Current state of risk stratification for sudden cardiac death in adults with congenital heart disease

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Abstract

Sudden cardiac death (SCD), mainly caused by ventricular arrhythmias, is one of the leading causes of mortality in adult congenital heart disease (ACHD) patients. An implantable cardioverter defibrillator (ICD) may prevent SCD, but risk stratification remains challenging. In this review, we will address the current guideline recommendations for ICD implantation in ACHD patients, as well as review a recent study in which the discriminative ability for SCD of these guidelines is evaluated. In this study, the guideline recommendations were applied to patients who died of SCD and living controls. Among SCD cases, 35%-41% of patients were recommended ICD, whereas 16%-17% of controls were recommended ICD. The discriminative ability for SCD of the guidelines was poor, with an area under the receiver operating characteristic curve of 0.61-0.63. Risk stratification for SCD in ACHD patients, therefore, remains to be a work-in-progress. *(Anatol J Cardiol 2018; 19: 401-3)*

Keywords: death, sudden, cardiac, defibrillators, implantable, evaluation studies, guideline, heart defects, congenital, primary prevention

Introduction

Adult congenital heart disease (ACHD) patients are at risk of a wide range of late complications originating from the congenital heart defect itself and its associated surgical repair. Currently, one of the main challenges is to prevent premature death in the growing and aging group of ACHD patients. Sudden cardiac death (SCD) is a major cause of mortality, accounting for roughly 19%–26% of all deaths in ACHD patients (1, 2). It occurs at a young age, often before the age of 40 years (1). As SCD in ACHD patients is often due to ventricular arrhythmias, implantable cardioverter defibrillator (ICD) may seem an ideal option to prevent SCD in these patients. However, ACHD patients are also at an increased risk of complications due to ICD implantation and inappropriate ICD shocks (3). In addition, the financial aspect of ICD implantation is also of importance. Therefore, under-implantation of ICDs, causing mortality in ACHD patients because of a preventable cause of death, as well as over-implantation is an important issue. Thus, it is very important to develop a risk stratification tool that reliably differentiates patients who are at a high risk of SCD from those who are not at risk of SCD. An ICD can then be implanted selectively in patients who are at a high risk of SCD. However, although robust guidelines for the prevention of SCD and indication for ICD implantation based on large clinical trials are available for patients with acquired heart disease (4, 5), these are not available for ACHD patients. Instead, the evidence is either extrapolated from the trials on patients with acquired heart disease or obtained from observational studies in ACHD patients and expert consensus (1, 2, 6). These studies have defined several risk factors of importance for SCD in ACHD patients, such as impaired systemic and subpulmonary ventricular function, heart failure symptoms, atrial arrhythmias, and longer QRS duration.

Recently, two documents were published that, for the first time, provided recommendations on ICD implantation for primary prevention of SCD in ACHD patients. In 2014, the PACES/HRS Expert Consensus Statement on the Recognition and Management of Arrhythmias in Adult Congenital Heart Disease was published (7). In 2015, the European Society of Cardiology (ESC) dedicated a section of the 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death for ICD recommendations specifically for ACHD patients. The recommendations in both documents are similar, although not entirely the same. There are several classes of recommendation for primary prevention ICD implantation in these

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Table 1. Primary prevention indications listed in the guideline documents

Primary prevention indications	Both documents
Class I	Systemic left ventricular ejection fraction ≤35%, biventricular physiology, and New York Heart Association (NYHA) class II or III symptoms (Level of evidence: B).
Class IIa	Adults with tetralogy of Fallot and multiple risk factors for sudden cardiac death, such as left ventricular systolic or diastolic dysfunction, nonsustained ventricular tachycardia, QRS-duration ≥180 ms, extensive right ventricular scarring, or inducible sustained VT at electrophysiologic study (Level of evidence: B).
Class IIb	Adults with a single or systemic right ventricular ejection fraction <35%, particularly in the presence of additional risk factors such as complex ventricular arrhythmias, unexplained syncope, NYHA functional class II or III symptoms, QRS-duration ≥140 ms, or severe systemic AV-valve regurgitation (Level of evidence: C).
Class III	All Class III recommendations listed in current ACC/AHA/HRS guidelines apply to adults with CHD (Level of evidence: C).
	PACES/HRS Consensus Statement only
Class IIb	Adults with a systemic ventricular ejection fraction <35% in the absence of overt symptoms (NYHA class I) or other known risk factors (Level of evidence: C).
Class III	Adults with CHD and advanced pulmonary vascular disease (Eisenmenger syndrome) are generally not considered candidates for ICD therapy (Level of evidence: B).

guidelines, which are listed in Table 1. Although these guidelines are important for highlighting the risk of SCD in ACHD patients, it is unclear whether these guidelines can effectively differentiate high-SCD-risk patients from low-SCD-risk patients.

