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Resuscitation for out-of-hospital cardiac arrest in adults with congenital heart disease

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ABSTRACT

Aims: Adult congenital heart disease (ACHD) patients are at increased risk of sudden cardiac death and out-of-hospital cardiac arrest (OHCA). Currently, insufficient data exist on outcome, causes and circumstances of OHCA of ACHD patients resuscitated for OHCA. We investigate these parameters in ACHD patients in comparison to OHCA in the general population.

Methods and results: We identified ACHD patients with OHCA by linking data from a Dutch nationwide registry of ACHD patients (CONCOR, n = 15,727), and ARREST, a cohort of OHCA cases (n = 17,868). 62 ACHD patients with OHCA were identified. Ventricular septal defect (n = 11), bicuspid aortic valve (n = 10) and atrial septal defect (n = 8) were the most common diagnoses. We included OHCA cases from the general population as controls. ACHD patients were younger than controls (n = 11,624) at the time of OHCA (47 (SD ± 17) years vs. 66 (SD ± 15) years, respectively, $p < 0.001$), and more often had a shockable initial rhythm (67% vs 40%, respectively, $p < 0.001$). A cardiac cause of OHCA was identified in 76% of ACHD patients, with only 7% due to myocardial infarction or ischemia. Survival was better in ACHD patients than in controls (44% vs. 19%, $p < 0.001$), but this difference disappeared after correction for age, gender, witnessed arrest, bystander resuscitation, public location and shockable rhythm.

Conclusions: OHCA in ACHD patients occurs at young age, is rarely caused by ischemia and occurs mainly in patients with simple congenital defects. Risk stratification efforts should therefore not be restricted to ACHD patients with severe congenital defects.

1. Introduction

Congenital heart defects (CHD) affect over 1% of all live births [1]. Due to advancements in medical and surgical care, survival of CHD patients into and throughout adulthood has improved [2]. Consequently, the adult congenital heart disease (ACHD) population is growing, with an estimated 1.4 million ACHD patients in the United States alone in 2010 [3].

Although these numbers are encouraging, ACHD patients remain at risk of a myriad of late complications, including sudden cardiac death (SCD) [4–8]. Despite still being a relatively rare event, the risk of SCD in ACHD is roughly a hundredfold greater than that of non-ACHD individuals of the same age [9]. SCD is one of the – if not the – leading causes of death in ACHD patients [4–6]. Moreover, since the risk of SCD increases with age, the absolute and relative rates of SCD are expected to rise within the growing and aging ACHD population. SCD is, in most cases, caused by ventricular arrhythmias, although complete atrioventricular conduction block or other late complications of congenital defects may also occur [7]. Implantable cardioverter-defibrillator (ICD) implantation may therefore be able to prevent a large portion of SCD cases [10].

As risk stratification for SCD is not well-defined, and ICD's are sparingly used in ACHD patients, the first manifestation of ventricular arrhythmia in ACHD patients may be an out-of-hospital cardiac arrest (OHCA) [11]. The causes and circumstances of OHCA in ACHD patients, as well as the outcome of cardiopulmonary resuscitation (CPR) are unknown; the causes and circumstances of OHCA in ACHD patients are largely unknown. Complex CHD, pulmonary hypertension and time to return of spontaneous circulation have been associated with worse outcome of OHCA in ACHD patients [12]. It is essential to collect data on resuscitation for OHCA in ACHD patients, in order to improve specialized care for ACHD patients presenting with OHCA. In addition, improving knowledge on the causes of OHCA in ACHD patients may have important implications for primary prevention of SCD. Data on long-term mortality are also needed for decisions regarding secondary prevention ICD implantation. Lastly, knowledge on the outcome of OHCA in ACHD

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patients is vital for carefully weighed Do-Not-Resuscitate (DNR) decision making at the outpatient clinic, should this issue arise. In this study, we assess the causes and circumstances of OHCA, as well as the outcomes of resuscitation in ACHD patients, and compare these results to OHCA in the general population.

