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CLINICAL RESEARCH

Comparing clinical performance of current implantable cardioverter-defibrillator implantation recommendations in arrhythmogenic right ventricular cardiomyopathy

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Aims Arrhythmogenic right ventricular cardiomyopathy (ARVC) patients have an increased risk of ventricular arrhythmias (VA). Four implantable cardioverter-defibrillator (ICD) recommendation algorithms are available The International Task Force Consensus ('ITFC'), an ITFC modification by Orgeron *et al.* ('mITFC'), the AHA/HRS/ACC guideline for VA management ('AHA'), and the HRS expert consensus statement ('HRS'). This study aims to validate and compare the performance of these algorithms in ARVC.

Methods and results We classified 617 definite ARVC patients (38.5 ± 15.1 years, 52.4% male, 39.2% prior sustained VA) according to four algorithms. Clinical performance was evaluated by sensitivity, specificity, ROC-analysis, and decision curve analysis for any sustained VA and for fast VA (>250 b.p.m.). During 6.4 [2.8–11.5] years follow-up, 282 (45.7%) patients experienced any sustained VA, and 63 (10.2%) fast VA. For any sustained VA, ITFC and mITFC provide higher sensitivity than AHA and HRS (94.0–97.8% vs. 76.7–83.5%), but lower specificity (15.9–32.0% vs. 42.7%-60.1%). Similarly, for fast VA, ITFC and mITFC provide higher sensitivity than AHA and HRS (95.2–97.1% vs. 76.7–78.4%) but lower specificity (42.7–43.1 vs. 76.7–78.4%). Decision curve analysis showed ITFC and mITFC to be superior for a 5-year sustained VA risk ICD indication threshold between 5–25% or 2–9% for fast VA.

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Conclusion The ITFC and mITFC provide the highest protection rates, whereas AHA and HRS decrease unnecessary ICD placements. ITFC or mITFC should be used if we consider the 5-year threshold for ICD indication to lie within 5–25% for sustained VA or 2–9% for fast VA. These data will inform decision-making for ICD placement in ARVC.

Keywords Arrhythmogenic right ventricular cardiomyopathy • Prognosis • Risk stratification • Implantable cardioverter-defibrillator • Ventricular arrhythmias

What's new?

- There are currently four implantable cardioverter-defibrillator (ICD) recommendation algorithms for patients with arrhythmogenic right ventricular cardiomyopathy available, but their relative clinical performance is unknown.
- This study showed the performance of the International Task Force Consensus (ITFC) and ITFC modification (mITFC) recommendations for ICD implantation to be nearly identical, as well as the performance of AHA and HRS.
- Our results suggest that the AHA and HRS recommendations have higher overall accuracy, but ITFC and mITFC provide better protection rates.
- If only fast ventricular arrhythmia (VA) (sustained ventricular tachycardia > 250 b.p.m./ventricular fibrillation/flutter/sudden cardiac death) is considered a relevant outcome for ICD indication, all four ICD recommendation algorithms perform poorly.
- At a ≥6% 5-year fast VA risk threshold for ICD implantation (as currently applied to hypertrophic cardiomyopathy patients), using ITFC results in the highest clinical benefit.

Introduction

Patients with arrhythmogenic right ventricular (RV) cardiomyopathy (ARVC) are at risk of sudden cardiac death (SCD), even at a young age.[1] This inheritable cardiomyopathy is characterized by progressive fibrofatty replacement of myocardium and intercalated disk remodelling,[2,3] leading to life-threatening ventricular arrhythmias (VA) and heart failure. A critical goal in clinical management is SCD prevention, for which implantable cardioverter-defibrillators (ICD) use is the only proven effective treatment. However, this invasive treatment inherently comes with risk of complications and inappropriate shocks.[4] Especially in ARVC, in which young patients may live with an ICD for decades, the life-time risk of complications can accumulate significantly.[5] Hence, this risk should be balanced against the risk of SCD, which varies widely amongst individuals.

Assessment of arrhythmic risk in ARVC has been an important research focus in the past decades, which resulted in the identification of a myriad of risk factors.[6] However, the majority of studies presented relative risks of single predictors, with no direct clinical translation. Therefore, expert consensus and guideline documents have been published, proposing risk stratification algorithms for ICD implantation. Today, three major consensus-derived algorithms are available: the 2015 International Task Force Consensus (ITFC) statement[7]; 2017 AHA/ACC/HRS Guideline for management of patients with VA[8]; and 2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy.[9] In addition, Orgeron *et al.*[10] suggested a modification of the ITFC (mITFC) for improved performance, creating a fourth algorithm. In the absence of clinical validation studies comparing their performance, it remains uncertain which algorithm should be recommended. Therefore, we designed this study to provide a comprehensive comparison of the clinical performance of these four risk stratification algorithms in a large multicentre ARVC cohort.

Methods

Study design

This is a multicentre, observational, longitudinal cohort study, based on two established patient registries in which data are both retro- and prospectively collected. The study conforms to the Helsinki declaration and was approved by local ethics and/or institutional review boards.

Study population

The population was drawn from the Netherlands (acmregistry.nl)[11] and Johns Hopkins (arvd.com) ARVC Registries. Eligible for inclusion were all patients with definite ARVC diagnosis according to the 2010 Task Force Criteria (TFC),[12] with available follow-up data. Patients were excluded if missing data prohibited classification by at least one algorithm, with exception of missing electrophysiology study data as described below.

Of note, the patients in our cohort from Johns Hopkins were used to derive the mITFC algorithm. As such, a sensitivity analysis was performed to validate the mITFC algorithm using Dutch patients only.

Data collection

For each participant, we extracted data from the registries required for the four stratification algorithms. This included demographics, genetics, family history, history of cardiac syncope or VAs, and clinical test results at baseline. Baseline was defined as the date of diagnosis per 2010. Outcome data were collected from all available follow-up, as described below.