Discriminative ability of Guideline Recommendations

In our recent study, we aimed to test the primary prevention ICD recommendations in the two abovementioned guidelines in a population of ACHD patients who died from SCD and living controls. These were matched to SCD cases by age, gender, congenital diagnosis, type and date of surgical intervention, and treating medical center (8). The guidelines were then tested using statistical analyses in a manner similar to that of validating a risk prediction model.

A total of 25,790 patients were included in three combined registries from the Netherlands (CONCOR), Leuven (Belgium), and Toronto (Canada). A total of 171 patients died of SCD due to arrhythmia. Because a matching control could not be found, not all data were available, or patients had a class III indication, 157 cases were included for the analyses for the ESC Guidelines. Because there is an additional class III indication for patients with Eisenmenger's syndrome in the Consensus Statement, 124 cases were included for analyses of recommendations in this document. The analyses of discriminative ability of the Consensus Statement and the ESC Guidelines were conducted separately because of this difference in ICD recommendations.

For the 124 cases analyzed for the Consensus Statement, 230 controls were available. The median age at death was 33 years [interquartile range (IQR) 26-44 years], and 32% were females. When all ICD recommendations listed in the Consensus Statement were combined, 41% of cases and 17% of controls had an ICD recommendation [odds ratio, 5.9 (95% confidence interval, 2.8-12.4), p<0.001]. When analyzing the discriminative ability of a multivariable model including all recommendations, the area under the ROC curve was 0.63 (0.58-0.68). A prediction model with an area under the ROC curve of 0.6-0.7 is generally considered to be of poor discriminative ability (9).

Performing the same analyses for the ESC Guidelines in 157 cases and 292 controls, the median age at death was 33 years (IQR, 26-48 years), and 35% were female. A total of 35% of cases and 16% of controls had an ICD recommendation according to the ESC Guidelines [odds ratio, 4.8 (95% confidence interval, 2.6-9.1), p<0.001]. The discriminative ability of the ESC Guidelines was also poor, with an area under the ROC curve of 0.61 (0.56-0.65).

Both guidelines performed poorly, with only 41% (Consensus Statement) and 35% (ESC Guidelines) of SCD cases having an ICD recommendation. Applying these guidelines would, therefore, have resulted in the majority of SCD cases (59% and 65%, respectively) being unrecognized. This may cause underimplantation of ICDs in ACHD patients at a high risk of SCD. Approximately 17% of controls also have a recommendation for ICD implantation. When implanted with an ICD, these patients may unnecessarily be exposed to the risks of ICD itself, such as inappropriate shocks and predominantly lead-related complications (3). However, it should be noted that we do not know the fate of control patients after the study period, and these control patients may have SCD over time. Therefore, this statement exclusively applies to the study period.

Among others, this study shows that risk stratification for SCD in ACHD patients is still a work-in-progress. One of the most important reasons for this is that the population of ACHD patients is highly heterogeneous. Many different congenital defects exist,

each with its own surgical repair or palliation, and each with its own course of complications. Because the data on SCD in ACHD patients is so limited, it may be necessary to generalize these patients with very different types of defects to some extent, as the guidelines did. However, this may decrease the predictive and discriminative ability of these guidelines. In addition, in these guidelines, data are extrapolated from studies on patients with acquired heart disease (5). These patients are often different from ACHD patients because the impairment of ventricular function occurs at a much higher age and over a shorter period of time.

Conclusion

The ICD recommendations in the current guidelines on the primary prevention of SCD in ACHD patients currently only recognize 35%-41% of SCD cases and have a poor discriminative ability. It is therefore highly important to focus future research on ICD recommendations specific for ACHD patients. This will require international multicenter cooperation, additional funding, and great effort from physicians and researchers as the population of ACHD patients continues to increase and grow older.

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