HeartRhythm

The Official Journal of the Heart Rhythm Society, The Cardiac Electrophysiology Society, and The Pediatric & Congenital Electrophysiology Society

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Personalized sudden cardiac death risk prediction in genetic heart diseases: Beyond one-size-fits-all

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ABSTRACT

Sudden cardiac death (SCD) risk prediction in genetic heart diseases is essential to identify patients who will benefit from implantable cardioverter-defibrillator (ICD) implantation. Although many prediction tools have been developed, risk prediction remains challenging due to variability in underlying arrhythmic substrates and statistical modeling approaches. This review addresses 2 major challenges in current clinical practice. First, the use of surrogate SCD end points, such as appropriate ICD therapy, can potentially and actually does lead to overestimation of the "true" SCD risk. This may result in unnecessary ICD implantation in low-risk patients and exposing them to device-related complications. Second, most risk models are static and do not account for temporal changes in risk. We provide an overview of SCD prediction models and offer recommendations to address these challenges. This review underscores the need for disease-specific surrogate end points and dynamic risk models that reflect individual risk over time.

KEYWORDS Genetic heart diseases; Sudden cardiac death; Risk prediction tools; Surrogate SCD end points; ICD implantation

(Heart Rhythm 2026;23:e62–e74)

Patients with genetic heart diseases, either inherited cardiomyopathies or primary electrical heart disorders, are at risk of sudden cardiac death (SCD).[1–16] Risk stratification remains challenging because of the variability in risk depending on the genetic variant, disease expression, and modifying external factors. Over the past 2 decades, an increasing number of risk prediction models have been developed for specific genetic heart diseases and variants. However, these models do not follow the same structure and methodology, making interpretation and comparison difficult.

This review addresses 2 major challenges in current SCD risk prediction. First, there is no consensus on which definition of life-threatening ventricular arrhythmia (LTVA) can serve as a valid surrogate SCD end point. The composite end points often include appropriate implantable cardioverter-defibrillator (ICD) therapies, sustained ventricular tachycardia (VT) above a certain rate, hemodynamically instability, and associated symptoms. And rarely, risk prediction models have included pre-defined ICD settings. The inclusion of these surrogate end points may lead to overestimation of the 'true' SCD risk, although the degree likely varies between disease.

Second, most risk models rely on a static baseline model, whereas new insights suggest that the predictive value of certain variables can change over time.[17,18] These changes can result from disease progression or treatment effects. Static models do not account for such dynamics, which may lead to inaccurate risk estimates. This highlights the need for dynamic prediction models that take time effects and individual disease trajectories into account.

The aim of this review is to provide an overview of SCD risk prediction models in genetic heart diseases, discuss ongoing dilemmas, and offer recommendations for future improvement.

Surrogate markers for SCD predictions

In most SCD prediction models, the main driver of events is appropriate ICD therapy, as displayed in Figure 1A. Without

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https://doi.org/10.1016/j.hrthm.2025.07.041

