

Prevention of Sudden Cardiac Death in Adults With Congenital Heart Disease Do the Guidelines Fall Short?

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Background—Sudden cardiac death (SCD) is a major cause of mortality in adult congenital heart disease (ACHD) patients. SCD may be prevented by implantable cardioverter-defibrillator (ICD) implantation, but patient stratification remains troublesome. The 2014 Consensus Statement on Arrhythmias in ACHD patients and the 2015 European Society of Cardiology Guidelines specified recommendations for ICD implantation in ACHD patients for the first time. We assess the discriminative ability of these ICD recommendations for SCD in ACHD patients.

Methods and Results—Of 25 790 ACHD patients in an international multicenter registry, we identified all SCD cases, matched to living controls by age, sex, congenital defect, and surgical repair. We assessed all primary prevention ICD recommendations listed in both documents. We used conditional logistic regression models to calculate odds ratios and receiver operating characteristic curves with area under the curve. *Consensus Statement*: One hundred twenty-four cases (median age at death, 33 years [26–44]; 67% men) and 230 controls were studied. In total, 41% of SCD cases and 17% of controls had an ICD recommendation (odds ratio, 5.9; $P < 0.001$). *European Society of Cardiology Guidelines*: Of one hundred fifty-seven cases (median age at death, 33 years [26–48]; 64% men) and 292 controls, 35% and 14% had an ICD recommendation, respectively (odds ratio, 4.8; $P < 0.001$).

Conclusions—A minority of SCD cases had an ICD recommendation according to these guidelines, whereas the majority of SCD victims remained unrecognized. With an area under the curve of 0.6 to 0.7, the discriminative ability of both guidelines was mediocre. Critical clinical reasoning when deciding on ICD implantation in ACHD patients, therefore, remains vital. (*Circ Arrhythm Electrophysiol.* 2017;10:e005093. DOI: 10.1161/CIRCEP.116.005093.)

Key Words: death, sudden, cardiac ■ defibrillators, implantable ■ evaluation studies ■ guideline ■ heart defects, congenital ■ primary prevention

Adult congenital heart disease (ACHD) patients are at considerably increased risk of sudden cardiac death (SCD) compared with individuals of the same age with structurally normal hearts.^{1,2} Moreover, the risk of SCD in ACHD patients often already occurs at a young age, adding to the tragedy of these events. Because of improvements in surgical and medical management, ACHD patients, even those with complex defects, will reach older ages; therefore, SCD rates among ACHD patients are expected to rise.³ Although acute nonarrhythmic death also occurs in ACHD patients, SCD is mainly driven by ventricular arrhythmias and, therefore, may largely be prevented by implantable cardioverter-defibrillator (ICD) placement.⁴ The choice for an ICD may be evident after

survived sudden cardiac arrest or in the presence of sustained ventricular arrhythmias, but ICD implantation for primary prevention of SCD can also be indicated in ACHD patients. However, the inappropriate shock rates and predominantly lead-related complication rates are markedly higher in ACHD patients than in the ICD population with acquired heart disease.⁵ This dictates careful weighing of the risks and benefits of primary prevention ICD implantation in ACHD patients. A robust risk stratification model for SCD in ACHD patients with sufficient discriminative power is, therefore, essential. However, because of the scarcity of data on SCD in ACHD patients, the realization of such a model poses a tremendous problem, and currently, no validated risk stratification models

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WHAT IS KNOWN

- Sudden cardiac death (SCD) is one of the main causes of mortality in adults with congenital heart disease.
- Implantable cardioverter-defibrillator (ICD) implantation may prevent SCD, but patient stratification is difficult, and guideline recommendations for ICD implantation are mainly extrapolated from acquired heart disease.

WHAT THE STUDY ADDS

- This study provides an estimate of the diagnostic accuracy of the current guideline recommendations for ICD implantation and the prevention of SCD in patients with adult congenital heart disease.
- More accurate risk stratification methods are urgently needed to prevent more SCDs from occurring in this rapidly growing patient population.

are available. Recently, a consensus document was published, in which criteria for primary prevention of SCD with an ICD were provided for the first time: the 2014 Pediatric and Congenital Electrophysiology Society/Heart Rhythm Society expert consensus statement on the recognition and management of arrhythmias in ACHD.⁶ The recommendations listed in that document were later adopted to a great extent in the 2015 European Society of Cardiology (ESC) Guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD.⁷ Some differences between these 2 documents exist: the Consensus Statement lists an additional class IIb recommendation for patients with a systemic ventricular ejection fraction <35% without heart failure symptoms, and a class III recommendation for patients with the Eisenmenger syndrome, both of which are not present in the ESC Guidelines.