Patient classification

All patients were retrospectively classified at baseline (i.e. time of diagnosis) as Class I (strong), Class IIa (moderate), or Class IIb/III (weak/no benefit) ICD indication, using the four stratification algorithms: (i) the 2015 International Task Force Consensus (onwards referred to as 'ITFC'), (ii) the modified ITFC as suggested by Orgeron *et al.* (onwards referred to as 'mITFC'), (iii) the 2017 AHA/ACC/HRS Guideline for the management of patients with VA (onwards referred to as 'AHA'), and (iv) the 2019 HRS

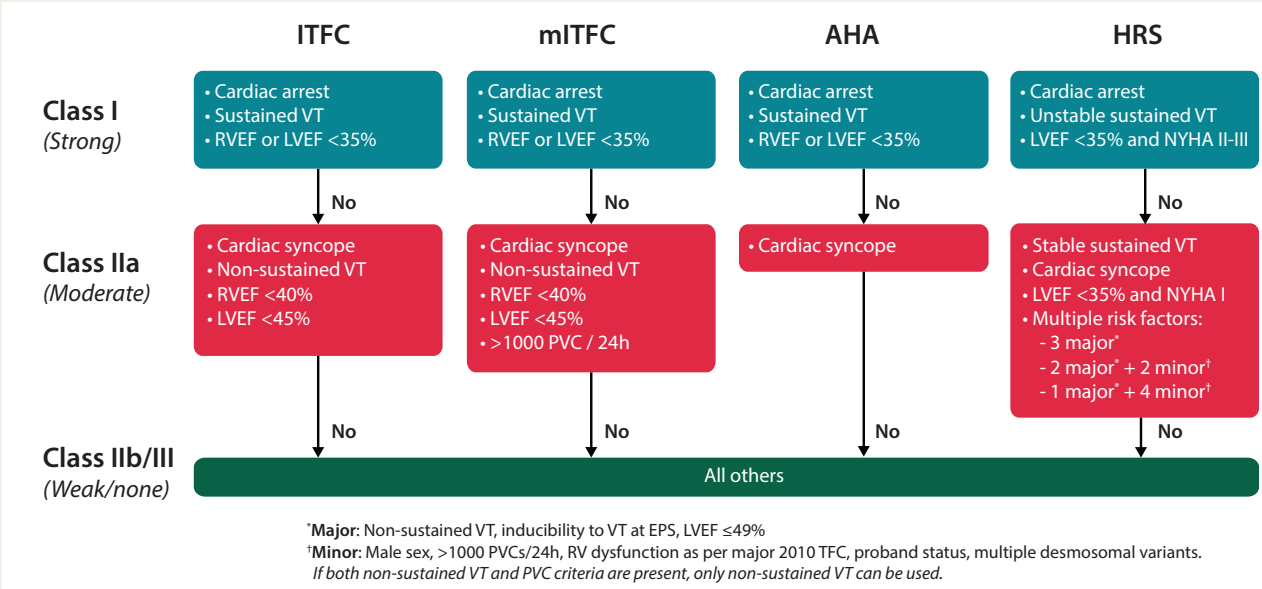

Figure 1 Schematic overview of the four ICD placement algorithms. ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; PVC, premature ventricular complex; RVEF, right ventricular ejection fraction; VA, ventricular arrhythmia; VT, ventricular tachycardia.

Expert consensus statement (onwards referred to as 'HRS'). A visual representation of these algorithms is provided in *Figure 1*. Of note, the Class I indication is nearly identical across the four algorithms—with exception of HRS not including RVEF ≤ 40% and stable sustained ventricular tachycardia (VT)—so differences observed will reflect primarily whether or not patients meet Class IIa criteria.

We assumed Class IIb indications to have limited value in prescribing ICD implantation. This reflects the fact that not all algorithms specify a Class IIb indication, and the strength of this indication is weak ('may be considered'). Furthermore, the risk factors that classify Class IIb indication in ITFC are not clearly defined. Since including a separate Class IIb group would introduce considerable subjective interpretation in the context of a weak ICD indication, we grouped these with Class III.

2015 International Task Force Consensus ('ITFC')

In this algorithm, patients had a Class I indication if they had a history of cardiac arrest, sustained VT, and/or severe ventricular dysfunction (RV fractional area ≤ 17%/RVEF ≤ 35% or LVEF ≤ 35%). Class IIa includes patients who had cardiac syncope, non-sustained VT, and/or moderate ventricular dysfunction (RV fractional area ≤ 24%/RVEF ≤ 40% or LVEF ≤ 45%). All others were classified as Class IIb/III.

2018 Orgeron *et al.* modification of ITFC ('mITFC')

In this algorithm, classification is as per ITFC, except for the addition of >1000 premature ventricular complexes (PVCs)/24 h on Holter as a Class IIa criterion.

2017 AHA/ACC/HRS Guideline for management of patients with VA ('AHA')

In this algorithm, criteria specified for Class I indication are identical to the ITFC. For Class IIa, only those with a history of cardiac syncope classified. All other patients were classified as IIb/III indication.

2019 HRS Expert Consensus statement ('HRS')

Patients had a Class I indication if they had a history of cardiac arrest, unstable sustained VT, and/or LVEF ≤ 35% with New York Heart Association (NYHA) functional Class II/III. Class IIa indication was defined as those with a history of cardiac syncope, stable sustained VT, LVEF < 35% with NYHA I, and/or a combination of at least three major risk factors, two major and two minor, or one major and four minor risk factors. Major risk factors were defined as non-sustained VT, inducible VT at electrophysiology study (EPS), and LVEF < 49%. Minor risk factors included: male sex, >1000 PVCs/24 h, major 2010 TFC criterion for RV function, proband status, and two or more desmosomal (likely) pathogenic genetic variants.

Missing data

Of the 650 patients found eligible for inclusion, 33 (5.3%) were excluded due to missing data preventing classification in at least one algorithm. Of the remaining 617 patients, all data required for classification was complete except for EPS results on VT inducibility. Missing EPS results were relevant for HRS classification of 31 (5.0%) patients. As the reason for not performing EPS in these patients was a clinically assumed low pre-test probability (all classified as IIb/III in absence of risk factors), we followed clinical practice by assuming VT inducibility to be negative. We repeated the analysis assuming a positive EPS result as sensitivity analysis.

Study outcomes

The outcome of interest in this study is the occurrence of potentially life-threatening ventricular arrhythmias during follow-up. We used two definitions: (i) any sustained VA, defined as VT > 100 b.p.m. lasting >30 s or with haemodynamic instability, ventricular fibrillation/flutter (VF), SCD or appropriate ICD therapy; and(ii) fast VA, defined as sustained VT > 250 b.p.m. lasting >30 s or terminated by ICD, VF, or SCD.