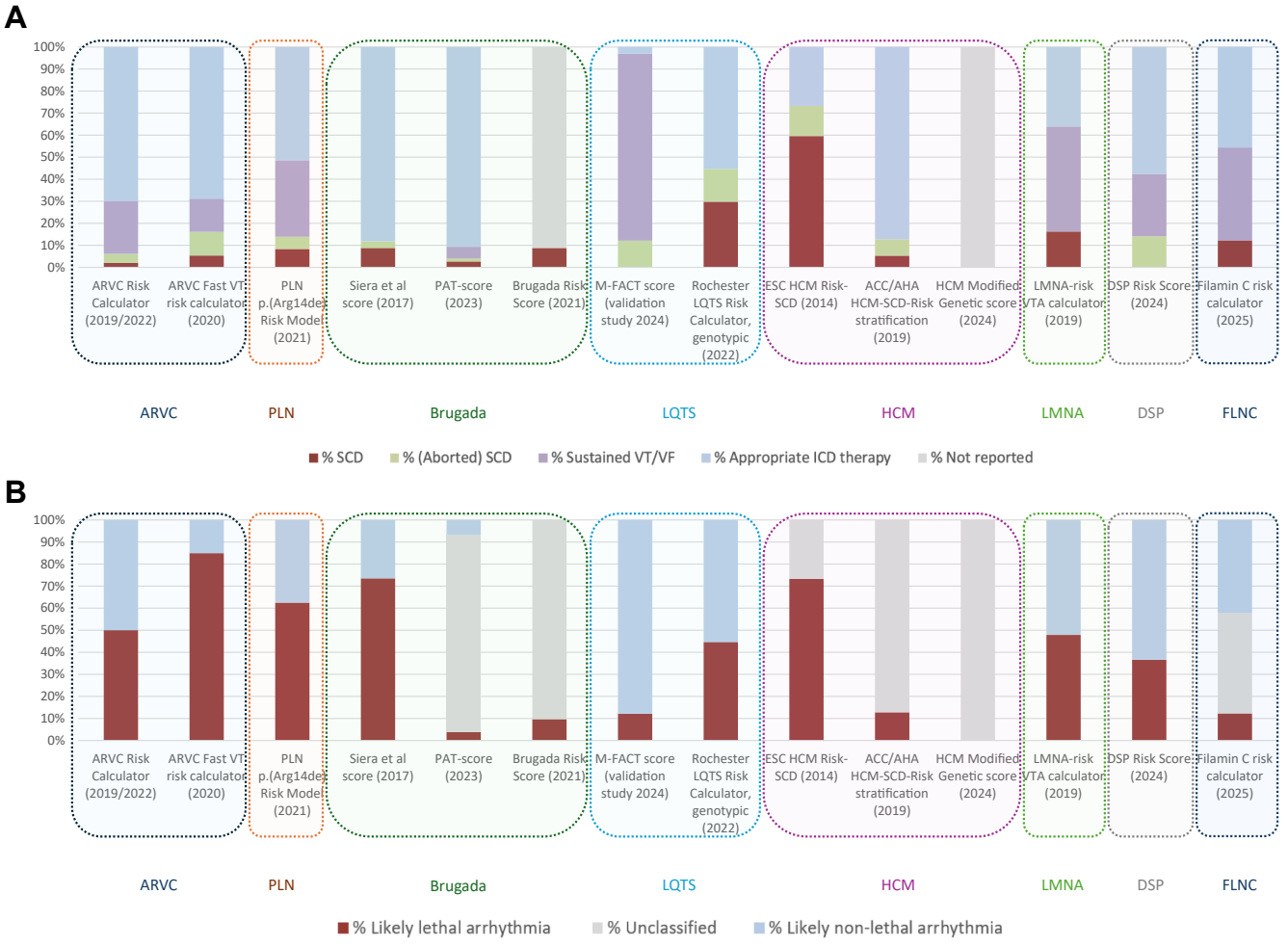

Figure 1

Overview of SCD risk prediction tools. **A:** Shows the composition of combined SCD end points across various risk prediction models. **B:** Illustrates the estimated distribution of 'likely lethal arrhythmia' and 'likely non-lethal arrhythmia', based on the following classification criteria: (aborted) SCD or VT/VF $\geq$ 250 bpm. and/or associated with hemodynamic instability were considered likely lethal, and all other VT/VF and ICD therapy events were considered likely non-lethal. ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.

inclusion of this surrogate end point, many models would lack sufficient power and event rates for development and validation. Moreover, excluding patients with an ICD would remove a substantial high-risk population from analysis. However, the use of appropriate ICD intervention as a surrogate marker for SCD has limitations. Not all ventricular arrhythmias that trigger ICD intervention would actually be life threatening. This depends on factors such as VT cycle length, cardiac function, and the circumstances under which VT occurs.[19] As a result, relying on appropriate ICD therapy as a surrogate end point may lead to overestimation of the true SCD risk and unnecessary ICD implantations in low-risk patients, exposing them to complications such as inappropriate therapy and lead infections. This is particularly relevant in patients with genetic heart diseases, who often receive their ICD at a younger age and are therefore longer at risk.[20] The DANISH trial illustrates this concern.[21] Among patients with non-ischemic cardiomyopathy and symptomatic systolic heart failure (left ventricular [LV] ejection fraction [LVEF] $\leq$35%), SCD occurred in 4.3% of the ICD group, compared to 8.2% in the control group, resulting in an absolute SCD risk difference of 3.9%. However, in the ICD group, antitachycardia pacing terminated VT in 17.4% of patients, and 11.5% received appropriate ICD shock. These rates of appropriate therapy far exceed the observed SCD risk difference of 3.9%, underscoring that ICD therapy is not a direct 1:1 surrogate for SCD. The actual ratio is more likely to be 1:3 or even higher. The DANISH trial outcomes are presented in Figure 2.

It is worth noting that the patient population in the DANISH trial was not fully genotyped. In a large multicenter study of genotyped patients with dilated cardiomyopathy, it was found that those with a likely pathogenic (LP)/pathogenic (P) variant had a higher risk of major ventricular arrhythmia (VA) than genotype-negative patients when LVEF $\leq$35%, and the risk of major VA varied depending on the affected gene.[22]

This dilemma in risk prediction modeling is complex and does not have a one-shoe-fits-all solution. It requires disease-specific recommendations for each genetic heart

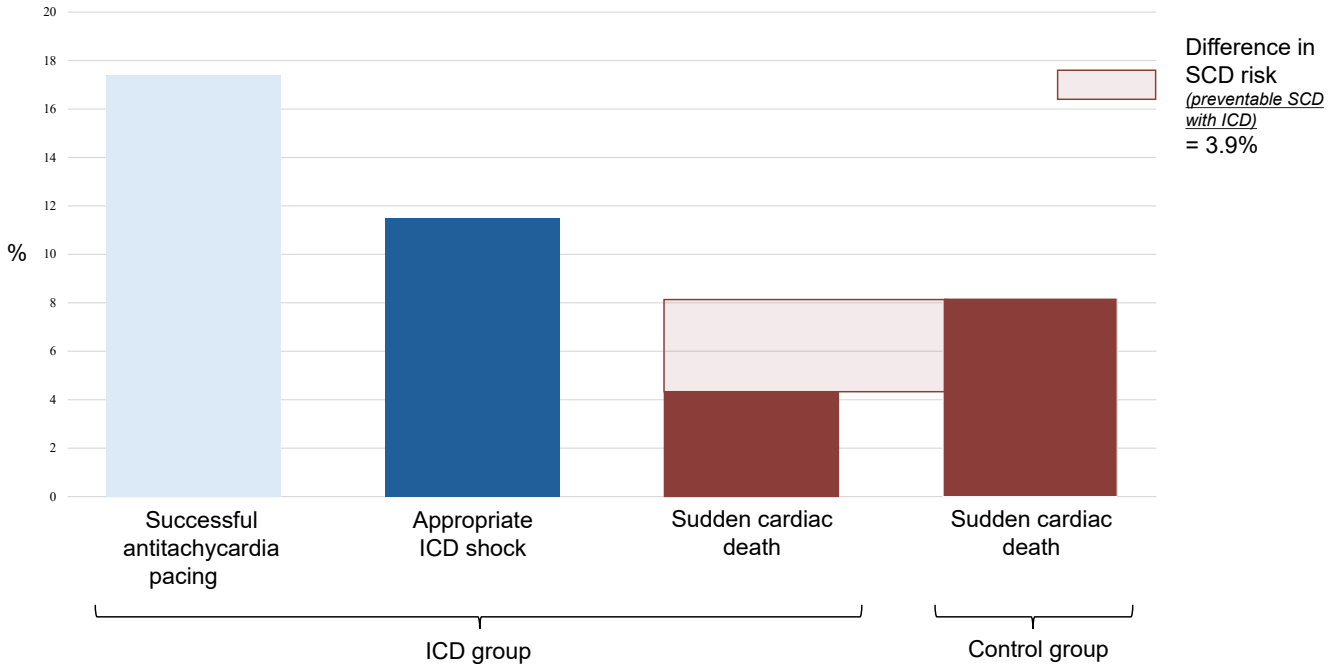

Figure 2
Outcomes in DANISH trial. The difference in SCD risk between the ICD group and control group was 3.9%. This is regarded as SCD prevented with ICD implantation. Note that appropriate ICD shock has a higher incidence than (preventable) SCD incidence. ICD = implantable cardioverter-defibrillator; SCD = sudden cardiac death.

disease. A summary of the prediction models included in this review is provided in Table 1. In the following sections, we provide a detailed discussion of each genetic heart disease.