The criteria leading to a recommendation for ICD implantation from both these documents are largely extrapolated from patients with acquired heart disease^{8,9} or from retrospective data in tetralogy of Fallot (ToF) patients.^{10–13} The substrate for SCD in ACHD patients is likely to be similar but not equivalent to that in patients with acquired heart disease, for example, ventricular scarring, impaired ventricular function and heart failure, and prolonged QRS-duration.^{4,11,14} Because ACHD patients are a distinctive but also heterogeneous patient group, direct reproduction of guidelines for acquired heart disease may not be optimal for ACHD patients.

The ability of these guidelines to accurately discriminate high-risk from low-risk ACHD patients has never been verified. Independent validation of diagnostic tests is highly important, and several statistical methods exist to achieve this.^{15–17} However, a diagnostic test is derived from statistical analysis of patient data, whereas these guideline recommendations are largely based on expert opinions and extrapolation from scientific data in other patient groups. In this study, the predictive and discriminative ability of the guideline recommendations are assessed in the same manner as one may validate a diagnostic test because both are designed to distinguish

high-risk from low-risk patients. Thus, we evaluate the ability of the ICD recommendations from both guidelines to discriminate SCD cases from controls in a large cohort of ACHD patients who died of SCD and matched controls.

Methods

The study design and population of this study have been presented elsewhere in detail.⁴ In short: this was an international, multicenter case control study, including ACHD patients (≥18 years old) from 3 different registry databases (total n=25 790). CONCOR (CONgenital CORvitia) is a Dutch nationwide registry of adults with congenital heart disease started in 2001 and included 11 535 patients.¹⁸ Data from all consecutive patients at The Toronto Congenital Cardiac Center for Adults since 1980 have been registered, and this database contains ≈8000 ACHD patients. The University Ziekenhuis Leuven collected data from ≈6255 ACHD patients since 1970. All patients with proven or presumed tachyarrhythmic SCD in these databases were included (cases, n=171). SCD was defined as (1) proven or documented arrhythmic death or (2) arrhythmic death by exclusion (instantaneous death or circumstances compatible with SCD, without disease that would lead to death in the near future, and in the absence of a nonarrhythmic cause of death at autopsy) and (3) arrhythmic death by default (abrupt loss of consciousness and absence of pulse, without further data).

Case Control Design

Each SCD case was matched to living controls by age, sex, congenital diagnosis, type and date of surgical intervention, and treating medical center. A 1:n ratio (≤3 controls per case, depending on availability) was used to improve the accuracy of results over a 1:1 design. Medical records of included patients were reviewed, and patient data were deidentified and entered into a database. Data on variables that are part of the guideline ICD recommendations were obtained through medical records and letters, 12-lead electrocardiograms, and reports of medical imaging. Based on the variables listed in the guidelines, we scored each primary prevention ICD recommendation for each case and control as present or not present.

Recommendations for ICD Therapy

The primary prevention criteria for ICD implantation in both guidelines were applied to SCD cases and controls; these recommendations were class I, systemic left ventricular ejection fraction ≤35%, biventricular physiology, and New York Heart Association class II or III symptoms; class IIa, adults with ToF and multiple (defined as ≥2) risk factors for SCD, such as left ventricular systolic or diastolic dysfunction, nonsustained ventricular tachycardia, QRS duration ≥180 ms, extensive right ventricular scarring, or inducible sustained ventricular tachycardia at electrophysiological study; class IIb (1), adults with a single or systemic right ventricular ejection fraction <35%, particularly in the presence of additional risk factors, such as complex ventricular arrhythmias (defined as nonsustained ventricular tachycardia), unexplained syncope, New York Heart Association functional class II or III symptoms, QRS duration ≥140 ms, or severe systemic AV-valve regurgitation.^{6,7} The 2014 Consensus Statement—but not the 2015 ESC Guidelines—specifies an additional class IIb (2) recommendation, adults with a systemic ventricular ejection fraction <35% in the absence of overt symptoms (New York Heart Association class I) or other known risk factors. For patients with severe pulmonary hypertension, the Eisenmenger syndrome, there is a class III indication in the 2014 Consensus Statement, whereas in the ESC Guidelines, this contraindication is not described.⁶ We, therefore, excluded Eisenmenger patients from analyses of ICD recommendations in the Consensus Statement but included these in analyses of ICD recommendations in the ESC Guidelines. Cases for whom no control was identifiable, with New York Heart Association class IV, and those without data on systemic ventricular function were also excluded from analysis.

