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The wide spectrum of ventricular arrhythmias: From out-of-hospital cardiac arrest to advanced in-hospital treatment

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The wide spectrum of ventricular arrhythmias: From out-of-hospital cardiac arrest to advanced in-hospital treatment

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Editorial: The wide spectrum of ventricular arrhythmias: from out-of-hospital cardiac arrest to advanced in-hospital treatment

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Editorial on the Research Topic
The wide spectrum of ventricular arrhythmias: from out-of-hospital cardiac arrest to advanced in-hospital treatment

Introduction

Ventricular arrhythmias (VAs) are one of the most life-threatening acute clinical conditions (1) and may be responsible of a different clinical scenarios from out-of-hospital cardiac arrest (OHCA), whose outcome is bounded to the speed and effectiveness of rescue system, comprising both citizen-rescuers and emergency medical system (EMS) (2), to isolated or recurrent relapses in patients with an implantable cardioverter-defibrillator (ICD) or hospitalized for different medical conditions. Their prediction and treatment are some of the most fascinating fields for physicians involved in the management of patients with VAs. Despite a significant progress made in recent years, many gaps in knowledge exist. To refine our capability of arrhythmic risk stratification by advanced imaging tools and electrophysiological tests is a challenge for clinicians, both in patients with ischemic and non-ischemic cardiomyopathies and in those with inherited cardiac arrhythmias. Finally, the acute and chronic treatment of VAs, starting from the pre-hospital setting throughout the in-hospital phase and after discharge regardless of the clinical presentation, is crucial for survival. New techniques emerged over the last years that let us imagine even better outcomes in the future. The goal of the Research Topic was to expand the knowledge regarding all the aspects related to VAs.

Arrhythmic risk stratification

Russo et al. reported an association, in a patient with a family history of sudden death and dilated cardiomyopathy, and inducibility of polymorphic ventricular tachycardia at electrophysiological study, of a drug-induced type 1 Brugada pattern and a Ser573Leu missense variant on the Lamin A/C (*LMNA*) gene. The authors suggested that the Brugada pattern might be part the cardiolaminopathies spectrum, proposing *LMNA* genetic testing for all the patients with drug-induced type 1 Brugada pattern.

Moreover, Tsartsalis et al. carried out a review of fifty-five meta-analyses of observational and randomized controlled trials to explore the modifiable risk and protective factors of sudden cardiac death (SCD). The authors concluded that lifestyle risk factors (physical activity, smoking), comorbidities as diabetes, and electrocardiographic features like early repolarization constitute modifiable risk factors of SCD. Alternatively, the use of mineralocorticoid receptor antagonists (MRAs), beta-blockers, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors are protective factors. This evidence opens the possibility for future investigations targeted in specific populations aimed to reduce the SCD burden.

Improving the "chain of survival"

In a survey conducted by Kovoor et al. among the Australian public, a newly designed yellow-red signage for AEDs and cabinets was preferred by 73.0% and 88%, respectively, over the green-white counterparts. The authors therefore proposed to standardize yellow-red signage of AED and cabinet as it is easier to identify over the green-white one.

Furthermore, Nielsen et al. demonstrated a four-fold increased odds ratio for bystander CPR and a three-fold increased odds ratio for bystander defibrillation when volunteer responders accepted the alarm and arrived before EMS. This study, which used data from 1877 OHCAs with volunteer responders activation in Denmark, stresses the importance of the activation of persons trained in CPR/AED, which can also improve patients' survival (3).

Advanced pre-hospital treatment strategies

In an international multicenter observational study, Gentile et al. evaluated the value of Amplitude Spectral Area (AMSA) of VF of 2077 shocks. This study, called MOSAIC study, demonstrated that the administration of amiodarone was independently associated with the probability of recording lower values of AMSA. Moreover, the authors highlighted the fact that the predictive value of AMSA for shock success is significantly lower, but still statistically significant, in patients who have received amiodarone during cardiac arrest. This topic seems to be of great clinical importance considering that AMSA is an emerging indicator that might guide defibrillation and resuscitation efforts (4). Taking into account the results of the MOSAIC study, further randomized study are needed to clarify the effect of amiodarone on AMSA.