Arrhythmogenic right ventricular cardiomyopathy

The arrhythmogenic right ventricular (RV) cardiomyopathy (ARVC) risk calculator was first developed in 2019 and corrected in 2022.[1] The development cohort consisted of 528 patients with ARVC, 64.4% of whom had a LP/P variant, most commonly in PKP2 (48.9%). The model performed moderate with a C-statistic of 0.77 and was validated in external cohorts. In 2021, the predictors of the ARVC risk score were reassessed for a LTVA end point in even a larger cohort of 864 patients with ARVC, including patients with prior sustained VT (38.8%),[2] and the event rate dropped from 5.6% to 1.6%. This study compared both models in terms of individual predicted risk and revealed substantial variation in patients with different risk profiles.

The inclusion of appropriate ICD therapy (68.8%) in the composite SCD end point undoubtedly results in overestimating the true SCD risk, as many arrhythmias are scar-related, hemodynamically stable monomorphic VT episodes that are likely non-fatal.[23] This is reflected in the low annual LTVA event rate of 1.6%.

The LTVA end point limits overestimation, and on the contrary, it may potentially underestimate SCD risk in some patients, particularly in those with compromised LV and/or RV function as they cannot tolerated slower VT's. Though, this is probably applicable to only a small subgroup, as the mean LVEF% of the patients with sustained VA in the original model was 56.34% (±9.34).

Conclusion/recommendation:

- The original ARVC risk model certainly overestimate, while the ARVC risk model for fast VT may potentially underestimate the true SCD risk.
- We recommend using both prediction models. These risk models are complementary, as the true SCD risk lies somewhere in between. This approach provides a more balanced and truthful risk assessment in this specific patient population.

Phospholamban p.(Arg14del) cardiomyopathy

The phospholamban (PLN) p.(Arg14del) risk calculator was published in 2021.[3] In a cohort of 679 PLN p.(Arg14del)-positive individuals, 72 individuals (10.6%) experienced malignant VA. The model demonstrated good discrimination with a C-statistic of 0.83, although it has only been validated longitudinally through a landmark analyses and has not been externally validated, as this is the only available cohort.[24]

This study included appropriate ICD therapy in the composite SCD end point to a large extent (51.4%), and therefore, the true SCD risk may be overestimated. In patients with preserved LVEF, VA events may have been hemodynamically tolerated rather than life threatening. This is supported by the original publication, in which all 10 patients who experienced SCD had reduced LVEF. However, the PLN p.(Arg14del)-associated cardiomyopathy is a progressive disease, with heart failure often developing in conjunction with arrhythmia.[25]

The authors assessed the robustness of the composite end point by comparing the predictors for the appropriate

Table 1 Overview of sudden cardiac death risk scores used in genetic heart diseases

Risk score (y)	Derivation cohort (N)	Predictors	Outcome	Annual event rate	C-index	Calibration slope	External validation
ARVC Risk Calculator (2019/2022)[1]	528	Sex (male), age, recent cardiac syncope, prior NSVT, 24-hour PVC count, sum of anterior and inferior leads with T-wave inversion, and RVEF.	5-Year risk of sustained VA: SCD (2%), aborted SCD (4.1%), VF, VT (≥30 s at ≥100 bpm. or with hemodynamic compromise requiring cardioversion) (23.9%), and appropriate ICD intervention (70%).	5.6%	0.77 (95% CI: 0.73–0.81)	0.93 (95% CI: 0.92–0.95).	Yes[37–40]
ARVC Risk Calculator Fast VT (2020)[2]	864	Sex (male), age, 24-hour PVC count, sum of anterior and inferior leads with T-wave inversion.	5-Year risk of LTVA: SCD (5.4%), aborted SCD (10.8%), VF and rapid VT (>250 bpm and ≥30 s) (15.1%), and appropriate ICD therapy (68.8%).	1.6%.	0.74 (95% CI: 0.69–0.80)	0.95 (95% CI: 0.94–0.98).	No
PLN p.(Arg14del) Risk Model (2021)[3]	679	LVEF, number of leads with negative T wave, low-voltage ECG, 24-hour PVC count.	5-Year malignant VA risk: SCD (8.3%), aborted SCD (5.6%), VF and VT (≥30 s at ≥100 bpm or terminated electrically or pharmacologically) (34.7%), and appropriate ICD intervention (51.4%).	2.0%	0.83 (95% CI: 0.78–0.88)	0.91	No
Sieira et al Brugada Risk Score (2017)[4]	400	Spontaneous type I pattern, early familial antecedents of SCD in first-degree relatives, VA inducibility, presentation as syncope, aborted SCD, and SND.	5-Year arrhythmic risk: (aborted) SCD (11.8%) and appropriate ICD shocks (88.2%).	1.4%.	0.82 (whole cohort), 0.81 (in asymptomatic patients)	Not reported	Yes[4,6,41–45]
BRUGADA-RISK (2021)[5]	1110	Probable arrhythmia-related syncope, spontaneous type 1 Brugada ECG pattern, early repolarization in peripheral leads, type 1 Brugada pattern in peripheral leads.	5-Year risk of VA: SCD (9.6%), aborted SCD by cardioversion of VT/VF or documented sustained VT (>200 bpm) or VF, and appropriate ICD shocks (not reported).	1.5%	0.88 (95% CI: 0.82–0.95) and 0.80 (95% CI: 0.72–0.88) (in asymptomatic patients)	Not reported	Yes[6,44]