Statistical Analysis

We analyzed all data using SPSS, version 23.0 (IBM Corp, Armonk, NY), and R, version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics for nominal data are expressed in numbers and percentages. For normally distributed continuous variables, we calculated mean values and SDs. We present non-normally distributed data in medians and interquartile range. For comparison of proportions, conditional logistic regression analysis was performed. For analysis of guideline performance, per recommendation, we performed univariable analysis, and subsequently multivariable analysis, using conditional logistic regression models. In the multivariable analysis, the log odds was modeled as an additive function of the ICD indications. No selection was performed. The results are displayed in odds ratios (ORs) with 95% confidence intervals (CI). From the multivariable conditional logistic regression models, we produced receiver operating characteristic curves with corresponding areas under the curve (AUC) to assess the discriminative abilities of the guideline criteria. For all analyses, we considered 2-tailed *P* values <0.05 considered to be statistically significant.

Results

Characteristics

There were a total of 171 SCD cases in the combined data set. Six patients were excluded because no control patient could be identified because of a combination of congenital defect, age, and nonrepaired status. The median age at death of these 6 patients was 38 (interquartile range, 23–51) years, and 4 were men. One patient had ventricular septal defect with Eisenmenger syndrome, 1 had surgically repaired aortic stenosis and ventricular septal defect, 1 unrepaired ToF, 2 had unrepaired (congenitally corrected) transposition of the great arteries with a systemic right ventricle, and 1 had aortic and mitral regurgitation without operation indication. One patient did not have any data on systemic ventricular function, and 1 patient had an ICD indication according to either guideline.

Of the remaining 165 cases, 63 were from the Dutch CONCOR database, 79 from the Toronto Congenital Cardiac Center for Adults, and 23 from University Ziekenhuis Leuven. Because the Eisenmenger syndrome is a class III indication in the Consensus Statement, but not in the ESC Guidelines, the number of included cases and controls differed between the 2 analyses. For analysis of the Consensus Statement 124 cases and 230 controls were included, and of the ESC Guidelines, 157 cases and 292 controls without a class III indication were included. The flowchart for patient selection is displayed in Figure 1. The characteristics of SCD cases and controls are displayed in Table 1. ToF, univentricular heart, and transposition of the great arteries were the most common diagnoses among SCD cases (Figure 2), with an equivalent distribution in controls.

2014 Consensus Statement

According to the Consensus Statement recommendations, applied to 124 (non-Eisenmenger) SCD cases and 230 controls, a class I indication was present in 12% of cases and 2% of controls (OR, 11.9; 95% CI, 2.7–52.8; *P*=0.001). In ToF patients, 11 of 28 (39%) cases and 14 of 61 (24%) controls had a class IIa recommendation (OR, 1.8; 95% CI, 0.61–5.3; *P*=0.28). A class IIb (1) recommendation was present in 16% of cases versus 8% of controls (OR, 6.5; 95% CI, 1.8–23.4; *P*=0.004), and a class IIb (2) recommendation in 35% versus

14%, respectively (OR, 7.0; 95% CI, 3.1–16.1; *P*<0.001). After removal of patients who also had another recommendation, therefore, removing those with additional risk factors, the OR for SCD of patients with a class IIb (2) recommendation was 4.7 (95% CI, 0.95–23.1; *P*=0.058). The sensitivity and specificity of each recommendation is displayed in Table 2. Combining all ICD recommendations, 41% of SCD cases and 17% of controls had any ICD recommendation (OR, 5.9; 95% CI, 2.8–12.4; *P*<0.001); hence, 59% of SCD victims remained unrecognized by the Consensus Statement. Multivariable analysis was performed for all ICD recommendations (Figure 3). The area under the receiver operating characteristic curve of this model was 0.63 (0.58–0.68; Figure 4A).