Improving hospital treatment and long-term management

The features of patients who underwent subcutaneous implantable cardiac defibrillator (S-ICD) implantation in the clinical practice of a single center, as well as the ICD-related complications and the inappropriate therapies during follow-up were described by Russo et al. The authors highlighted that the choice to implant an S-ICD was mainly driven by the younger age and by the presence of a channelopathy; conversely ischemic cardiomyopathy reduces the probability to use this technology. As in previous reports (5), no differences in inappropriate ICD therapies were shown among S-ICD vs. transvenous ICDs (TV-ICD) and a lower rate of infectious and non-infectious complications leading to surgical revision or extraction were observed in S-ICD recipients. Also with regard to ICD patients, Regoli et al. carried out a review on the management of hemodynamically stable, incessant wide QRS complex tachycardia in patients who already received an ICD, which represents a challenging situation. The authors proposed an approach based on four different phases to deal with these patients: hemodynamic status assessment; preparation for therapy and removal of potential triggers; therapy administration including anti-arrhythmic drugs, device reprogramming and acute neuromodulation, which is promising in treating this type of patients (6); hospitalization and prevention of arrhythmic relapses.

Concerning patients with drug-refractory electrical storm (ES), Cojocaru et al. highlighted that patients with non-revascularized chronic total occlusions (NR-CTO) demonstrated a higher ratio of border-zone to total scar area compared to patients without NR-CTO. Moreover, NR-CTO seemed to be associated with worse acute procedural results and may as well impact long-term outcomes.

Moving to non-invasive VAs ablation, Whitaker et al. carried out a review concerning cardiac stereotactic body radiation therapy (cSBRT) for VAs refractory to medical therapy and catheter ablation. The authors stressed how this technique is promising to treat VAs, but also that many aspects related to this technique are currently unknown, especially concerning the radiobiology of the anti-arrhythmic effect, representing an exciting opportunity for future research.

In conclusion, VAs represent a complex challenge which requires the involvement of multiple actors, from the community to expert in hospitals, and the use of multiple techniques to increase the patients' chances of survival.

Conclusion and future perspective

VAs' treatment relies on a multifaceted approach including risk stratification, out and inside hospital treatment and long-term management. Emerging techniques will help clinicians in the future to refine risk and improve treatment to increase outcome, which represent the final aim of research.

Author contributions

EB: Conceptualization, Writing – original draft. HT: Writing – review & editing. VD: Writing – review & editing. RR: Writing – review & editing. AZ: Writing – review & editing. SS: Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Device-Related Complications and Inappropriate Therapies Among Subcutaneous vs. Transvenous Implantable Defibrillator Recipients: Insight Monaldi Rhythm Registry

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Introduction: In the context of randomized clinical trials, subcutaneous implantable cardiac defibrillators (S-ICDs) are non-inferior to transvenous ICDs (T-ICDs) concerning device-related complications or inappropriate shocks in patients with an indication for defibrillator therapy and not in need of pacing. We aimed at describing the clinical features of patients who underwent S-ICD implantation in our clinical practice, as well as the ICD-related complications and the inappropriate therapies among S-ICD vs. T-ICD recipients during a long-term follow-up.

Materials and Methods: All patients undergoing ICD, both S-ICD and TV-ICD, at Monaldi Hospital from January 1, 2015 to January 1, 2019 and followed up at our institution were included in the present analysis. The clinical variables associated with S-ICD implantation were evaluated by logistic regression analyses. We collected the ICD inappropriate therapies, ICD-related complications (including both pulse generator and lead-related complications), ICD-related infections, appropriate ICD therapies, and overall mortality. Kaplan-Meier (KM) analyses were performed to assess the risk of clinical outcome events between the two subgroups. A time-dependent Cox regression analysis was performed to adjust the results.

Results: Total 607 consecutive patients (mean age 53.8 ± 16.8, male 77.8%) with both TV-ICD (*n*: 290, 47.8%) and S-ICD (*n*: 317, 52.2%), implanted and followed at our center for a mean follow-up of 1614 ± 1018 days, were included in the study. At multivariate logistic regression analysis, an independent association between S-ICD implantation and ionic channel disease [*OR*: 6.01 (2.26–15.87); $p < 0.0001$] and ischemic cardiomyopathy [*OR*: 0.20 (0.12–0.35); $p < 0.0001$] was shown. The KM analysis did not show a significantly different risk of the inappropriate ICD therapies (*log rank* $p = 0.64$) between the two subgroups; conversely, a significant increase in the risk of ICD-related complications (*log rank* $p = 0.02$) and infections (*log rank* $p = 0.02$) in TV-ICD group was shown. The adjusted risk for ICD-related

infections [*OR*: 0.07 (0.009–0.55), $p = 0.01$] and complications [0.31 (0.12–0.81), $p = 0.01$] was significantly lower among patients with S-ICD.

Conclusions: The choice to implant S-ICD was mainly driven by younger age and the presence of ionic channel disease; conversely ischemic cardiomyopathy reduces the probability to use this technology. No significant differences in inappropriate ICD therapies were shown among S-ICD vs. TV-ICD group; moreover, S-ICD is characterized by a lower rate of infectious and non-infectious complications leading to surgical revision or extraction.