(*continued*)

Table 1 Continued

Risk score (y)	Derivation cohort (N)	Predictors	Outcome	Annual event rate	C-index	Calibration slope	External validation
PAT-score (2023)[6]	7358 (from a pooled-analyses including 67 studies)	Type 1 ECG in peripheral leads, T-peak to T-end duration ≥100 ms, aVR sign, arhythmic syncope, unexplained syncope, prolonged PR duration ≥200 ms, MAE during drug challenge testing, fragmented QRS, and early repolarization in inferolateral leads.	Risk of major arrhythmic events: SCD (2.7%), aborted SCD (1.3%), VF and sustained VT/VF (5.3%), and appropriate ICD therapy (90.7%; 91.2% for VF and 8.8% for VT).	7.14%	0.73 (95% CI 0.64–0.82) (overall score), and 0.95 (95% CI 0.91–0.99) (in asymptomatic patients)	Not reported	Yes[44]
M-FACT score (2010)[7]	233	QT interval levels (≤500, >500 to 550, and >550 milliseconds), age at the decision to implant with cutoff ≤20 ys, cardiac events on therapy, and cardiac arrest. Previously symptomatic patients who on therapy had no cardiac events in the >10 ys preceding the decision to implant received −1 point.	Risk of appropriate ICD therapy.	6.06%	Not reported	Not reported	Yes[8]
M-FACT score validation study (2024)[8]	946	QT interval levels (≤500, >500 to 550, and >550 milliseconds), age at the decision to implant with cutoff ≤20 ys, cardiac events on therapy, and cardiac arrest. Previously symptomatic patients who on therapy had no cardiac events in the >10 ys preceding the decision to implant received −1 point.	Risk of CEs: SCD, aborted SCD (12.1%), arrhythmic syncope (including episodes of asymptomatic self-terminating TdP lasting at least for 10 beats) (84.8%), and appropriate ICD shocks (3%). MCEs: SCD, aborted SCD (80%), and appropriate ICD shocks (20%).	0.5%	Not reported	Not reported	/

1-2-3-LQTS-Risk (2018)[9]	1070	QTc interval corrected with Bazett formula, and genotype.	5-Year risk of LVTA: SCD, aborted SCD, and hemodynamically non-tolerated polymorphic VT.	0.47%	0.79 (95% CI: 0.70–0.88)	Not reported	Yes[32]
Rochester Long QT Syndrome Risk Calculator: genotypic cohort (2022)[10]	1288	QTc interval corrected with Bazett formula, age at enrollment (10–20 ys or 20–50 ys), syncope while on or off beta blocker, time-dependent beta-blocker (yes vs no), sex by time-dependent age (female vs male, <13 ys or ≥13 ys), and genotype LQT1, LQT2 or LQT3.	5-Year risk of LVTA: SCD (29.8%), aborted SCD (14.9%), and appropriate ICD shocks for TdP, PMVT, or VF (55.3%).	0.33%	0.79 (95% CI: 0.72–0.85)	Not reported	Yes[10]
ESC HCM Risk-SCD (2014)[11]	3675	Maximal wall thickness (mm), maximal wall thickness (mm^2), left atrial diameter, maximal left ventricular outflow gradient (mmHg), family history SCD, NSVT, unexplained syncope, and age at clinical evaluation (ys).	5-Year risk of SCD: SCD (59.6%), aborted SCD (13.6%), appropriate ICD shock (26.8%) (considered appropriate when the treated tachyarrhythmia was ventricular in origin in an identical manner to previous studies).	0.81%	0.70 (95% CI: 0.68–0.72)	0.91 (95% CI: 0.74–1.08)	Yes[11,13,46–53]
AHA HCM SCD risk stratification (2019)[12]	2094	Family history of SCD, LV hypertrophy with wall thickness of 30 mm or greater, unexplained syncope, NSVT, LGE, LVEF <50%, and LV apical aneurysm.	5-Year risk of SCD: SCD (5.3%), aborted SCD (7.4%), and appropriate ICD therapy (87.2%) for VF or sustained monomorphic VT with a rate >180 bpm.	1.03%	0.81 (95% CI: 0.77–0.85)	Not reported	Yes[13,48,49,51–53]
Modified Genetic score (2024)[13]	283	Maximal wall thickness (mm), maximal wall thickness (mm^2), left atrial diameter, maximal left ventricular outflow gradient (mmHg), family history SCD, NSVT, unexplained syncope, age at clinical evaluation (ys), and genotype positive (yes).	5-Year risk of SCD: VF, documented hemodynamically relevant persistent VTs >30 s, and appropriate ICD therapy.	0.86%	0.76 (95% CI: 0.71–0.81)	Not reported	No

(*continued*)

Table 1 Continued

Risk score (y)	Derivation cohort (N)	Predictors	Outcome	Annual event rate	C-index	Calibration slope	External validation
LMNA-risk VTA calculator (2019)[14]	589	Sex (male), non-missense LMNA mutation, first degree and higher atrioventricular block, NSVT, and LVEF.	5-Year risk of LTVA: SCD (16.3%), other manifestations of hemodynamically unstable VTA (47.7%), and appropriate ICD therapy (36%).	3.9%	0.78 (95% CI: 0.71–0.84)	0.83	Yes[14,54]
DSP Risk Score (2024)[15]	471	Sex (female), NSVT, LVEF <50%, moderate-severe RV dysfunction, and 24-hour PVC count.	5-Year risk of first sustained VA event: SCD, aborted SCD (14.1%), VF and sustained VT (lasting ≥30 s at ≥100 bpm) or with hemodynamic compromise requiring cardioversion) (28.2%), and appropriate ICD intervention (57.7%).	2.6%	0.78 (95% CI: 0.77–0.80)	1.08	Yes[15]
The Filamin C risk calculator[16]	308	Older age, male sex, previous syncope, non-sustained VT, and LVEF.	Risk of SCD/MVA: SCD (12.3%), VF and sustained VT (lasting >30 seconds or which requires an intervention for termination) (42.1%), and appropriate ICD interventions (45.6%) (shock or ATP for VF or sustained VT).	4%	0.76 (95% CI: 0.67–0.86) at 1 y and 0.78 (95% CI: 0.70–0.86) at 6 ys	1.60 (95% CI: 0.86–2.33) at 1 y, and 1.52 (95% CI: 0.86–2.17) at 2 ys	No