2015 ESC Guidelines

According to the 2015 ESC Guidelines, 15% of cases and 3% of controls had a class I indication (OR, 9.4; 95% CI, 3.2–27.4; *P*<0.001). A class IIa recommendation was present in 10 of 29 (35%) SCD cases with ToF and 15 of 56 (27%) controls (OR, 1.6; 95% CI, 0.56–4.4; *P*=0.38). A class IIb (1) recommendation was present in 15% of cases and 8% of controls (OR, 5.8; 95% CI, 1.9–17.9; *P*=0.002). The sensitivity and specificity of each recommendation is displayed in Table 2. When all recommendations were combined, 35% of cases and 16% of controls had any ICD recommendation (OR, 4.8; 95% CI, 2.6–9.1; *P*<0.001); hence, 65% of SCD victims remained unrecognized by the ESC Guidelines. The AUC of the multivariable analysis model (Figure 3) was 0.61 (0.56–0.65; Figure 4B).

Discussion

Main Findings

The currently available guideline recommendations for ICD implantation in ACHD patients have a limited ability to distinguish SCD cases from controls. In general, diagnostic tests with an AUC between 0.6 and 0.7 are considered to be poor models.¹⁹ When considering the aggregate guideline ICD recommendations as if they were a diagnostic test, both the 2014 Consensus Statement and the 2015 ESC Guidelines performed poorly. In addition, the 95% CIs of the AUC of both models approach 0.5, which is the line of no discrimination. These guidelines identified only 41% (Consensus Statement) and 35% (ESC Guidelines) of cases as high-risk patients in this cohort of SCD ACHD patients. However, this also means that 59% and 65% of cases, respectively, would have gone unrecognized. This may lead to underimplantation of ICDs in patients at high risk of SCD, leaving them with no protection from life-threatening arrhythmias. On the contrary, a poorly functioning model also increases the risk of overimplantation of ICDs in low-risk individuals, exposing these patients to the complications of ICDs at rates much higher than in acquired heart disease.⁵ It is, therefore, important to realize that these documents are not based on randomized controlled trials in ACHD patients, and can, therefore, not be applied in the same manner as the guidelines for acquired heart disease. That is not to say that these guidelines should not be followed; it is clearly important to provide patients with an ICD recommendation according to these guidelines with an ICD. However,

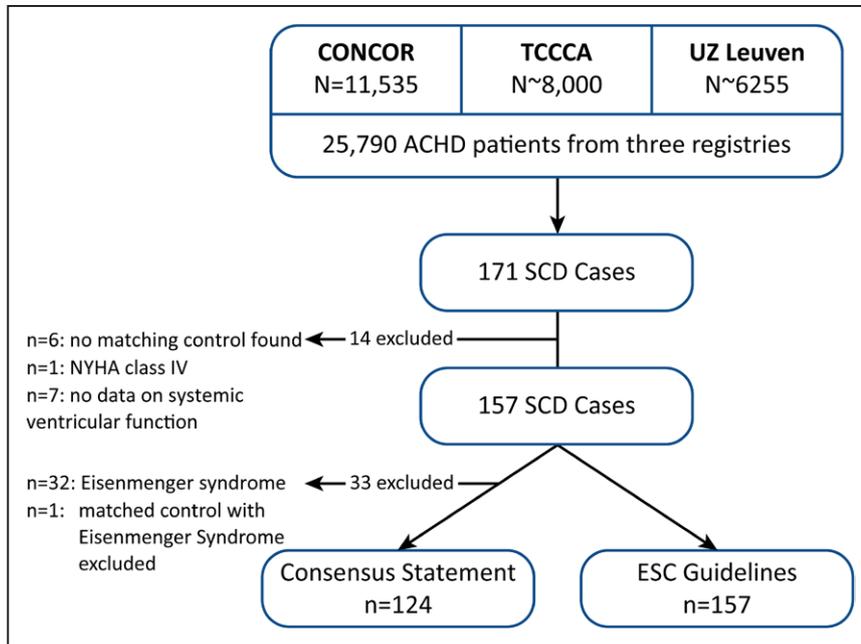


Figure 1. Selection of sudden cardiac death cases. CONCOR: nationwide registry from The Netherlands; TCCCA: registry from Toronto, Canada; and UZ Leuven: registry from Leuven, Belgium. CONCOR indicates CONgenital CORvita; ESC, European Society of Cardiology; NYHA, New York Heart Association; SCD, sudden cardiac death; TCCCA, Toronto Congenital Cardiac Center for Adults; and UZ Leuven, University Hospital Leuven.

because a large proportion of SCD cases are not regarded as ICD candidates by these guidelines, they do not absolve physicians from critical clinical reasoning and decision-making as much as the guidelines for acquired heart disease do.