Keywords: subcutaneous ICD (S-ICD), transvenous ICD, complications, infections, inappropriate shock therapy, mortality

INTRODUCTION

The subcutaneous implantable cardioverter-defibrillator (S-ICD) is an established therapy for the prevention of sudden cardiac death (SCD) (1) and an alternative to a transvenous implantable cardioverter-defibrillator (T-ICD) system in selected patients (2). S-ICD may be particularly useful in patients with channelopathies (3) since several studies showed a high complication rate in those implanted with T-ICD (4–6). S-ICD is non-inferior to T-ICD concerning device-related complications or inappropriate shocks in patients with an indication for defibrillator therapy and not in need of pacing (7–12); however, these data are limited to short follow-up observational case-control studies (7–10) or the context of the randomized clinical trial (11, 12). Moreover, few data about the clinical drivers of S-ICD vs. T-ICD implantation in clinical practice have been still provided. We therefore aimed at describing the clinical features of patients who underwent S-ICD implantation, as well as the ICD-related complications and the inappropriate therapies among S-ICD vs. T-ICD recipients in the clinical practice of a high-volume implantation center.

MATERIALS AND METHODS

Database

Data for this study were sourced from the Monaldi Hospital Rhythm Registry (NCT05072119), which includes all patients who underwent ICD implantation and followed up at our Institution through both outpatient visits, every 3–6 months, and remote device monitoring. During the follow-up, the occurrence and the causes of inappropriate and appropriate ICD therapies, ICD-related complications, and deaths were assessed and recorded in the electronic data management system. For the present analysis, we selected all consecutive patients who received *de novo* both subcutaneous (S-ICD Group) and transvenous (TV Group), from January 1, 2015 to January 1, 2019, according to the European guidelines and recommendations available at the time of implantation (13, 14). We excluded patients with pacing indications (*n*: 87), CRT (*n*: 232), upgrade of an existing device (*n*: 56), incomplete baseline (*n*: 36) or follow-up data (*n*: 48). The local institutional review boards approved the study (ID 553-19), and all patients provided written informed consent for data storage and analysis.

ICD Programming

The programming of the parameters for the detection of VT/VF was done according to the guidelines recommendations at the time of implant. In particular, we routinely activate for primary prevention only one VF zone (30 intervals at 250 bpm) and for secondary prevention two windows of detection (VF: 30 intervals at 250 bpm; VT2: 30 intervals at 187 bpm or 10–20 bpm < VT rate) with shocks only in VF zone and up to three ATPs and eight shocks in VT2 zone. S-ICD devices were programmed with a conditional zone, between 200 and 250 bpm, and a shock zone > 250 bpm. The programmed sensing vector was primary (48.42%) or secondary (43.4%) for most patients and alternate in a small percentage of cases (8.18%). The bicycle ergometer test was not routinely performed in patients who implanted S-ICD at our Hospital.

Outcomes

The primary study endpoints were: ICD inappropriate therapies, defined as anti-tachycardia pacing (ATP) and/or shocks for conditions other than ventricular tachycardia (VT) or ventricular fibrillation (VF); ICD-related complications, defined as all pulse generator (PG) or lead-related complications requiring surgical intervention; ICD-related infections, defined as all systemic infections requiring complete removal of the system including the leads extraction. The secondary endpoints were the clinical variables associated to S-ICD implantation, appropriate ICD therapies and all-cause mortality. Moreover, the type and distribution of ICD-related complications, defined as early when appearing during the first 30 days after device implantation or late, when occurred after the first-month post-implantation, were assessed.

Statistical Analysis

Categorical data were expressed as number and percentage, whereas continuous variables were expressed as either median [interquartile range (*IQR*)]) or mean ± SD, based on their distribution as assessed both by the Kolmogorov–Smirnov and the Shapiro–Wilk tests. Between-group differences, for categorical variables, were assessed by the chi-square test, with

the application of Yates correction where appropriate. Either parametric Student's *t*-test or nonparametric Mann–Whitney U test and Wilcoxon test were instead used to compare continuous variables, according to their distribution. Kaplan–Meier analysis was performed to assess the risk of both inappropriate ICD therapies and ICD-related complications between the two subgroups. Univariate and multivariate logistic regression was used to assess the clinical characteristics associated with S-ICD implantation. A time-dependent Cox univariate (unadjusted) and multivariate (adjusted) regression model was used to evaluate the association between S-ICD and clinical outcome events. The multivariate model was computed on all covariates with a p-value < 0.05. A 2-sided probability p-value < 0.05 was considered statistically significant. All analyses were performed using SPSS statistical software (version 24.0, SPSS, Chicago, Illinois) and STATA 14.0 software (StataCorp, College Station, Texas).