ARVC = arrhythmogenic right ventricular (RV) cardiomyopathy; ATP = antitachycardia pacing; CI = confidence interval; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; LGE = late gadolinium enhancement; LQT = long QT; LTVA = life-threatening ventricular arrhythmia; MAE = major arrhythmic events; MVA = major ventricular arrhythmias; NSVT = non-sustained ventricular tachycardia; PLN = phospholamban; PVC = premature ventricular contraction; QTc = corrected QT; RVEF = right ventricular ejection fraction; SCD = sudden cardiac death; SND = sinus node dysfunction; VA = ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia.

ICD therapy end point with those for other malignant VA, and by comparing predictors for LTVA with other VA. These analyses showed largely similar hazard ratios, supporting the use of malignant VA as a valid surrogate.

Conclusion/recommendation:

- The PLN p.(Arg14del) risk model overestimates the true SCD risk.
- In our view, a higher threshold for primary prevention ICD implantation may therefore be warranted in PLN p.(Arg14del)-positive individuals.

Brugada syndrome

Brugada syndrome (BrS) SCD risk stratification has a history of 3 (most well-known) calculators. First, the Sieira et al[4] score, then the Brugada risk score,[5] and the most recent is the PAT score,[6] published in 2023. The Shanghai score system[26] is not included here, because this score was designed for the diagnosis of BrS and not for the prediction of SCD. All models were derived from large cohorts: 400 patients (25.5% positive *SCN5A* variant) in the Sieira et al[4] score, 1110 patients (15.8% positive *SCN5A* variant) in the Brugada risk score, and 7358 patients (19.6% positive *SCN5A* variant) from a pooled analyses in the PAT score. The performance was good with a C-index $\geq$0.80 in patients without prior syncope or major arrhythmic events. However, external validation showed varying results in performance.

All 3 models defined the composite SCD end point differently, although all models included some type of ICD intervention. In the Sieira et al[4] score and the PAT score, the end point predominantly consisted of appropriate ICD therapy (88.2% and 90.7%; 91.2% for ventricular fibrillation [VF] and 8.8% for VT, respectively). The Brugada risk score did not specify their events except for SCD (9.6%).

The inclusion of appropriate ICD therapy in the composite end points may have led to an overestimation of the true SCD risk, although the extend may be minimal. BrS is associated with polymorphic VT (PMVT) originating from the RV outflow tract, and because these arrhythmias are frequently sustained, they are considered 'life threatening'. However, sustained monomorphic VT (MVT) is also observed in a minority: in a large cohort of 834 patients with BrS, 114 (13.7%) patients experienced at least 1 appropriate ICD intervention, with 21 (2.5%) MVT without PMVT/VF in follow-up.[27] These results imply that only circa one-fifth (21 of 114) of the ICD intervention surrogate events include likely non-threatening events.

Conclusion/recommendation:

- The inclusion of appropriate ICD therapy may have led to a minor overestimation of the true SCD risk.
- In our view, all surrogate SCD markers are acceptable in SCD risk predictions in BrS.

Long QT syndrome

Risk prediction modeling in long QT syndrome (LQTS) began in 2012 with the M-FACT score,[7] followed by the 1-2-3-LQTS risk calculator in 2018[9] and the Rochester LQTS risk calculator in 2022.[10]

The M-FACT score was originally intended to assess the probability of receiving appropriate ICD shocks in patients already implanted, but was recently externally validated in a cohort of 946 patients without aborted cardiac arrest (CA) before diagnosis or cardiac events (CEs) below age 1, to predict CEs.[8] No model performance metrics were reported, only a significant association between the M-FACT score and the risk of CEs ($P < .001$), and a non-significant association with the risk of major CEs, likely due to the limited number of events (5 events in total, 1 appropriate ICD shock and 4 aborted SCD). As most events were classified as arrhythmic syncope (also comprising episodes of asymptomatic self-terminating PMVT/Torsade de Pointes [TdP] $\geq$10 beats) (85%), and with very few major CEs, the M-FACT score might be useful in predicting arrhythmic events, but not in predicting SCD.

The 1-2-3-LQTS risk score is omitted from this discussion as the score does not include ICD intervention in the composite end point and only considers hemodynamically instable VA. However, we will discuss this calculator in the next 'Baseline vs dynamic prediction' discussion (see later).

The Rochester LQTS risk score was developed and externally validated in large cohorts comprising circa >1000 patients with LQTS, and showed moderate performance with a C-index of 0.79 in the derivation cohort. In a subgroup analyses of genotyped patients, the composite LTVA end point consisted mainly of appropriate ICD shock events (55.3%).

In LQTS, the inclusion of appropriate ICD therapy likely results in overestimation of true SCD risk, as VAs (particularly TdP subtype) are often self-terminating, and therefore, not all life threatening without ICD intervention. This finding is reflected in the large proportion of sustained VT/VF in the M-FACT external validation study (85%) without SCD, conducted in a cohort with only 3% patients having an ICD, compared to 21.1% in the Rochester LQTS risk calculator study, where the main driver of the SCD end point was appropriate ICD therapy.

Another indicator for overestimation of the true SCD risk lies in the Rochester LQTS risk score. In an external validation cohort, the model had a calibration coefficient below 1 (0.744, 95% CI 0.491–0.997, $P < .001$ [significant discrimination], $P = .048$ [significant miscalibration]). Although the calibration was not plotted for the risk groups, it suggests significant overestimation of the true SCD risk in the lower risk groups, and underestimation in the higher risk groups.