2. Methods

2.1. Databases

To identify ACHD patients with OHCA we combined data from two large prospective registries in The Netherlands: CONCOR and ARREST. *CONgenital CORvitia* (CONCOR) is a Dutch nationwide population-based registry of ACHD patients, which started inclusion in 2002 [13] and encompasses 15,727 ACHD patients from 102 different hospitals, including all 8 academic medical centres in The Netherlands. CONCOR was designed to facilitate studies on the prevalence and long-term outcome of specific congenital heart defects. In the CONCOR registry, data are collected on demographics, congenital defects, surgical repair or palliation using the European Pediatric Cardiac Code Short List scheme, and patients are followed up prospectively [14]. Written informed consent is given by all participants of CONCOR.

Likewise, the *AmsteRdam REsuscitation STudies* (ARREST) is an ongoing Dutch regional registry of OHCA cases [15–17], including a total of 17,868 subjects in whom resuscitation for OHCA was attempted since 2005. The ARREST research group maintains a prospective database of all resuscitation efforts in several areas of The Netherlands, the largest being the province of North Holland, which includes the Dutch capital of Amsterdam and its surrounding suburbs. North Holland has a population of ~2.8 million people and covers an area of 2671 km^2, including both urban and rural communities. The organization of the emergency medical services (EMS) and data collection in the study region have been described previously [16]. In short, in case of suspected OHCA at dispatch, two ambulances are referred to the scene, equipped with a manual defibrillator; in addition, a first responder (i.e. firefighters, police, general practitioner) equipped with an automated external defibrillator (AED) is alerted. Increasingly, on-site AEDs are connected, either by bystanders or by lay-rescuers alerted by text-messages [18]. Rhythm data from all manual defibrillators and AED's are collected and categorized by the study group. Data concerning CPR procedure are collected following the Utstein recommendations [19]. Since 2009, medical history of OHCA patients is retrieved retrospectively using a questionnaire that is sent to the patients' general practitioner (GP). This questionnaire includes a question on congenital heart defects, asking the GP to describe any of the patient's known congenital heart defects.

2.2. Patient selection

Adult (≥18 years old) congenital heart disease patients with an OHCA were included in this study. To select ACHD patients with OHCA, we identified patients included in both the CONCOR and the ARREST database. Since ACHD databases include patients that are regularly followed up at secondary, and mostly tertiary, medical centres, these have a selection bias towards more severe congenital defects. In our study, we attempted to reduce this selection bias: in order to avoid missing patients with simple congenital heart defects and an OHCA that are not included in CONCOR, we identified additional patients through the abovementioned questionnaire from GPs. Data of OHCA patients with presumed ACHD as described by patients' GPs were confirmed by investigators (J.V. and R.K.) using hospital medical records and paramedic run sheets.

To place the results of ACHD patients with resuscitation for OHCA in perspective, we compare these cases to all other OHCA cases in the province of North-Holland.

2.3. Data collection

We collected congenital heart disease data from CONCOR, including the patients' main congenital heart disease diagnoses. As per CONCOR study protocol, in case a patient has multiple congenital defects, the main diagnosis is determined as the diagnosis with the worst prognosis according to a consensus-based hierarchical classification of CHD severity [20]. For patients identified through the GP questionnaires, we employed the same approach. We collected data concerning the OHCA and following hospital admission from ARREST, as well as from hospital records and medical letters collected in the ARREST database. We identified survival data from both databases.

The study complied with the Declaration of Helsinki. The Medical Ethics Review Board of the Academic Medical Center, Amsterdam, approved both registries, including the use of data from patients who did not survive OHCA. Written informed consent was obtained from all participants who survived OHCA.

2.4. Statistical analysis

We analysed all data using R, version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) [21]. Descriptive statistics for nominal data are expressed in numbers and percentages. For normally distributed continuous variables, we calculated mean values and standard deviations (SDs). We present non-normally distributed data in medians and interquartile range (IQR). For comparison of normally distributed continuous variables we used the One-way ANalysis Of VAriance. For non-normally distributed continuous variables we used the Kruskal-Wallis test. Kaplan-Meier curves were generated to estimate survival after OHCA. Logistic regression models were used to assess factors associated with survival to discharge. For all analyses, we considered two-tailed p-values <0.05 to be statistically significant.

3. Results

A total of 62 ACHD patients with OHCA in whom resuscitation was attempted were included in this study, of which 47 were patients that were identified by combining the two registries, and an additional 15 were found by reviewing information from general practitioners. A flowchart of the patient selection is presented in Supplemental Fig. 1.