RESULTS

General Characteristics of the Study Population

A total of 607 consecutive patients (mean age 53.8 ± 16.8, male 77.8%) with both TV-ICD (*n*: 290, 47.8%) and S-ICD (*n*: 317, 52.2%) followed at our center for a mean follow-up of 1,614 ± 1,018 days were included in the study. The indication for ICD implantation was primary prevention in 542 patients (89%) and secondary prevention in 65 patients (11%). S-ICD group showed more likely younger age (49 ± 17 vs. 60 ± 14 years; $p < 0.0001$), higher left ventricular ejection fraction (LVEF) (41 ± 17 vs. 35 ± 12 %; $p < 0.0001$), and lower prevalence of cardiovascular comorbidities. Ischemic cardiomyopathy (44.5 vs. 27%; $p < 0.0001$) and idiopathic dilated cardiomyopathy (32.4 vs. 17.3 %; $p < 0.0001$) were more frequent in the TV-ICD group; conversely, ionic channel disorders (16.7 vs. 2.75 %; $p < 0.0001$) were more frequent in S-ICD group. The ionic channel disorders group included patients with long QT syndrome (*n*: 8) and Brugada syndrome (*n*: 53). All baseline clinical characteristics of the study population are summarized in **Table 1**.

TABLE 1 | Baseline characteristics of the study population.

Parameter	TV-ICD group *n: 290*	S-ICD group *n: 317*	*p*
Male gender, *n* (%)	228 (79)	239 (75)	0.24
Age (years), mean ± SD	60 ± 14	49 ± 17	<0.0001
LVEF (%), mean ± SD	35 ± 12	41 ± 17	<0.0001
Idiopathic dilated cardiomyopathy, *n* (%)	94 (32.4)	55 (17.3)	<0.0001
Ischemic cardiomyopathy, *n* (%)	129 (44.5)	86 (27)	<0.0001
Hypertrophic cardiomyopathy, *n* (%)	29 (10)	48 (15)	0.06
ARVD, *n* (%)	3 (1)	10 (3)	0.08
Ionic channel disorders, *n* (%)	8 (2.75)	53 (16.7)	<0.0001
Primary prevention, *n* (%)	239 (82.4)	303 (95)	<0.0001
Secondary prevention, *n* (%)	51 (17.5)	14 (4.4)	<0.0001
NYHA I, *n* %	15 (5)	55 (17.3)	<0.0001
NYHA II, *n* %	151 (52)	123 (38.8)	0.001
NYHA III, *n* %	105 (36)	74 (23.3)	0.0006
NYHA IV, *n* %	19 (7)	2 (0.6)	<0.0001
Hypertension, *n* (%)	190 (65.5)	93 (29)	<0.0001
Diabetes, *n* (%)	87 (30)	38 (12)	<0.0001
COPD, *n* (%)	41 (14)	45 (14)	1
CAD, *n* (%)	121 (41.7)	79 (25)	<0.0001
AF history, *n* (%)	72 (24.8)	44 (13.9)	0.0006
CKD, *n* (%)	46 (16)	34 (11)	0.07
Previous valve replacement, *n* (%)	17 (5.8)	15 (4.7)	0.54
Previous CABG, *n* (%)	22 (7.5)	22 (6.9)	0.77

LVEF, left ventricular ejection fraction; ARVD, arrhythmogenic right ventricular dysplasia; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease, CAD, coronary artery disease; CKD, Chronic Kidney Disease; AF, Atrial fibrillation; CABG, Coronary Artery Bypass Graft.

Clinical Variables Associated With S-ICD Implantation

We assessed potential clinical variables associated with S-ICD implantation among our study population. At multivariate logistic regression analysis, an independent association between S-ICD implantation and ionic channel disease [*OR*: 6.01 (2.26–15.87); $p < 0.0001$], ischemic cardiomyopathy [*OR:* 0.20 (0.12–0.35); $p < 0.0001$] was shown. All data are shown in **Table 2**.

Clinical Outcomes Between the Groups

Inappropriate ICD Therapies

Among our study population, ICD inappropriate therapies were experienced by 14 patients (2.31%). Out of these, seven patients (2.41%) in the TV-ICD group and seven patients (2.2%) in S-ICD group ($p = 0.56$). The annual incident rate of ICD inappropriate therapies over the follow-up was 0.6%. The Kaplan–Meier analysis did not show a significantly different risk of inappropriate ICD therapies between the two subgroups (*log-rank* $p = 0.64$) (**Figure 1**). At Cox univariate analysis no baseline patients' characteristic, including the S-ICD (*OR*: 1.30; 95% *CI*: 0.43–3.96; $p = 0.64$), was associated with inappropriate ICD therapies (**Supplementary Table 1**).