Conclusion/recommendation:

- The M-FACT score may be useful in predicting VA, but not for predicting SCD.
- The Rochester LQTS risk score likely overestimates the true SCD risk because of inclusion of ICD intervention in the composite end point, and because of miscalibration.
- In our opinion, clinicians should interpret the results of the Rochester LQTS risk calculator with caution. Excluding appropriate ICD therapy from the composite end point is

not feasible because of the resulting lack of statistical power. A higher threshold for ICD implantation should be debated.

Hypertrophic cardiomyopathy

Risk prediction modeling for assessing SCD risk in hypertrophic cardiomyopathy (HCM) patients is studied extensively; however, designing a satisfactory risk tool for a heterogeneous disease with a low-event rate remain challenging. In this review, we discuss 3 calculators: the European Society of Cardiology (ESC) HCM Risk-SCD score,[11] the enhanced 2019 American College of Cardiology/American Heart Associations (ACC/AHA) guidelines-based risk factor algorithm,[12] and the modified genetic score.[13]

The ESC HCM Risk-SCD score was developed in a large cohort of 3675 patients and demonstrated moderate performance with a C-statistic of 0.70. It was designed to predict a composite SCD end point, which included appropriate ICD shock (27%). The score was included in the 2014 ESC guidelines on diagnosis and management of HCM, and remains part of the 2022 ESC guidelines for the management of patients with VA and the prevention of SCD. The latter also incorporated the ACC/AHA strategy in the algorithm, which we will discuss in the next paragraph.[19]

In 2019, the existing ACC/AHA HCM risk marker strategy was enhanced by inclusion of new CMR risk factors.[12] According to this strategy, the presence of only 1 risk factor is sufficient to justify prophylactic ICD implantation. The model performed well with a C-statistic of 0.81 and events consisted mainly of appropriate ICD therapy (87.2%). Note that this is a much higher proportion than in the ESC score. This is probably the result of more patients treated with an ICD in this cohort during follow-up (25% vs 15%). This strategy was adopted in the latest 2024 AHA/ACC HCM guidelines.[28]

More recently, both risk calculators were externally validated in a German cohort of 283 patients with HCM, and a third model was created by adding genetic information to the ESC score, the so called "modified genetic score."[13] In this cohort, 30% of the patients had an ICD implanted; however, the proportion of appropriate ICD therapy events in the composite SCD end point was not reported. This studied showed that the ESC score had a low sensitivity (29%) and high specificity (83%), whereas the ACC/AHA strategy had a high sensitivity (93%) and low specificity (28%). The modified genetic score outperformed both, with an area under the curve (AUC) of 0.76 (compared to 0.74 for the ESC score and 0.70 for the ACC/AHA strategy), and had a sensitivity of 86% and specificity of 69%.

Overall, it is difficult to estimate the extent of overestimation of true SCD risk in this population using these calculators. The number of ICD therapies that truly would have prevented SCD is largely unknown, as the severity of a sustained VT is likely influenced by many individual factors, such as the maximal wall thickness and the maximal LV outflow gradient. Moreover, when evaluating calibration by risk group in the ESC score, the 2 lowest risk groups show overestimation, whereas the 2 highest risk groups show underestimation of SCD risk.

To further explore the debate of surrogate markers for SCD in HCM, some might question whether appropriate ICD therapy in a first-degree relative could be considered equivalent to sudden cardiac arrest(SCA)/SCD in the class IIa recommendation for ICD implantation. In our opinion, if this is the sole risk factor, the argument in favor of ICD implantation may be less convincing compared to cases were the family history includes actual SCA/SCD.

Conclusion/recommendation:

- The modified genetic score demonstrates the best performance; however, over- or underestimation of true SCD risk cannot be assessed because of the lack of information regarding the end point. Further validation in larger, and more ethnically diverse cohorts is required.
- Both the ESC HCM Risk-SCD score and ACC/AHA HCM risk marker strategy can be used to identify patients at low and high risk, accordingly. However, the ACC/AHA HCM risk marker strategy likely overestimates the true SCD risk because of the high proportion of appropriate ICD therapy events in the composite end point.

LMNA

Risk prediction of SCD in LMNA patients began in 2012 with a study identifying 4 risk predictors: non-sustained ventricular tachycardia (NSVT), male sex, LVEF, and non-missense mutations.[29] These predictors formed the foundation for the LMNA-VTA-risk calculator,[14] published in 2019, and incorporated in the 2022 ESC guidelines for the management of patients with VA and the prevention of SCD. This calculator was developed in a cohort of 589 LMNA patients, added 1 additional variable to the equation (first-degree and higher atrioventricular block), and demonstrated moderate performance with a C-statistic of 0.78.

The proportion of ICD therapy in the composite LTVA end point was 36%. All appropriate ICD therapies were administered for VA with a ventricular rate of $\geq$165 bpm. However, it is still unknown whether these events would be truly life threatening, as a considerable amount of sustained VA occurs in LMNA patients with preserved LVEF,[30] potentially allowing better hemodynamically tolerance. This may result in an overestimation of the true SCD risk.

Conclusion/recommendation:

- The LMNA-VTA-risk calculator likely overestimates the true SCD risk. This should be taken into consideration when using the calculator for clinical decision-making.
- Our view is in line with the recommendation of the 2022 ESC guidelines for the management of patients with VA and the prevention of SCD: "In patients with a 5-year estimated risk $\geq$10% and a manifest cardiac phenotype (NSVT, LVEF <50%, or AV conduction delay), a primary prevention ICD implantation should be considered to avoid potential over-implantation in variant carriers

without a cardiac phenotype, class IIa.". This recommendation prevents potential risk overestimation and unnecessary ICD implantation.