Table 1 Baseline characteristics

	Overall	Sustained VA in follow-up		P-value	Fast VA in follow-up		P-value
		No	Yes		No	Yes	
n	617[a]	335	282		554	63	
Age at diagnosis (years)	38.5 ± 15.1	39.8 ± 15.8	36.9 ± 14.0	0.020	39.6 ± 15.0	28.7 ± 12.3	<0.001
Male sex	323 (52.4)	142 (42.4)	181 (64.2)	<0.001	282 (50.9)	41 (65.1)	0.045
Proband	339 (54.9)	125 (37.3)	214 (75.9)	<0.001	283 (51.1)	56 (88.9)	<0.001
Pathogenic mutation	422 (68.4)	232 (69.3)	190 (67.4)	0.595	377 (68.1)	45 (71.4)	0.585
Cardiac syncope	158 (25.6)	64 (19.1)	94 (33.3)	<0.001	133 (24.0)	25 (39.7)	0.011
24 h PVC count	1200 [354–4181]	887 [175–3014]	2363 [849–5655]	<0.001	1076 [306–3866]	3021 [982–5882]	0.001
History of non-sustained VA	277 (44.9)	141 (42.1)	136 (48.2)	<0.001	241 (43.5)	36 (57.1)	0.086
History of sustained VA	242 (39.2)	73 (21.8)	169 (59.9)	<0.001	214 (38.6)	28 (44.4)	0.447
VT inducible on EPS (*n* = 311)	217 (35.2)	64 (19.1)	153 (54.3)	<0.001	185 (33.4)	32 (50.8)	0.022
RVEF (%)	43 ± 10	45 ± 9	41 ± 10	<0.001	43 ± 10	42 ± 9	0.547
LVEF (%)	58 ± 8	58 ± 8	58 ± 7	0.961	58 ± 8	57 ± 8.24	0.664
ICD implanted At baseline	314 (50.9)	144 (43.0)	170 (60.3)	<0.001	276 (49.8)	38 (60.3)	0.148
ICD implanted At follow-up	149 (24.1)	53 (15.8)	96 (34.0)	<0.001	129 (23.3)	20 (31.7)	0.183
Follow-up (years)	6.4 [2.8–11.5]	4.2 [1.7–8.8]	9.3 [4.6–14.4]	<0.001	6.4 [2.7–11.4]	6.5 [3.2–11.9]	0.319

[a]340 patients from Johns Hopkins ARVD Registry and 277 from Netherlands ACM Registry.
EPS, electrophysiologic study; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; PVC, premature ventricular complex; RVEF, right ventricular ejection fraction; VA, ventricular arrhythmia; VT, ventricular tachycardia.

Statistical analysis

Analyses were performed using Rstudio v1.1.414 (Boston, MA, USA). Variables were presented as frequencies (*N*, %), mean ± standard deviation, or median [interquartile range]. Incidence rates were calculated in person-years by Fishers mid-P Exact method. Event-free survival was determined by the Kaplan–Meier analysis. Pairwise comparisons were made using the log-rank test with Bonferroni correction. Baseline was defined as time of diagnosis (2010 TFC), and patients were censored at last clinical follow-up, death from any other cause, or heart-transplantation. Time-dependent sensitivity, specificity, and receiver-operatur characteristics curve (ROC)-analysis area under the curve (AUC) were based on presence/absence of ICD indication (present if Class I or IIa), and the presence/absence of the outcome during follow-up. Time-dependent clinical performance results are presented at a 5-year interval. Clinical benefit of the algorithms was compared by decision curve analysis based on the 'net benefit'[13]; a weighted ratio between 'true positive' and 'false positive' ICD indications. Higher values indicate greater benefit, which are graphically presented for a range of risk thresholds that can be considered to indicate an ICD. A two-sided *P*-value <0.05 was considered significant.

Results

Study population

The baseline characteristics of the 617 patients are shown in *Table 1*. Half (52.4%) of the population was male, with an average age at diagnosis of 38.5 ± 15.1 years. Overall, 242 (39.2%) patients had a history of sustained VA (i.e. secondary prevention). Over the course of 6.4 [2.8–11.5] years of follow-up, 282 (45.7%) experienced any sustained VA (median cycle length 280 ms [250–320]), and 63 (10.2%) experienced fast VA (median cycle length 225 ms [210–230]). This corresponded to an incidence rate of 10.2% (9.1–11.5) and 1.4% (1.1–1.8) per person-year, respectively. The characteristics separated by country are provided in Supplementary material online, *Table S1*.

Outcome per classification

Any sustained ventricular arrhythmia

As demonstrated in *Figure 2*, all four algorithms showed a significant difference in arrhythmia-free survival between ICD indications overall ($P < 0.001$). For the survival difference between indication classes, only AHA showed no significant difference between Class I and IIa ($P = 0.190$). In the groups without ICD indication (i.e. class IIb/III), mIFTC showed the lowest incidence rate of sustained VA with 1.7% (0.8–3.3) per person-year, followed by ITFC with 2.4% (1.4–3.9), and both AHA and HRS with 3.6% (2.7–4.8) per person-year (*Table 2*).

Fast ventricular arrhythmia

For fast VA (*Figure 3*), only AHA and HRS showed a significant difference in arrhythmia-free survival between ICD indications overall ($P = 0.033$ and $P = 0.016$, respectively). For the survival difference between indication classes, only AHA and HRS showed a significant difference, between Class IIa and no indication ($P = 0.041$ and $P = 0.015$, respectively). Stratification by ITFC and mITFC resulted in the lowest incidence rate of fast VA with 0.6% (0.1–1.6) per person-year for patients without an ICD indication (i.e. Class IIb/III), followed by HRS with 0.8% (0.4–1.4) and AHA with 0.9% (0.5–1.6) person-year (*Table 2*).