ICD-Related Complications

ICD related complications in need of surgical revision occurred in 24 patients (3.9%); 18 (6.2%) in TV-ICD group and 6 (1.9%) in S-ICD group ($p = 0.006$); mainly due to increased lead-related complications in TV-ICD vs. S-ICD group (5.9 vs. 0.3%; $p = 0.001$). In contrast, no significant differences were shown in PG-related complications between the two subgroups (0.34 vs. 1.72%; $p = 0.09$). The Kaplan–Meier analysis showed a significantly increased risk of ICD-related complications among the TV-ICD group (*log-rank* $p = 0.02$) (**Figure 2**). At Cox multivariate analysis, S-ICD was the only variable significantly associated with a reduction of ICD-related complications (*OR*: 0.31; 95% *CI* 0.12–0.83; $p < 0.01$) (**Supplementary Table 2**).

ICD-Related Infections

ICD-related infections in need of leads extraction occurred in 11 patients (1.8%); 10 (3.4%) in TV-ICD group and 1 (0.3%) in S-ICD group ($p = 0.004$). The annual incident rate of ICD-related infections over the follow-up was 0.4%. The Kaplan-Meier analysis showed a significantly

TABLE 2 | Association between S-ICD implantation and clinical covariates: univariate and multivariate analysis.

	Univariate Analysis OR [95% CI]	*p*	Multivariate Analysis OR [95% CI]	*p*
Male gender	0.91 [0.62–1.35]	0.65	-	-
Age	0.96 [0.96–0.98]	<0.0001	0.99 [0.98–1.01]	0.11
LVEF	1.03 [1.02–1.04]	<0.0001	0.98 [0.97–1.01]	0.09
Idiopathic dilated cardiomyopathy	0.44 [0.31–0.64]	<0.0001	0.80 [0.42–1.56]	0.5
Ischemic cardiomyopathy	0.46 [0.33–0.65]	<0.0001	0.20 [0.12–0.35]	<0.0001
Hypertrophic cardiomyopathy	1.62 [0.99–2.64]	0.06	-	-
ARVD	3.12 [0.85–11.44]	0.09	-	-
Ionic channel disorders	7.07 [3.30–15.16]	<0.0001	6.01 [2.26–15.87]	<0.0001
Hypertension	0.23 [0.16–0.32]	<0.0001	0.62 [0.27– 1.13]	0.25
Diabetes	0.33 [0.22–0.51]	<0.0001	0.55 [0.34–1.07]	0.08
COPD	1.03 [0.65–1.63]	0.8	-	-
CAD	0.48 [0.34–0.67]	<0.0001	0.60 [0.34–1.12]	0.12
CKD	0.66 [0.41–1.05]	0.08	-	-
AF history	0.49 [0.32–0.74]	0.007	0.67 [0.41–1.09]	0.11
Previous valve replacement	0.81 [0.40–1.65]	0.55	-	-
Previous CABG	0.94 [0.51–1.73]	0.83	-	-

LVEF, left ventricular ejection fraction; ARVD, arrhythmogenic right ventricular dysplasia; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CKD, Chronic Kidney Disease; AF, Atrial fibrillation; CABG, Coronary Artery Bypass Graft.