3.1. Characteristics of ACHD patients and circumstances of OHCA

The main characteristics of ACHD patients and circumstances of OHCA are presented in Supplemental Table 1. ACHD patients were relatively young at the time of OHCA (mean age 47 ± 17 years), and 66% was male. More than half of all OHCAs occurred at home. Sixty-four percent of patients had a shockable rhythm at the time of first rhythm recording. The majority (86%) of OHCAs were witnessed by either a bystander (75%) or EMS personnel (11%). CPR was started by a bystander in 41/47 (non-EMS) witnessed OHCAs and in 5/7 non-witnessed OHCAs. An AED was used in 23 (42%) non-EMS witnessed cases.

3.2. Congenital heart defects

A large portion of patients had relatively simple congenital lesions, with ventricular septal defect (n = 11), bicuspid aortic valve (n = 10), atrial septal defect (n = 8) and aortic coarctation (n = 7) being the most prevalent diagnoses (Fig. 1). Characteristics of patients with different congenital defects are presented in Table 1.

3.3. Causes of OHCA

When examining the causes of OHCA, as stated by the treating medical centre at the time of OHCA, the majority of patients had a cardiac cause of OHCA. Proven or suspected myocardial infarction or ischemia only accounted for 7% of OHCA causes (Supplemental Table 2).

3.4. Survival after OHCA

The characteristics of OHCA cases who survived to hospital discharge versus those who did not are shown in Supplemental Table 3. Out of 62 ACHD patients with OHCA in whom resuscitation was attempted, 48 (77%) arrived at a hospital emergency room alive. In 44% of OHCA cases, ACHD patients survived to hospital discharge. Of patients with a shockable rhythm, 63% survived to hospital discharge, whereas 10% of patients without a shockable rhythm survived. One year after OHCA, 40% of ACHD patients were still alive. Of patients who survived to hospital discharge, 93% was still alive after one year, signifying that although many patients do not survive the initial OHCA and subsequent hospital admission, one-year survival is good in those that recover to be discharged from the hospital.

3.5. Comparison with other OHCA cases

Other cases of OHCA with an attempted resuscitation (n = 11,624) were significantly older at the time of OHCA, with a mean age of 66 (SD ± 15) years, $p < 0.001$. Fewer patients had a shockable rhythm compared to ACHD patients (Table 2). Survival to hospital discharge was significantly better in patients with congenital heart defects compared to the overall OHCA population: 44% vs 19%, odds ratio 3.1, 95% CI 1.9–5.1, $p < 0.001$. However, after correction for age, gender, witnessed arrest, bystander resuscitation, public location and shockable rhythm, survival to discharge was no longer significantly different between ACHD

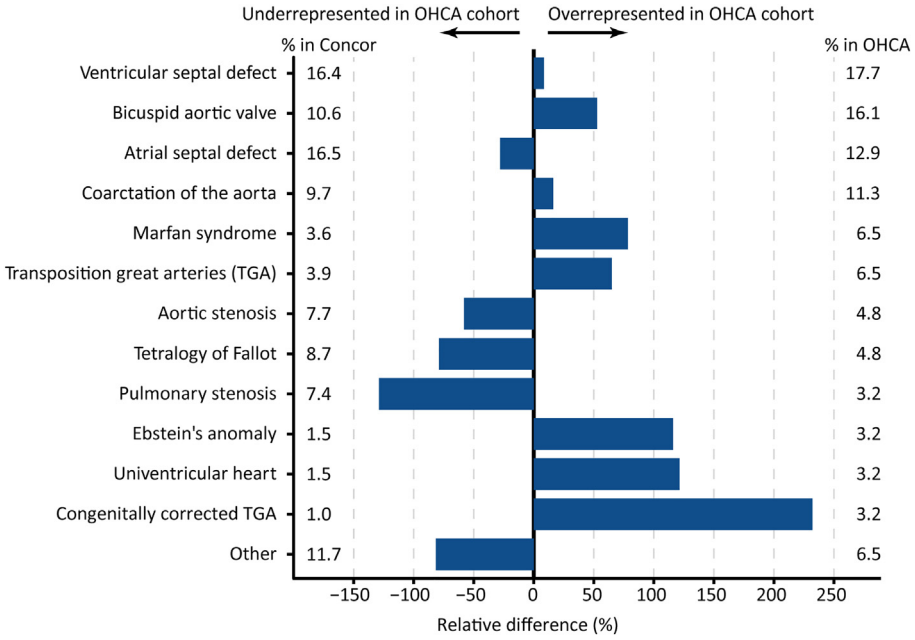

Fig. 1. Proportion of cases in OHCA cohort relative to the overall proportion of congenital defects of patients in the adult congenital heart disease population in the CONCOR database (total n = 15,727). Diagnoses for which bars point to the right are overrepresented in OHCA cases, such as ventricular septal defect, bicuspid aortic valve and coarctation of the aorta.

