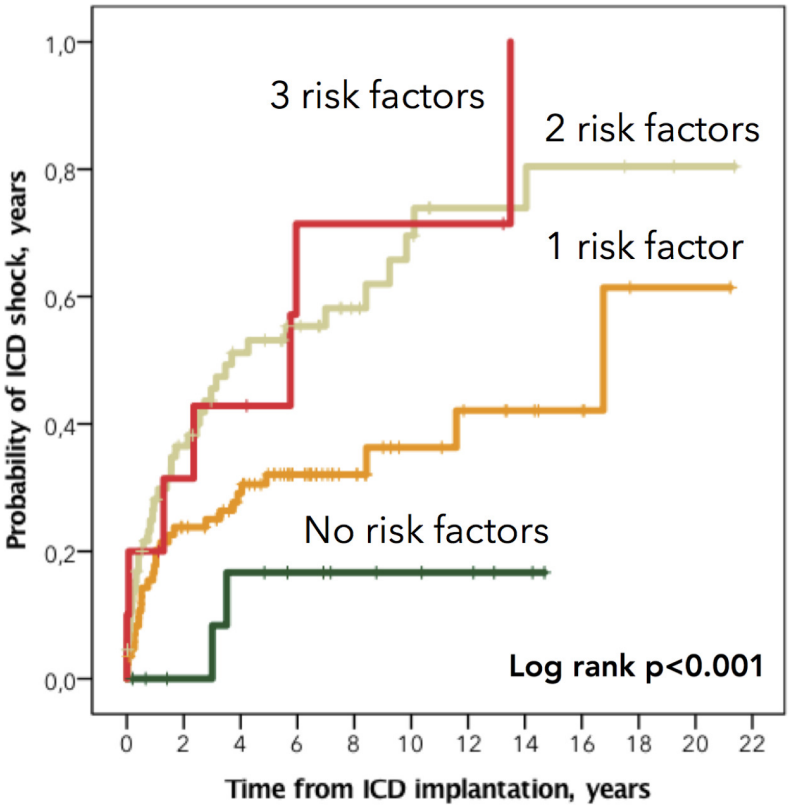


Title: Kaplan-Meier curve analysis of the relationship between the number of risk factors (history of syncope, VT or age at ARVC diagnosis under 40 years) and the time to appropriate ICD shocks in primary prevention ICD recipients from the Nordic ARVC Registry.

Caption: Compared to patients without risk factors, those with two or three risk factors had significant risk increase (HR=6.39, 95%CI 1.54 – 26.51, p=0.011) while differences between patients with one risk factors and those without were not significant. A significant risk increase was observed between patients with two vs. one risk factor (HR=2.13, 95%CI 1.31-3.44, p=0.002) while no further risk increase was seen when patients with three risk factors were compared with those with two.


Probability of appropriate ICD therapy
1,0
0,8
0,6
0,4
0,2
0,0
Syncope
No syncope
Log rank p=0.017
0 2 4 6 8 10 12 14 16 18 20
Time from ICD implantation, years
VT
No VT
Log rank p=0.003
Time from ICD implantation, years
Age at ARVC Ds <40
Age at ARVC Ds ≥40
Log rank p=0.066
Time from ICD implantation, years


Probability of appropriate ICD therapy, years
1,0
0,8
0,6
0,4
0,2
0,0
2 risk factors
3 risk factors
1 risk factor
No risk factors
Log rank p<0.001
0
2
4
6
8
10
12
14
16
18
20
Time from ICD implantation, years


Probability of ICD shock, years
1,0
0,8
0,6
0,4
0,2
0,0
3 risk factors
2 risk factors
1 risk factor
No risk factors
Log rank p<0.001
0
2
4
6
8
10
12
14
16
18
20
22
Time from ICD implantation, years