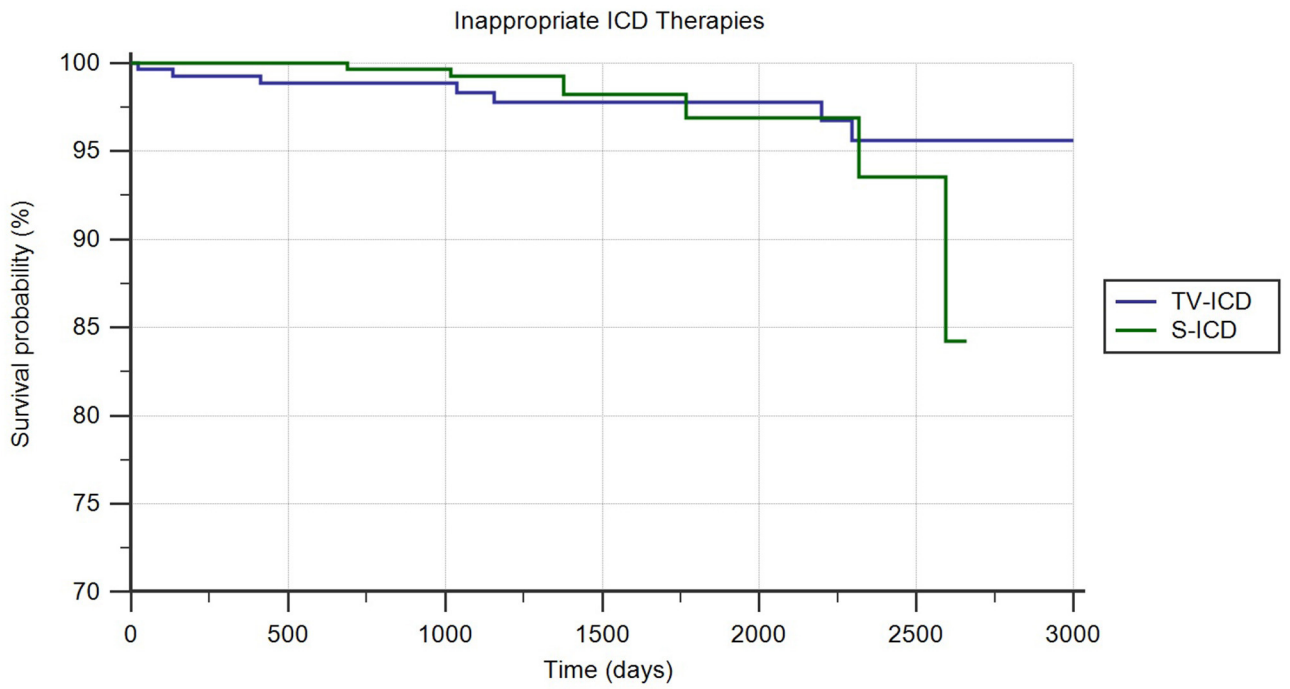

FIGURE 1 | Kaplan-Meier curve comparing survival without ICD-related infections among S-ICD vs. TV-ICD groups.

increased risk of ICD-related infections among the TV-ICD group (*log-rank* $p = 0.02$) (**Figure 3**). At Cox multivariate analysis, S-ICD was the only variable significantly associated with a reduction of ICD-related infections (*OR*: 0.07; 95% *CI* 0.009–0.55; $p < 0.01$); in contrast previous valve replacement (*OR*: 7.22; 95% *CI* 2.34–22.22; $p = 0.0006$) was associated with an increased risk of ICD-related infections (**Supplementary Table 3**).