Clinical performance

Any sustained ventricular arrhythmia

As can be observed in *Figure 4A*, ITFC and mITFC show high sensitivity (94.0% and 97.8%, respectively) and consequently a low number

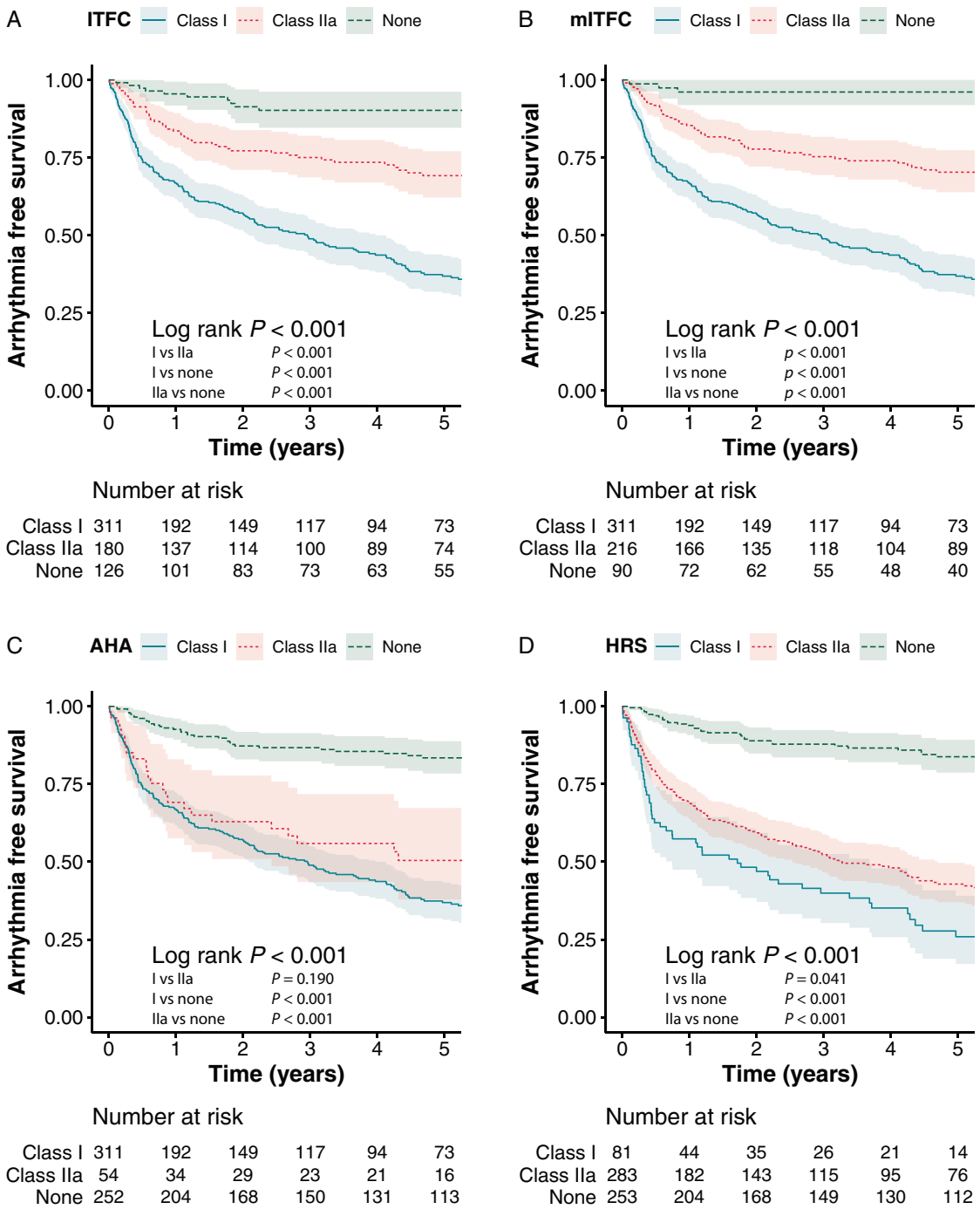

Figure 2 Kaplan–Meier plots with 95% CI for survival free from any sustained VA for each of the four ICD placement algorithms; ITFC (*A*), mITFC (*B*), AHA (*C*), and HRS (*D*). Survival is significantly worse concordant with the class of ICD indication. ICD, implantable cardioverter-defibrillator; VA, ventricular arrhythmia.

of patients with sustained VA without ICD indication (i.e. 'false negatives', 2.6% and 1.0%, respectively). Their specificities however were low (32.0% and 24.2%), resulting in an overall AUC of 0.63 and 0.61. This subtle difference in performance was not statistically significant ($P = 0.229$).

Although AHA and HRS showed lower sensitivity (both 83.5%) resulting in more patients with sustained VA without ICD indication (both 7.2%), they showed superior specificity (59.9% and 60.1%, respectively). Their AUC of 0.72 (identical in both algorithms) was significantly higher than ITFC and mITFC ($P < 0.001$). An overview of

Table 2 Incidence rates per ICD placement algorithm

	ITFC	mITFC	AHA	HRS
Incidence of any sustained VA (%/year)				
Class I	18.1 (15.7–20.7)	18.1 (15.7–20.7)	18.1 (15.7–20.7)	24.5 (18.7–31.5)
Class IIa	6.6 (5.0–8.5)	6.1 (4.7–7.7)	11.8 (7.7–17.2)	15.4 (13.2–17.9)
None	2.4 (1.4–3.9)	1.7 (0.8–3.3)	3.6 (2.7–4.8)	3.6 (2.7–4.8)
Incidence of fast VA (%/year)				
Class I	1.5 (1.1–2.1)	1.5 (1.1–2.1)	1.5 (1.1–2.1)	1.6 (0.8–2.9)
Class IIa	1.7 (1.0–2.6)	1.5 (0.9–2.3)	2.5 (1.1–4.8)	1.8 (1.2–2.4)
None	0.6 (0.1–1.6)	0.6 (0.1–1.6)	0.9 (0.5–1.6)	0.8 (0.4–1.4)

VA, ventricular arrhythmia; algorithm names are abbreviated as in text.

the time-dependent AUC plotted over time is provided in Supplementary material online, *Figure S1*.

The decision curve analysis (*Figure 5A*) showed that the ITFC and mITFC algorithm result in the greatest net benefit for a sustained VA risk threshold for ICD placement ranging from 5 to 25% over 5-years, while AHA and HRS both had greater benefit for a risk threshold >25%.

Fast ventricular arrhythmia

Similar to the sustained VA outcome, ITFC and mITFC showed the highest sensitivity and therefore the lowest proportion of patients suffering from an event without ICD indication ('false negatives' 0.5% and 0.3%, respectively)(*Figure 4B*), but with low specificity (22.3% and 15.9%, respectively). Although AHA and HRS had superior specificity for predicting fast VA (42.7% and 43.1%), the overall AUC of all four algorithms was relatively low within a narrow range from 0.57 (mITFC) to 0.61 (HRS), showing no statistically significant difference in performance.