Causes of Poor Discriminative Ability

It is essential to develop guidelines for ICD implantation in ACHD patients to support cardiologists in the difficult decision for or against ICD implantation. However, both the Consensus Statement and ESC Guidelines may identify high-risk patients correctly in part of the cases, but excessively generalize ACHD patients, who have a large variety of defects, each with their own specific issues. However, this may be a necessity because of the limited defect-specific data. It is, therefore, important to note that these guidelines are a

work in progress. Moreover, a model with a high sensitivity is more important than one with a high specificity because the implications of 1 missed case of SCD far outweigh the implications of having an ICD implanted unnecessarily. Nonetheless, because SCD is rare, and ICD implantation carries its own risk, the specificity of a model is also of great importance.

Most recommendations for ICD implantation in ACHD patients in these guidelines are based on the large ICD trials performed in patients with nonischemic cardiomyopathy.^{8,9} The role of ICDs in nonischemic cardiomyopathy has been subject of debate recently.²⁰ Nonetheless, there is also evidence that an impaired systemic ventricular function is a risk factor for SCD in ACHD patients.^{1,14} However, because SCD is a rare event, all studies on SCD in ACHD patients have been

Table 1. Characteristics of Patients Analyzed With the Consensus Statement and ESC Guidelines

	Consensus Statement			ESC Guidelines		
	Case	Control	PValue	Case	Control	PValue
n	124	230		157	292	
Age, y*; median (IQR)	33 (26–44)	33 (26–44)	0.75	33 (26–48)	35 (27–46)	0.81
Women, n (%)	40 (32)	80 (35)	0.196	55 (35)	108 (37)	0.322
Impaired SVF†, n (%)	44 (35)	32 (14)	<0.001	56 (36)	40 (14)	<0.001
Heart failure symptoms, n (%)	41 (33)	24 (10)	<0.001	89 (57)	92 (32)	<0.001
QRS >140 ms, n (%)	59 (50)	73 (32)	<0.001	67 (44)	84 (29)	<0.001
QRS >180 ms, n (%)	18 (15)	20 (9)	0.067	21 (14)	24 (8)	0.027
Nonsustained VT, n (%)	20 (16)	25 (11)	0.160	25 (16)	27 (9)	0.028
Severe SAVR, n (%)	8 (7)	5 (2)	0.041	11 (7)	7 (2)	0.028
ICD implanted	2 (2)	5 (2)	0.79	2 (1)	5 (2)	0.79

ESC indicates European Society of Cardiology; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; SAVR, systemic atrioventricular valve regurgitation; SVF, systemic ventricular function; and VT, ventricular tachycardia.

*Age at death in cases and at ECG closest to age at death of respective matching case.

†SVF at least moderately impaired or ejection fraction ≤39%.

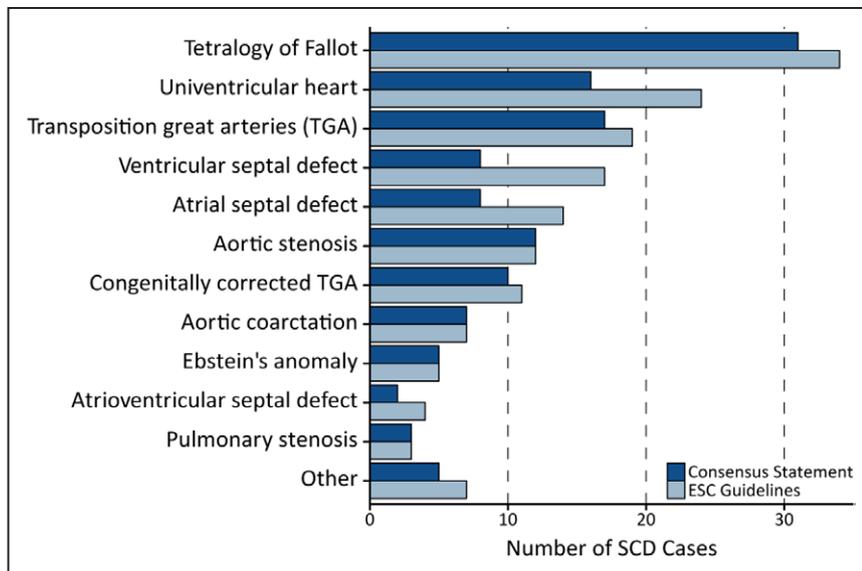


Figure 2. Distribution of congenital defects of cases assessed with the 2014 consensus statement (n=124; excluding Eisenmenger patients) and the 2015 European Society of Cardiology (ESC) Guidelines (n=157). SCD indicates sudden cardiac death; and TGA transposition of the great arteries.

limited by small patient numbers. The risk of SCD in ACHD patients is likely to be more multifactorial than ejection fraction and heart failure alone. Moreover, ACHD patients have hearts that have remodeled to adjust to an abnormal state from birth and have readjusted after surgery; therefore, the parameters that are associated with SCD in patients with nonischemic cardiomyopathy may not directly be extrapolated to ACHD patients.