patients and controls (odds ratio 1.3, 95% CI 0.71–2.46, p = 0.373). Long-term survival of patients who survived to hospital discharge after admission for OHCA was similar in ACHD patients compared to OHCA cases in the general population (Fig. 2).

4. Discussion

This study describes for the first time the circumstances of OHCA and outcome of resuscitation in ACHD patients, in comparison to the general OHCA population. ACHD patients are young at the time of OHCA, and mainly present with a shockable rhythm. This explains the higher survival of ACHD patients over OHCA cases in the much older general population. When adjusting for age, gender, witnessed arrest, bystander resuscitation, public location and shockable rhythm, an improved survival in ACHD patients was no longer observed. However, it was not significantly worse either. The latter is surprising, since ACHD patients more often have severely impaired ventricular function and valvular dysfunction. This is more so in ACHD patients than in other patients who are resuscitated for OHCA at a young age, for example patients with genetic arrhythmias or patients with a first myocardial infarction. In addition, resuscitation of ACHD patients may pose unique dilemmas for physicians, paramedics and other care providers. For example, effective defibrillation and chest compression may be hindered by an aberrant cardiac position of the heart, structural, valvular and vascular abnormalities. ICD implantation after successful resuscitation may also be technically complex and complication-prone because of implanting difficulties due to an abnormal anatomy, and it is associated with a higher rate of inappropriate shocks and –mainly lead-related– complications [10]. However, since survival after discharge from hospitalization for OHCA is good, there are no indications that OHCA is a harbinger of death from other causes, such as heart failure. Therefore, ICD implantation after surviving OHCA due to a shockable rhythm without a reversible cause is certainly warranted. In addition, a subcutaneous ICD may overcome many of the ICD-related complications [22]. Moreover, efforts should be made to improve SCD-risk stratification in order to refine primary prevention ICD indications. The large portion of shockable rhythms makes ACHD patients at risk of SCD particularly suited for ICD implantation. Moreover, since survival of ACHD patients is good, implantation of an ICD, be it for primary or secondary prevention, is likely to be more beneficial in ACHD patients than in patients with acquired heart disease [10].

Secondly, although this study cannot provide data on incidences of OHCA in congenital defects, a surprising finding is that a large portion of OHCAs in our study occurred in patients with relatively simple defects. A possible explanation for this is that these patients are being followed-up to a lesser extent than patients with more severe defects. For example, we have shown that only about half of the OHCA cases with VSD were included in CONCOR, signifying that the remainder may have been discharged from follow up. One could therefore argue that these data suggest that even patients with simple congenital defects should be evaluated by a cardiologist every few years, and particularly VSD patients, as they have a substrate for reentry. In addition, patients with simple defects rarely have an ICD implanted. Previous

Table 1
Characteristics of patients with different congenital diagnoses. Pt: patient, SD: standard deviation, VF: ventricular fibrillation, VT: ventricular tachycardia.

	n	Age Mean ± SD	Male %	Concor pt. %	VT or VF %	Discharged alive %
All diagnoses	62	47 ± 17	68	76	65	44
Ventricular septal defect	11	45 ± 16	91	55	55	36
Left sided obstructive lesions	10	46 ± 17	70	90	80	50
Bicuspid aortic valve	10	58 ± 14	80	90	60	40
Atrial septal defect	8	58 ± 16	62	75	100	50
(Congenitally corrected) TGA	6	34 ± 15	67	67	83	33
Fallot/PS	5	42 ± 20	0	80	80	80
Other	12	42 ± 13	67	75	25	33

Table 2
Characteristics of ACHD OHCA patients and OHCA cases without ACHD.