Based on the decision curve analysis (*Figure 5B*), using mITFC resulted in the highest net benefit for a fast VA risk threshold ranging from 2–4%, ITFC for 4–9%, and AHA and HRS both showed the highest benefit for a risk threshold >9%.

Sensitivity and subgroup analyses

By study design, we assumed 31 cases with missing EPS data to have no VT inducibility. If VT inducibility would have been positive, the HRS classification of these patients would shift from Class IIb/III to Class IIa. This would result in a non-significant decrease in AUC for any sustained VA (0.72–0.70, $P = 0.339$). The AUC for fast VA remained identical (0.61).

As shown in Supplementary material online, *Figure S2*, we conducted three sensitivity analyses. First, using only the Dutch cohort (as the Johns Hopkins cohort was used to derive the mITFC algorithm) showed nearly identical results. Next, we stratified the cohort by history of sustained VA. For primary prevention patients ($n = 375$), the AHA and HRS algorithms showed poor sensitivity, as low as 61.7%, meaning failure to protect 1 out of every 3 patients with incident sustained VA. Finally, we stratified the cohort into patients with ($n = 374$) and without ($n = 243$) pathogenic desmosomal variants. All four models performed somewhat better for patients with a desmosomal variant, with both a higher sensitivity and higher specificity.

Discussion

This study compares the clinical performance of all four available ICD placement recommendation algorithms in a large multicentre cohort of ARVC patients. In absence of a widely accepted ICD recommendation consensus, our study provides results highly relevant to clinical practice. First, we confirmed that all four algorithms are able to stratify the population in low-, intermediate- and high-risk, relative to the strength of ICD indication. Second, all four algorithms have limited accuracy, trading higher sensitivity for lower specificity (ITFC and mITFC) and vice versa (AHA and HRS). Lastly, we found that if we consider the 5-year risk threshold of ≥6% currently used in hypertrophic cardiomyopathy (HCM) patients to be reasonable for ARVC patients too, it would be best to use ITFC.

Implantable cardioverter-defibrillator placement recommendations in arrhythmogenic right ventricular cardiomyopathy: need for consensus

While multiple ICD placement recommendation algorithms have been proposed to guide clinical decision-making for patients with ARVC, a widely accepted consensus on which algorithm to use is lacking. In the absence of sufficient validation data, an evidence-based consensus is unlikely to emerge. Prior to this study, the ITFC algorithm was validated by Orgeron *et al.*[10]: using a cohort of 365 ARVC patients, the authors showed that the ITFC algorithm stratified the population with reasonable accuracy by comparing arrhythmia incidence rates to the strength of ICD indication, similar to our findings.

Of note, the four algorithms tested in this study are all flowchart based, depending on single risk factors sufficient to individually indicate an ICD, without considering the combined effect and interactions of other risk factors that may be present. Not only does this result in relatively crude stratifications, it may also fail to indicate an ICD in patients with high risk based on a combination of risk factors which individually