DSP

Recently, an SCD risk prediction model was developed in a cohort of 471 patients with a P/LP variant in the arrhythmogenic CM (ACM)-associated DSP gene.[15] The authors applied the same strategy as in the ARVC risk calculator, by defining both a sustained VA end point and an LTVA end point. The model demonstrated moderate performance for both end points (C-statistic of 0.782 for sustained VA in the derivation cohort and C-statistic of 0.752 for LTVA in the total cohort). The latter end point had too few events for model development, which already suggests a potential overestimation of the true SCD risk.

The model incorporated appropriate ICD therapy to a considerable extent. The sustained VA end point consisted of 18.3% ICD therapies for fast VA (VF or VF $\geq$250 bpm), and 39.4% for slower VA (<250 bpm). Most events were slower VA episodes, and therefore, possibly not life threatening, although the exact percentage is difficult to estimate. This pertains to the fact that the DSP variant causes a heterogeneous phenotype, including dilated cardiomyopathy, left-sided to biventricular ARVC, and non-dilated LV cardiomyopathy, as well as the fact that many DSP patients have LV dysfunction, making it difficult to estimate what the effect of sustained VA on hemodynamics was.

The authors proposed a risk threshold of 5%. At this threshold, the negative predictive value in the external validation cohort was 100%, meaning that no low-risk patients experienced a sustained VA event. This approach is quite conservative and would result in ~70% of the patients to be considered for ICD implantation (number needed to treat = 3).

Conclusion/recommendation:

- The DSP risk model likely overestimates the true SCD risk, although the extent is uncertain.
- In our opinion, the DSP risk score should be used with caution, and a higher threshold for primary prevention ICD implantation should be considered.

Filamin C

The Filamin C risk calculator is the most recent published genetic risk score for SCD.[16] It was developed in a cohort of 308 patients, and the model demonstrated moderate performance, with an AUC ranging from 0.76 for 1-year predictions to 0.78 (95% CI 0.70–0.86) for 6-year predictions.

The model likely overestimates the true SCD risk. First, because the composite SCD end point included appropriate ICD therapy (45.6%). It is most likely that not all therapies have prevented SCD, as the end point also includes a high rate of spontaneous VT/VF events (42.1%) with known non-lethal outcomes, compared to relatively low SCD rates (12.3%). Second, the reported calibration slope at 1 year was 1.60, indicating a potential overestimation among high-risk patients. This decreased to 1.52 (95% CI 0.86–2.17) at 2 years, although it appeared to increase visually at 4 years.

Conclusion/recommendation:

- The Filamin C calculator likely overestimates the true SCD risk.
- Similar to other ACM risk scores (eg, ARVC, PLN, LMNA, and DSP), we believe that using a stricter surrogate SCD end point, such as the LTVA end point, is preferable to minimize overestimation of true SCD risk and to help avoid unnecessary ICD implantations.

Static vs dynamic predictions

Most risk calculators are static 'baseline' models, which means that they were developed using patient data at time of diagnosis, before the initiation of treatment, and assume that the risk remains stable over a defined period. This approach is generally unsuitable for most heart diseases, both genetic and non-genetic.[17,18,31]

The first argument to choose a dynamic risk prediction model over a static baseline model is when treatment strategies might alter the predictors or even the risk of SCD. An example for both is risk prediction modeling in patients with LQTS. Following the 2022 ESC guidelines, beta-blockers are recommended in all patients with LQTS (class I, and class IIa in asymptomatic patients with a pathogenic mutation and without QT prolongation).[19] The Rochester LQTS risk calculator shows that the risk of SCD alters when incorporating the use of beta-blockers in the equation and previous research substantiates this finding.[10] Dusi et al[8] also demonstrated that the use of beta-blockers often shortened the corrected QT (QTc). Therefore, new risk prediction models for patients with LQTS should not only include the use of beta-blockers, such as the Rochester LQTS risk calculator, but should also include updated QTc during follow-up. The 1-2-3 LQTS risk calculator solely integrated QTc at baseline and genotype as predictors, consequently limiting its use to a very short timeframe when patients are not (yet) treated with beta-blockers.[32]

The second argument to use dynamic predictions is when predictors change during follow-up, regardless of the start of treatment. This effect was observed in the ARVC risk calculator. This model was tested longitudinally together with the ARVC risk calculator using updated predictors and a new time-varying Cox regression model.[33] First, a change in risk factors of the ARVC risk calculator was found from diagnosis to >5 years of follow-up; the 24-hour premature ventricular contraction (PVC) count and presence of NSVT both declined significantly. Additionally, the observed 5-year risk decreased from 29% to 16% between first diagnoses and after 5-year follow-up. This might also be a treatment effect, as significantly more patients had anti-arrhythmic medication prescribed (+16%) or a lifestyle effect as the exercise (metabolic equivalent [MET]*hr/week) decreased significantly (-4). Second, the time-varying Cox regression model had the best performance, with the ARVC risk calculator (updated)

following, and at last, the ARVC risk calculator (baseline risk factors only). The time-varying Cox regression model provided a good discrimination and calibration, while the ARVC risk calculator (updated) had a persistent overestimation of mean risk (+6%). These results indicate that a time-varying (dynamic) risk prediction model is a better fit in this cohort.

The third argument is the fluctuation of widely used predictors over time, such as the PVC count. Previous research has shown that the PVC count can fluctuate substantially over time, and this can result in different predictions.[34] When studying the PLN p.(Arg14del) risk score, the PVC count contributes significantly to the SCD risk prediction.[3] A fluctuation in this score can alter the recommendation for an ICD implantation. One solution is to incorporate the PVC count in a dynamic fashion, such as in a joint model, where the model uses trends of predictors over time, and thus corrects for these fluctuations. Another solution is to investigate longer-term monitoring (ie, 7 or 14 days) and the use of these data in risk calculators.