In addition to extrapolation from patients with acquired heart disease, the guidelines list 1 recommendation (class IIa), which is derived from studies in ToF patients. The number of studies providing evidence for risk prediction models for SCD in ACHD is low, although ToF is the most studied congenital defect.^{10–13} This is a probable reason for the low discriminative properties of the risk prediction model of ToF patients (class IIa). Another limitation of this recommendation is the fact that the wording multiple risk factors can be interpreted in several ways. In the present analysis, multiple was defined as ≥ 2 risk factors for SCD. It is also important to note that in our analysis, guideline recommendations for ToF patients were not superior to recommendations that encompassed several different defects.

Table 2. Sensitivity and Specificity of Univariable Conditional Logistic Regression Model of Each ICD Indication in both the Consensus Statement and ESC Guidelines

ICD Indications	Consensus Statement		ESC Guidelines	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Class I	12 (7–19)	98 (95–99)	15 (10–21)	97 (94–99)
Class IIa	39 (22–59)	76 (63–86)	34 (18–54)	73 (60–84)
Class IIb (1)	16 (10–24)	92 (88–95)	15 (10–22)	92 (88–95)
Class IIb (2)	35 (26–44)	86 (81–91)	NA	NA
Any indication	41 (32–51)	83 (77–88)	35 (27–43)	85 (80–89)

CI indicates confidence interval; ESC, European Society of Cardiology; ICD, implantable cardioverter-defibrillator; and NA, not available.

Comparison With Other Studies

The validation of guideline criteria for ICD implantation has been thoroughly performed for patients with hypertrophic cardiomyopathy. In the recent ESC Guidelines, patients are divided into 3 groups: low, moderate, and high risk. Maron et al¹⁶ found, similar to our own results, that most hypertrophic cardiomyopathy patients with SCD events did not have a high risk score. Vriesendorp et al¹⁷ found an AUC of 0.69 for the hypertrophic cardiomyopathy risk prediction model, which incidentally was an improvement compared with earlier risk prediction models.

The most striking example of validation of guideline ICD indications has been the DANISH trial (Danish Study to Assess the Efficacy of ICDs in Patients With Nonischemic Systolic Heart Failure on Mortality), in which patients with nonischemic cardiomyopathy with a class I guideline indication for ICD implantation were randomized to either receive an ICD or usual clinical care. There was no significant difference in all-cause mortality after a median follow-up of 67.6 months.²⁰ Since a randomized controlled trial involving ICD implantation is unlikely to be achieved in ACHD patients, observational data, such as in the current study, are likely to be the most complete and statistically sound.

Future Studies

It is tremendously important that future prospective research be focused on ICD recommendations specifically for ACHD patients. International multicenter cooperation is vital to gather sufficient data. However, partly because of a shortage of funding for studies on the prevention of SCD in ACHD patients, the conduction of such prospective studies is hindered. A risk prediction model, based on multiple variables including but not limited to impaired ventricular function and heart failure, is likely to have a greater discriminative ability for SCD in ACHD patients.

Strengths and Limitations

To our knowledge, this is the largest cohort of ACHD SCD cases worldwide. This study only included patients that