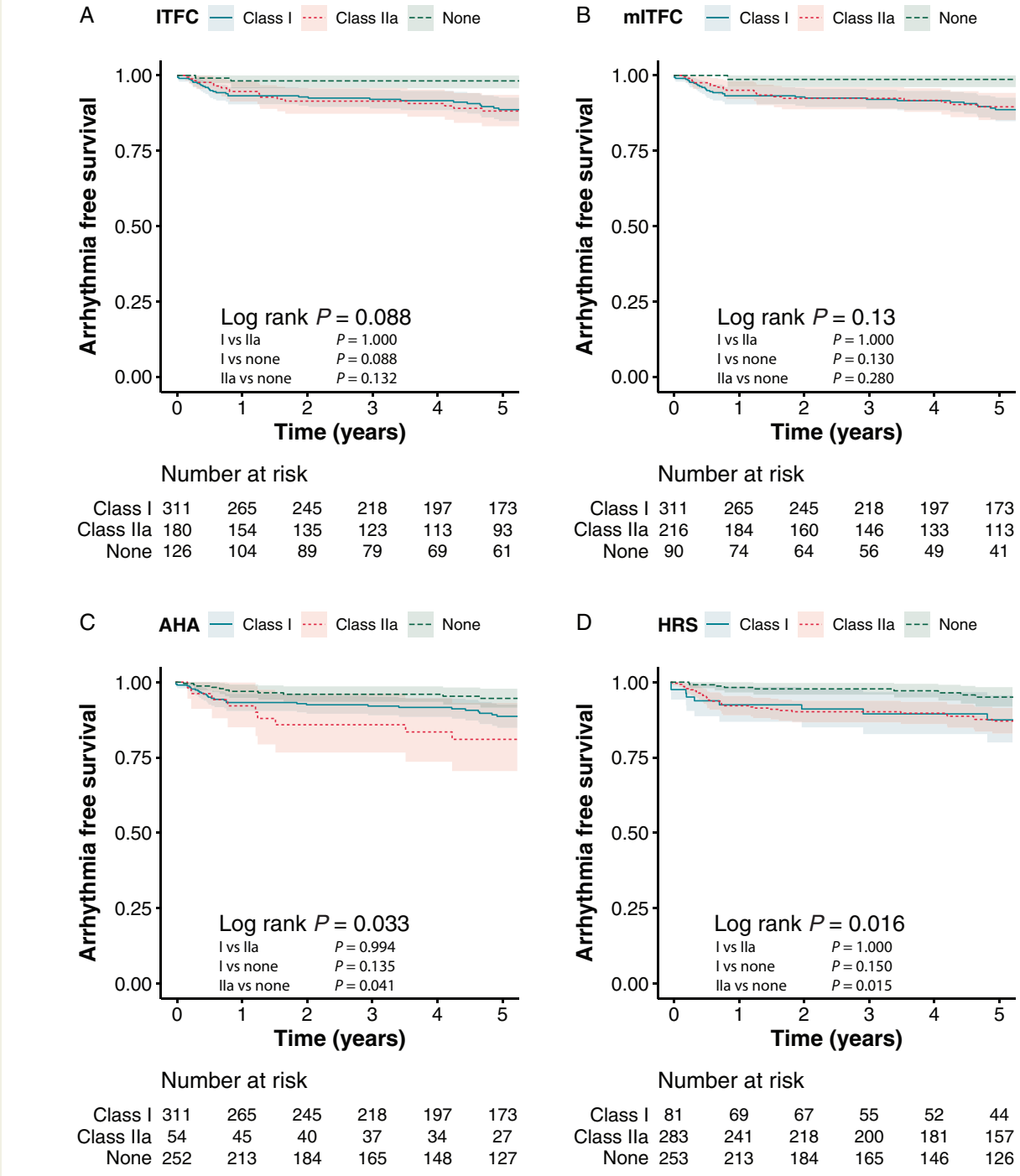

Figure 3 Kaplan–Meier plots with 95% CI for survival free from fast VA for each of the four ICD placement algorithms; ITFC (*A*), mITFC (*B*), AHA (*C*), and HRS (*D*). Only HRS showed a significantly different survival between ICD indication classes but only between class IIa and none (IIb/III). ICD, implantable cardioverter-defibrillator; VA, ventricular arrhythmia.

would not justify an ICD. An example would be young athletic male patients, who we know can be at high risk of cardiac arrest even in absence of prior VA or ventricular dysfunction therefore having no ICD indication.[14] Considering these limitations, a more elegant alternative may be multivariable prediction models, as previously established for HCM.[15] Two such models were recently developed for ARVC[16,17]; one to predict a first sustained VA for primary prevention, and one to predict fast (>250 b.p.m.) VA. Risk estimations are based on effect combinations from sex, age, syncope, T-wave inversions on electrocardiogram, PVC count, (non-)sustained VT, and RVEF.

As the cohort in this study greatly overlaps with the cohort from which these ARVC risk score models were derived, we did not add

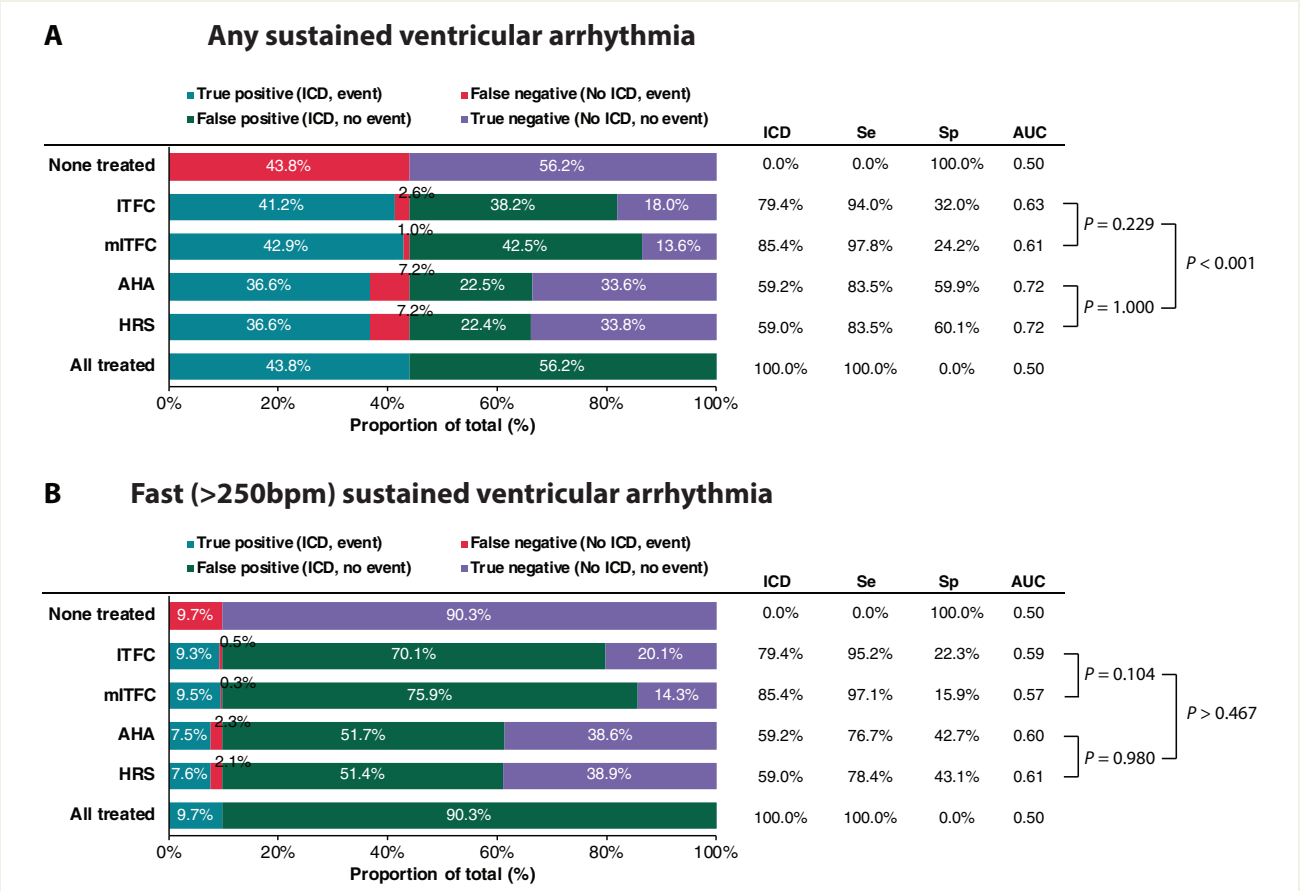

Figure 4 Clinical performance measures of the four ICD placement recommendation algorithms at a 5-year time point for (*A*) any sustained VA, and (*B*) fast VA. Bar chart shows the proportion of patients correctly classified (blue) and incorrectly classified (orange), with dark colouring for those with events and light colouring for those without. Table on the right shows total proportion with ICD, sensitivity (Se), specificity (Sp), and time-dependent area under the curve (AUC). ICD, implantable cardioverter-defibrillator; VA, ventricular arrhythmia.

the ARVC risk score models as a comparator in our main study results. For completeness, we do provide the results of this comparison in Supplementary material online, *Figure S3*. Similar to the results of Aquaro *et al.*,[18] who compared the clinical performance of the ITFC and HRS algorithms to the 5-year ARVC risk score in a cohort of 140 ARVC patients without prior VA, we observed that the risk score models have superior performance. However, prior to their widespread clinical application, external validation studies are required to confirm the performance of these models.