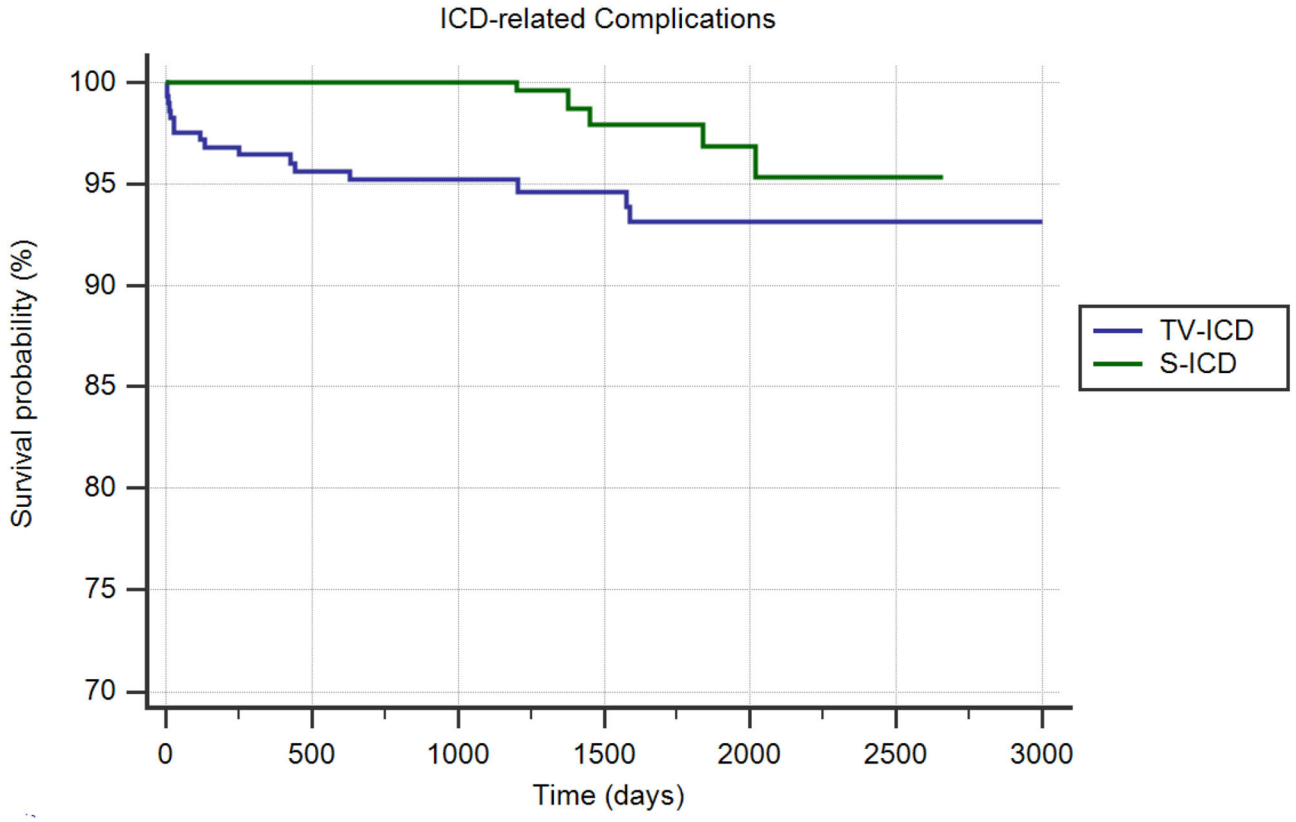

FIGURE 2 | Kaplan-Meier curve comparing survival without ICD related complications among S-ICD vs. TV-ICD groups.

In the **Table 3** were summarized all primary outcomes events at follow-up among the two subgroups.

Appropriate ICD-Therapies

Among our study population, ICD appropriate therapies were experienced by 56 patients (9.23%). Out of these, 46 patients (15.86%) in the TV-ICD group and 10 patients (3.15%) in S-ICD group ($p = 0.0001$). **Table 4** shows the number and the underlying disease of patients with at least one appropriate ICD therapy among our study population. The annual incident rate of ICD appropriate therapies over the follow-up was 2.3%. The Kaplan–Meier analysis showed a significantly increased risk of appropriate ICD therapies among the TV-ICD group (*log-rank* $p = 0.04$). At Cox multivariate analysis, no clinical variables were independently associated with an increased risk of ICD appropriate therapy (**Supplementary Table 4**).

All-Cause Mortality

During the follow-up period, 28 people (4.61 percent) died: 8 patients (2.52%) in the S-ICD group and 20 (6.9%) in the TV-ICD group ($p = 0.01$). The annual incident rate of mortality over the follow-up was 1.15%. The Kaplan–Meier analysis did not show a significantly different risk of death between the two groups (*log-rank* $p = 0.52$) (**Figure 4**). At Cox multivariate analysis, no clinical variables were independently associated with all-cause mortality (**Supplementary Table 5**). **Table 5** shows the unadjusted and adjusted odds ratio for the association between the clinical outcomes of interest and S-ICD.

DISCUSSION

The main results of our study are the following: younger age and ionic channel diseases are clinical variables independently associated with S-ICD implantation for sudden cardiac death prevention; conversely, ischemic cardiomyopathy reduced the probability to receive S-ICD among our study population. S-ICD patients showed a lower rate of both ICD-related complications and infections and no significant differences in inappropriate ICD therapies compared to TV-ICD patients during the follow-up. Finally, no differences inappropriate ICD therapies and overall mortality have been shown between the two groups. The lower age of the S-ICD group and the higher prevalence of ionic channel disease as clinical drivers of S-ICD implantation among our study population confirm the tendency to consider S-ICD the preferred choice for patients with an active lifestyle and long-life expectance. This is particularly true for inherited genetic arrhythmogenic syndromes (Brugada Syndrome and Long QT syndrome) where clinical arrhythmias are polymorphic VT or VF (not treatable with ATP) and the risk of bradycardia and monomorphic VT is very low (15, 16). The reduced probability