	ACHD	No ACHD	p
	n = 62	n = 11,624	
Age, mean ± SD	47 ± 17	66 ± 15	<0.001
Male gender, n (%)	41 (66)	8308 (71)	0.416
Initial rhythm, n (%)			0.001
Ventricular fibrillation/tachycardia	40 (65)	4653 (40)	
Pulseless electric activity	11 (18)	3050 (26)	
Asystole	7 (11)	3208 (28)	
Undefined, not-shockable/unknown	4 (6)	713 (6)	
Cause of OHCA, n (%)			0.026
Cardiac	47 (76)	6320 (54)	
Trauma	0 (0)	351 (3)	
Respiratory or other non-cardiac	5 (8)	1289 (11)	
Unknown	10 (16)	3664 (32)	
Witnessed arrest, n (%)			0.01
Yes	54 (87)	8559 (74)	
EMS personnel	7 (11)	989 (9)	
Life partner	12 (19)	2775 (24)	
Bystanders	35 (56)	4795 (41)	
None	7 (11)	2886 (25)	
Unknown	1 (2)	179 (2)	
AED connected, n (%)[a]			<0.001
Yes	23 (42)	4605 (43)	
No	28 (51)	6021 (57)	
Unknown	4 (7)	9 (0)	
OHCA location, n (%)			0.399
Place of residence	34 (55)	7571 (65)	
Public road	15 (24)	1679 (14)	
Public building	13 (21)	2284 (19)	
Other/unknown	0 (0)	90 (1)	
Time to rhythm analysis (min:sec), mean ± SD[a]	8:01 ± 4:28	8:43 ± 5:43	0.384

AED: automatic external defibrillator, EMS: emergency medical services, SD: standard deviation.
[a] Excluding OHCA witnessed by EMS personnel.

risk stratification efforts for SCD have mainly focused on patients with tetralogy of Fallot [23–25]. A recent systematic review and meta-analysis showed that over half of all ACHD patients who received an ICD are patients with tetralogy of Fallot [10]. This may explain the relatively low proportion of tetralogy of Fallot patients with an OHCA in our study, as it has been shown that ICD's are responsible for a decrease in the incidence of OHCA caused by VF –the main cause of OHCA in our study– by approximately one third [17]. Comparison with other studies.

Previous studies have reported on SCD in ACHD patients, and one study provided data on OHCA in children and adults with congenital heart disease [12]. In 2012, Koyak et al. described 168 SCD cases. The main difference with the current study is that cases in that study had more severe congenital defects: predominantly Eisenmenger patients, (congenitally corrected) TGA, and tetralogy of Fallot. In addition, patients in that study were younger (36 years old vs. 47 in our study). Importantly, our study suggests, also contrary to the data provided by Van Puyvelde et al. on OHCA in ACHD, that patients with a relatively simple defect may be at similar risk of OHCA [12]. A possible explanation for this is that the previous studies included patients from a congenital patient database, which likely included relatively more patients with severe congenital defects, whereas the current study is based on a database of all OHCA cases in a specific region. Additionally, our study represents a more contemporary patient group, whereas those studies also reported on SCD and OHCA cases that occurred decades ago. Surgical and medical management have come a long way since then, and ICD's are implanted much more often.

Several studies reported on OHCA in children and young adults. In a 2011 study of children and adolescents (0–20 years of age), Bardai et al. found a much lower rate of cardiac cause of OHCA (38% in children vs. 76% in ACHD patients in this study), a lower rate of shockable rhythms (36% in children vs. 67% in our study) and a worse survival to discharge in children: 24% vs. 46%, respectively [15]. In another 2011 study, Deasy et al. found in 841 patients aged 16–39 years with a presumed cardiac cause of OHCA, that 77% of patients died. In 40% of deaths a cardiac cause could be confirmed by coroner's findings and in 6.5% of these cases a congenital defect was identified as the cause of OHCA [26].

4.1. Strengths

A major strength of this study is the fact that this study combines data from two robust registries, one specifically designed to gather data on ACHD patients (CONCOR), and the other to provide information on causes, circumstances and outcomes of OHCA. This ensures that our data is as accurate as possible.

4.2. Limitations

This study was performed using two large databases. Both databases are well-maintained by full-time dedicated staff. The databases are regularly maintained and updated. However, there are some inherent limitations to database work. The results are observational in nature, thereby limiting the possibilities to study causal relationships.