Comparison of clinical performance

As demonstrated in *Figure 4*, the accuracy of all four algorithms was low to moderate for any sustained VA (AUC 0.61–0.72), and low for fast VA (AUC 0.57–0.61). However, an interesting pattern can be observed: ITFC and mITFC have superior sensitivity (94.0–97.8%) at the expense of lower specificity (15.9–32.0%), while the lower sensitivity of AHA and HRS (76.7–83.5%) is compensated by superior specificity (42.7–60.1%). Thus, as demonstrated in *Figure 4*, the ITFC and mITFC algorithms provide better protection rates but result in a considerable number of ICD placements in patients not experiencing events. In contrast, the AHA or HRS algorithms provide lower protection rates but result in a considerable reduction of patients treated with an ICD in whom outcomes do not occur.

The downside of the above-mentioned statistical measures is that patients developing the outcome while having no ICD indication ('false negative') weigh equal to patients not developing life. A better measurement of clinical performance with a direct translation to clinical practice is the net benefit.[13] The decision curve analysis (*Figure 5*) showed that ITFC and mITFC are the preferred algorithms to use when the desired sustained VA risk threshold for ICD implantation lies within 5–25%. For fast VA risk, mITFC is the preferred algorithm when the threshold lies within 2–4%, and ITFC for 4–9%. For both outcomes, AHA and HRS are superior when the risk threshold for ICD indication lies beyond those ranges (>25% sustained VA risk or >9% fast VA risk).

Any sustained ventricular arrhythmia vs. fast ventricular arrhythmia

Although SCD is the most clinically relevant outcome for ICD indication, studying this outcome would require a large prospective study in which patients do not receive an ICD, which cannot be justified ethically. Hence, sustained VA and appropriate ICD therapies are

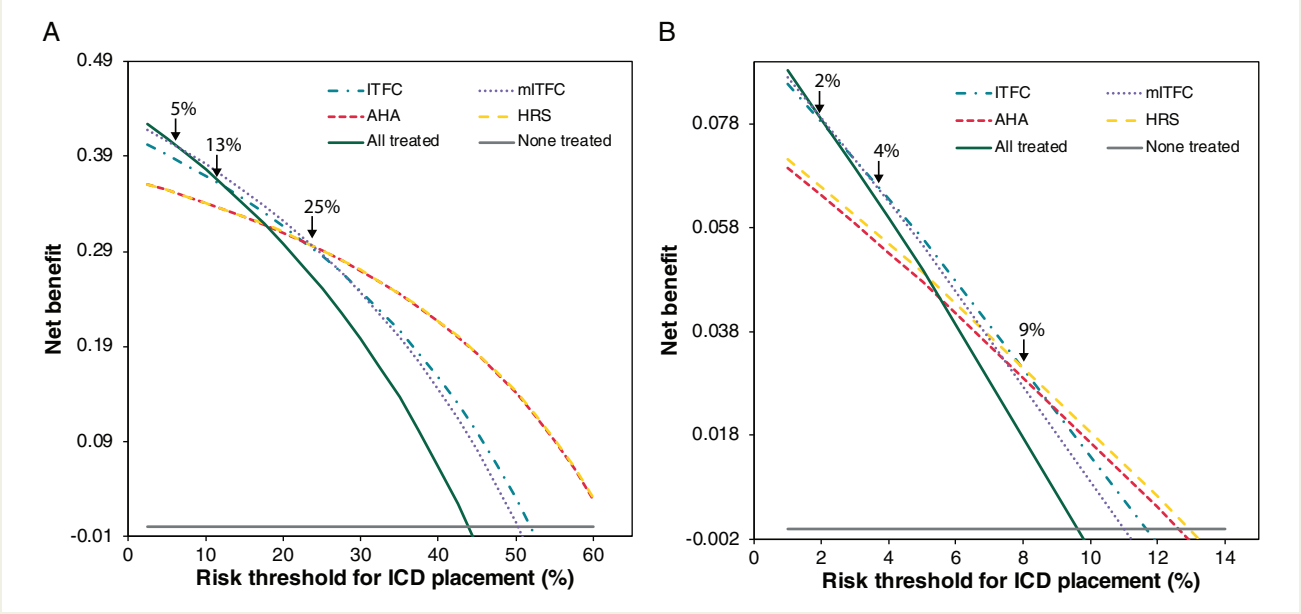

Figure 5 Decision curve analysis with the 5-year risk threshold for ICD placement on the X-axis and net benefit on the Y-axis. (*A*) For any sustained VA, this graph demonstrates that when the risk threshold justifying ICD placement lies between 5–25%, ITFC and mITFC algorithms had the best performance, while AHA and HRS perform best if the risk threshold is >25%. (*B*) For fast VA, mITFC performs best when the threshold lies between 2–4%, ITFC when between 4–9%, and AHA/HRS when >9%. ICD, implantable cardioverter-defibrillator; VA, ventricular arrhythmia.

generally used as a surrogate. Prior literature predominantly uses an outcome similar to our 'any sustained VA' outcome.[6] However, as most sustained events likely do not lead to SCD (e.g. 39.2% of patients in this cohort survived a prior sustained VA), this outcome likely overestimates the risk of SCD. Some recent studies have shifted towards using the outcome of fast VA (sustained VT > 250 b.p.m./VF/SCD) to better approximate the risk of SCD.[6] This aligns with the MADIT-RIT trial, which showed that more lenient ICD programming selectively targeting rapid and longer events reduces mortality.[19] In this study, results for both outcomes are presented, showing an alarming poor performance of the algorithms in predicting fast VA. While this is not surprising as the algorithms are based on literature that predominantly used the 'any sustained VA' outcome, this is an important limitation of these algorithms.

Clinical recommendations

Ideally, ICDs are implanted only in those who will experience SCD, avoiding the physical and emotional burden of ICDs in those who do not need the device.[20] However, the protection rates of the four ICD recommendation algorithms reviewed in this study come at cost of unnecessary ICD placements. Which of the algorithms performs 'best' depends on the preferred balance between protection rate and number of unnecessary ICD placements. Ultimately, the final decision as to whether to implant an ICD is based on a shared decision-making process taking into consideration the preferences and values of the patient and judgement of the clinician. Some patients are very uncomfortable with the concept of ICD implantation and are willing to accept a higher risk of SCD, whereas others are unwilling to accept even the smallest risk. In our experience, most ARVC patients who face this decision are often young and otherwise healthy, have family responsibilities, and an otherwise promising future, and therefore unwilling to accept even a small risk of SCD and elect to undergo ICD implantation.