When considering a baseline risk model, it should be validated longitudinally when used after baseline, especially when a specific baseline (eg, date of first presentation to a cardiologist) is used for model development. The individual risk of SCD might change during follow-up as disease progresses. The HCM-SCD risk calculator is an example of a calculator which did not specify a certain baseline and probably includes patients at different stages of disease. The individual risk; however, might still change during follow-up, and therefore the guidelines recommend using this calculator at first presentation and at 1–3 year intervals (or whenever there is a change in clinical status).[19,35,36] A dynamic risk model takes this time effect into account and can also correct for individual trajectories over time, and is therefore more suitable in this patient population. This is also applicable for ARVC, LMNA, and DSP patients.

Discussion

This review highlights the challenges in SCD risk prediction for genetic heart disease, with a focus on the use of surrogate SCD end points and the variability in type of risk prediction modeling.

Surrogate SCD end points

The use of surrogate SCD end points leads unquestionably to overestimation of the 'true' risk of SCD in many genetic cardiomyopathies. This may lead to ICD implantation in low-risk patients, potentially causing more harm than benefit due to device-related complications. The amount of overestimation is different for every risk tool, depending on several factors. First, the total number of appropriate ICD therapy events in the combined SCD end point. If the combined end point almost solely depends on ICD therapy, which is the case in the ACC/AHA HCM risk marker strategy for example, the chances are high of incorporating non–life-threatening events. BrS, however, is probably an exception, which brings us to the second factor: the underlying substrate. Some arrhythmic substrates are more malignant than others. In general, sustained monomorphic VT is considered less likely to be life threatening than sustained PMVT, which, for example, is much more present in patients with BrS. Therefore, BrS is one of the exceptions in which we expect a limited overestimation with the risk scores. Third, and lastly, cardiac function influences the hemodynamic tolerance of VT. In case of preserved LV function, particularly in most ARVC patients, fast VT could be well tolerated, and therefore be a poor surrogate marker for SCD, leading to overestimation of the true SCD risk.

This reasoning is applied to all risk prediction models included in this review to estimate the proportions of 'likely lethal' and 'likely non-lethal' events (Figure 1B and Supplemental Table 1). Events that could not be classified due to insufficient information or missing evidence of the pathology are indicated in gray. It is necessary to point out that these estimations are based on expert interpretation rather than objective classification and should be regarded as illustrative rather than definitive. Our goal is to highlight the potential magnitude of the dilemma and the variability across models.

Various solutions are opted. Some risk calculators use an additional stricter SCD end point, mostly referred to as "LTVA." This includes restricting VT to only "fast VT" with ≥250 bpm. Another solution is to use a higher risk threshold to correct for overestimation, and provide more tailored recommendations on top of the predicted risk. An example is the recommendation for LMNA patients in the 2022 ESC guidelines for the management of patients with VA and the prevention of SCD: "In patients with a 5-year estimated risk ≥10% *and* a manifest cardiac phenotype (NSVT, LVEF <50%, or AV conduction delay), a primary prevention ICD implantation should be considered to avoid potential over-implantation in variant carriers without a cardiac phenotype, class IIa." In our view, this recommendation strikes a good balance between the potential overestimation of the true SCD risk and the need to ensure adequate protection for high-risk patients with a manifest cardiac phenotype.

One additional note regarding all SCD risk prediction models is that their application to genotype-positive individuals who are either phenotype-negative or mildly phenotype-positive may be limited when the derivation cohort did not include this patient subgroup. Applying such risk scores in these patients may lead to misclassification in both directions if the calculated scores are taken at face value.

We believe that specific additional recommendations, along with an appropriate SCD (surrogate) end point that is suited to the underlying arrhythmic substrate, are essential steps toward improving risk prediction models. Such tailored strategies would enhance clinical decision-making for ICD implantation and reduce unnecessary implantation while protecting those at risk for SCD.

Risk prediction modeling strategies

The type of modeling should be chosen based on the model that provides the most accurate estimate of the truth. In this

review, we want to point out that most risk prediction models rely on static baseline models, even though this risk is not static in many heart diseases. Predictors in risk calculators can fluctuate over time, or change in predictive value, or even the risk itself can change during follow-up, for example when treatment modifies the risk.[31] Taking all these factors into account, most risk calculators would provide more accurate predictions when using dynamic models, such as time-varying Cox regression models or joint models combining a survival model with (multiple) longitudinal model(s). In addition, gene-specific risk prediction models require gene-specific risk factors for accurate risk estimation. However, many existing models still use the same risk factors to a certain extent. From our perspective, future prediction models should focus more on dynamic modeling approaches and gene-specific risk factors. Importantly, the 2022 ESC guidelines, which currently rely on static risk prediction models, may need to be revised in light of evidence supporting dynamic models.

Defining a cutoff value for ICD implantation

The appropriate cutoff for ICD implantation varies between risk models and underlying genetic variants. Although this might seem counterintuitive, it does reflect clinical reality. Each model has its own discrimination and calibration, which can differ across patient risk groups, and expected over- and underestimation of the 'true' SCD risk. As suggested earlier, it is possible to account for SCD overestimation by choosing a higher threshold. The optimal threshold should be considered model-specific and based on the balance between predicted/expected and observed risk. For this reason, once again, risk prediction cannot follow a one-size-fits-all approach.

Conclusion

This review underscores 2 major challenges in SCD risk prediction for genetic heart diseases: the overestimation of 'true' SCD risk due to surrogate end points, and the limitations of current statistical modeling approaches. Future risk prediction tools should incorporate disease-specific surrogate end points and use dynamic modeling strategies that reflect temporal changes in risk. Finally, any risk algorithm should not replace expert opinion, which essentially means that patients with rare cardiac conditions should be (co-) seen by expert physicians.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2025.07.041.

Funding Sources: This work was supported by ZonMw PSIDER-Heart.

Disclosures: Dr Wilde is an (unpaid) consultant for Thryv Therapeutics Inc and ARMGO, and a paid consultant of Rocket Pharma and SolidBio (<$5000); The institutions of Dr Wilde has received grants and/or fees from Abbott, Boston Scientific and Medtronic, all unrelated to this study.

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