We cannot be certain that we have identified all ACHD patients in the ARREST database. CONCOR does not include all Dutch patients

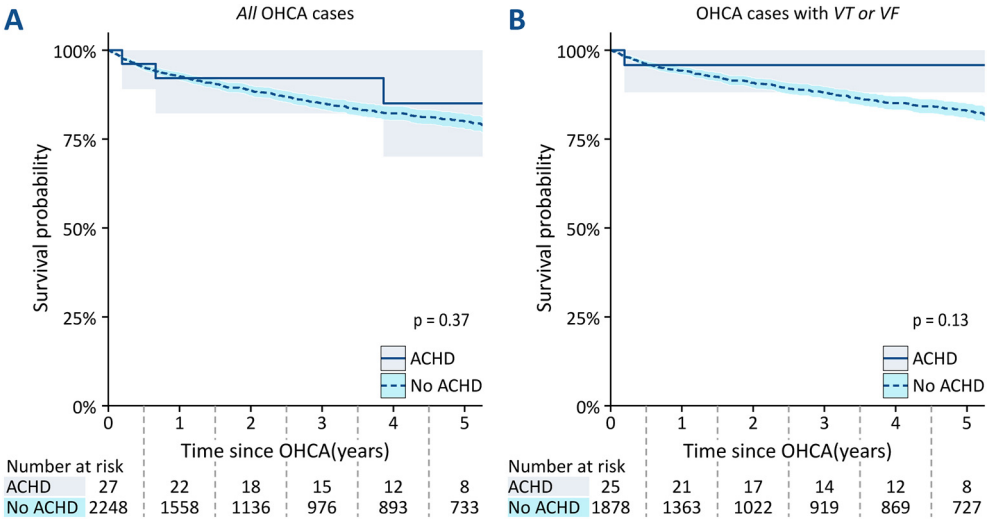

Fig. 2. Kaplan-Meier estimate of survival after discharge from admission for OHCA in ACHD patients vs. OHCA cases without ACHD (only including patients who were discharged alive from the hospital). Panel A: All out-of-hospital cardiac arrests, B: OHCA cases with VT or VF.

with congenital heart defects, and the surveys in ARREST were sent to only a part of OHCA cases' general practitioners. However, the number of ACHD patients in our control group will likely be insignificant. Likewise, as CONCOR is a nationwide registry, and ARREST is only regional, OHCA cases outside of the regions where ARREST is active are missed. The study may, therefore, be regarded as a regional study in a subset of CONCOR patients from the ARREST study region. Within this study region, we are convinced that we have identified all patients with OHCA for whom EMS was involved. The numbers we present here are by no means the incidence of OHCA in ACHD patients in The Netherlands; these cases are likely only a part of all OHCA cases that occurred in ACHD patients. However, we have no arguments to assume that the cases presented here are not representative of OHCA in other ACHD patients. Another limitation of this study is that simple congenital defects are much more prevalent in the general population than moderate or complex lesions. Therefore, this may cause an overrepresentation of patients with simple lesions in our study. However, the CONCOR database includes a relatively larger portion of moderate and complex congenital lesions compared to the prevalence in the general population, since patients with simple defects are more likely to be discharged from routine follow-up. The CONCOR database consists of roughly 16% of both VSD and ASD patients, and for 8% of tetralogy of Fallot patients. This may therefore reduce this overrepresentation of simple defects.

In this study, the cause of OHCA and use of automatic external defibrillators was significantly different between ACHD cases and controls (Table 2). However, this is likely a result of a relatively large portion of ACHD patients in whom AED use was not known.

For this study we did not match ACHD patients to other OHCA cases, since any match would have to involve the age characteristic. This would cause patients with, for example, genetic arrhythmias and premature atherosclerosis, rather than genuine controls, to be matched to ACHD patients. A comparison of ACHD patients with these specific patient groups was not the aim of this study; therefore, we chose not to perform any matching.

5. Conclusions

Adults with congenital heart defects are young at the time of OHCA compared to the general population, with more shockable rhythms. ACHD patients presenting with OHCA have relatively simple congenital defects. Risk stratification efforts should therefore be expanded to this patient group, as previous studies have focused mainly on patients with tetralogy of Fallot and other severe congenital defects. As the prevalence of congenital heart defects is rapidly growing, and the population is aging, physicians may encounter larger numbers of ACHD patients with an OHCA, especially if risk stratification and ICD implantation for primary prevention is not improved.

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Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.10.096.

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