For HCM patients, another group of relatively young often otherwise healthy patients, ICD placement is recommended at a 5-year risk of SCD ≥ 6%.[21] This is a reasonable threshold for ARVC patients as well. Based on the decision curve analysis in *Figure 5B*, at an ICD indication threshold of 5-year risk of fast VA ≥ 6% (closest approximation of SCD), the ITFC algorithm provides the best performance and should be the recommended algorithm to use. Nonetheless, both personal preference and healthcare system differences remain important considerations.

Limitations

Clinical testing was performed upon the discretion of the clinician, and not all tests required by the prognostic algorithms were available. Patients with missing data preventing their classification were therefore excluded, potentially introducing bias. However, as only 33 (5.3%) patients were excluded, the effect is likely minimal. In 31 patients, missing EPS results may have influenced the reported results for the HRS algorithm, although our sensitivity analysis showed no significant shift of results. As described above, both any sustained VA and fast VA are imperfect surrogates of SCD, which may have been further impacted by non-uniform ICD programming. Finally, this study assesses the performance of these risk stratification algorithms for ICD placement at diagnosis over approximately the ICD life time (i.e. 5–7 years). Arrhythmogenic right ventricular cardiomyopathy is a progressive disease with a long course and therefore arrhythmia risk needs to be periodically reassessed and ICD implantation decisions potentially revisited.

Conclusion

For sustained VA, ITFC and mITFC provide the highest ICD protection rates, whereas AHA and HRS have the highest overall accuracy (AUC 0.72) due to significantly less unnecessary ICD placements. However, for the arguable more clinically relevant fast VA outcome, all four algorithms performed poorly. If we consider a threshold of ≥6% 5-year risk of fast VA (similar to the threshold for HCM patients) to indicate an ICD in ARVC, the ITFC is the best performing algorithm. These data may inform decision-making for ICD placement in ARVC, but moreover indicate the need for better risk stratification methods to prevent SCD in this population.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

References

1. Groeneweg JA, Bhonsale A, James CA, Riele Te AS, Dooijes D, Tichnell C *et al.* Clinical presentation, long-term follow-up, and outcomes of 1001 arrhythmogenic right ventricular dysplasia/cardiomyopathy patients and family members. *Circ Cardiovasc Genet* 2015;**8**:437–46.
2. Delmar M, McKenna WJ, The cardiac desmosome and arrhythmogenic cardiomyopathies: from gene to disease. *Circ Res* 2010;**107**:700–14.
3. Corrado D, Link MS, Calkins H, Arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med* 2017;**376**:61–72.
4. Olde Nordkamp LRA, Postema PG, Knops RE, van Dijk N, Limpens J, Wilde AAM *et al.* Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: a systematic review and meta-analysis of inappropriate shocks and complications. *Heart Rhythm* 2016;**13**:443–54.
5. Orgeron GM, James CA, Riele TA, Tichnell C, Murray B, Bhonsale A *et al.* Implantable cardioverter-defibrillator therapy in arrhythmogenic right ventricular dysplasia/cardiomyopathy: predictors of appropriate therapy, outcomes, and complications. *J Am Heart Assoc* 2017;**6**:e006242.
6. Bosman LP, Sammani A, James CA, Cadrin-Tourigny J, Calkins H, van Tintelen JP *et al.* Predicting arrhythmic risk in arrhythmogenic right ventricular cardiomyopathy: a systematic review and meta-analysis. *Heart Rhythm* 2018;**15**:1097–107.
7. Corrado D, Wichter T, Link MS, Hauer R, Marchlinski F, Anastasakis A *et al.* Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. *Eur Heart J* 2015;**36**:3227–37.
8. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB *et al.* AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2017;**72**:e91–e220.
9. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC *et al.* HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy. *Heart Rhythm* 2019;**16**:e301–72
10. Orgeron GM, Riele Te A, Tichnell C, Wang W, Murray B, Bhonsale A *et al.* Performance of the 2015 International Task Force Consensus Statement Risk Stratification Algorithm for Implantable Cardioverter-Defibrillator Placement in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. *Circ Arrhythm Electrophysiol* 2018;**11**:e005593.
11. Bosman LP, Verstraelen TE, van Lint FHM, Cox MGPJ, Groeneweg JA, Mast TP *et al.* The Netherlands Arrhythmogenic Cardiomyopathy Registry: design and status update. *Neth Heart J* 2019;**27**:480–86.
12. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA *et al.* Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. *Eur Heart J* 2010;806–14.
13. Vickers AJ, Van Calster B, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. *BMJ* 2016;**352**:i6.
14. Gupta R, Tichnell C, Murray B, Rizzo S, Riele Te A, Tandri H *et al.* Comparison of features of fatal versus nonfatal cardiac arrest in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Am J Cardiol* 2017;**120**:111–7.
15. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C *et al.* A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J* 2014;**35**:2010–20.
16. Cadrin-Tourigny J, Bosman LP, Nozza A, Wang W, Tadros R, Bhonsale A *et al.* A new prediction model for ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J* 2019;**40**:1850–1858.
17. Cadrin-Tourigny J, Bosman LP, Wang W, Tadros R, Bhonsale A, Bourfiss M *et al.* Sudden cardiac death prediction in arrhythmogenic right ventricular cardiomyopathy: a multinational collaboration. *Circ Arrhythm Electrophysiol* 2021;**14**:e008509.
18. Aquaro GD, De Luca A, Cappelletto C, Raimondi F, Bianco F, Botto N *et al.* Comparison of different prediction models for the indication of implanted cardioverter defibrillator in patients with arrhythmogenic right ventricular cardiomyopathy. *ESC Heart Fail* 2020;**7**:4080–4088.
19. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP *et al.* Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med* 2012;**367**:2275–83.
20. James CA, Tichnell C, Murray B, Daly A, Sears SF, Calkins H, General and disease-specific psychosocial adjustment in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy with implantable cardioverter defibrillators: a large cohort study. *Circ Cardiovasc Genetics* 2012;**5**:18–24.
21. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P *et al.* ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J* 2014;**35**:2733–2779.