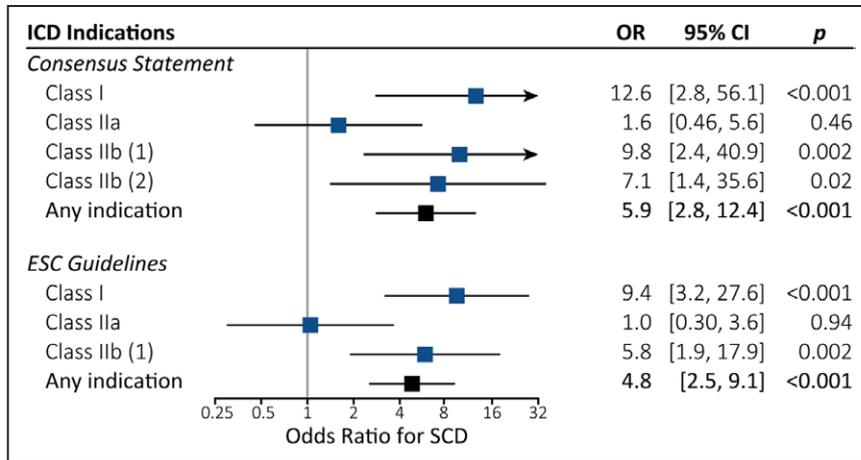


Figure 3. Multivariable models of implantable cardioverter-defibrillator (ICD) indications according to the consensus statement and the European Society of Cardiology (ESC) Guidelines (blue boxplots). Additional univariable analysis of a combined binary variable for any ICD indication (black boxplots). CI indicates confidence interval; OR, odds ratio; and SCD, sudden cardiac death.

actually died of SCD and matched living controls. Therefore, we can provide accurate data on the actual effect of risk stratification and ICD implantation on death rates because of SCD, which ultimately the ICD is designed to prevent.

Some limitations apply to this study. This was a retrospective analysis; the inherent limitations of this study design are, therefore, present in our study. Documentation of heart rhythms at the time of death was not available in all SCD cases, and autopsy was not performed in all cases. Thus, it cannot be excluded that some SCD cases died of another cause than of tachyarrhythmic SCD and would not have benefited from an ICD. However, we did use the most frequently used definition of SCD in this study. The criteria for SCD in this study were strict. Exact ejection fraction measurements were not available for all patients; therefore, we also scored patients of whom the left ventricular function was determined to be at least moderately impaired as equivalent to an ejection fraction $\leq 35\%$. However, this results in a slight overestimation of the number of SCD cases identified, that is, those who had an ejection fraction of 36% to $\approx 40\%$. For the analysis of class IIa recommendations in ToF patients, no data was available on diastolic dysfunction or inducible ventricular tachycardia at electrophysiological study. This is because of the fact that these measurements were not part of standard care in the patients in our cohort.

Conclusions

The ICD recommendations listed in both the 2014 Consensus Statement and the 2015 ESC Guidelines identify $\approx 40\%$ of SCD cases correctly but fail to do so in the remaining 60%. The low discriminative power may result in both underimplantation in patients who are truly at risk of SCD and overimplantation of ICDs in patients without actual risk of SCD. The guideline recommendations are mainly extrapolated from recommendations for patients with acquired heart disease, which only apply to ACHD patients to a limited extent. Risk stratification for SCD in patients with ACHD, therefore, remains a work in progress, and ICD recommendations specifically for ACHD patients are urgently needed.

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Disclosures

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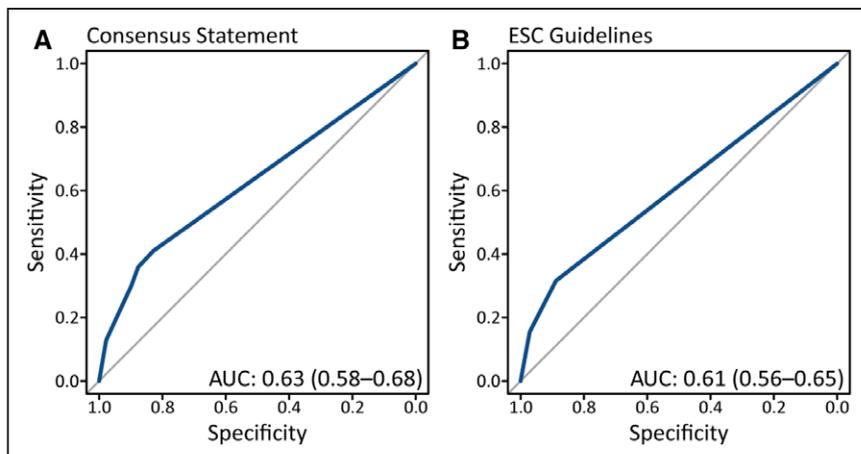


Figure 4. Receiver operating characteristic curves of multivariable conditional logistic regression models of all implantable cardioverter-defibrillator indications combined in the consensus statement (A) and the European Society of Cardiology (ESC) Guidelines (B). AUC indicates areas under the curve.

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