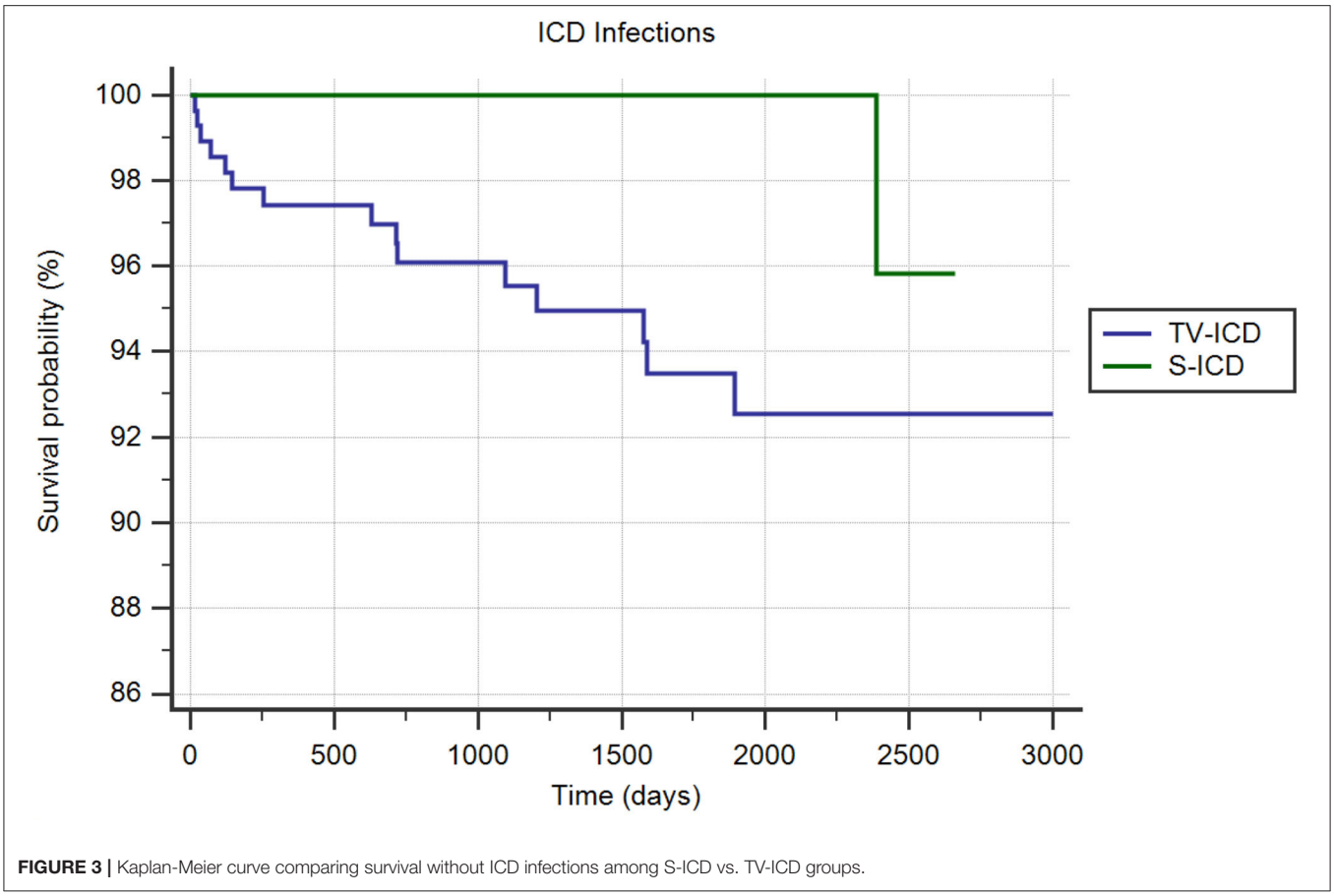

FIGURE 3 | Kaplan-Meier curve comparing survival without ICD infections among S-ICD vs. TV-ICD groups.

TABLE 3 | Primary outcome events at follow-up.

Parameter	TV-ICD group *n = 290*	S-ICD group *n = 317*	*p*
Inappropriate ICD therapies, *n* (%)	7 (2.4)	7 (2.2)	0.65
Inappropriate shock, *n* (%)	4 (1.37)	7 (2.2)	0.44
Inappropriate ATP, *n* (%)	3 (1)	0 (0)	0.07
Causes of inappropriate therapies			
T wave oversensing, *n* (%)	0 (0)	4 (1.3)	0.05
Myopotential oversensing, *n* (%)	0 (0)	2 (0.6)	0.19
Atrial fibrillation, *n* (%)	5 (1.7)	0 (0)	0.02
Atrial tachycardia, *n* (%)	2 (1.37)	1 (0.3)	0.14
ICD related complications, *n* (%)	18 (6.2)	6 (1.9)	0.007
PG related complications, *n* (%)	1 (0.34)	5 (1.72)	0.09
PG Malfunction, *n* (%)	1 (0.34)	5 (1.72)	0.09
Lead related complications, *n* (%)	17 (5.9)	1 (0.3)	<0.0001
Lead failure, *n* (%)	5 (2)	0 (0)	0.01
Lead dislodgement, *n* (%)	2 (0.7)	0 (0)	0.14
Lead Fracture, *n* (%)	10 (3.4)	1 (0.3)	0.004
ICD infectious complications	10 (3.4)	1 (0.3)	0.004
Timing of overall complications			
Early complications	8 (2.75)	0 (0)	0.003
Late complications	20 (6.9)	7 (2.2)	0.005

TABLE 4 | Number of patients with at least one appropriate ICD therapy across different patients subgroups.

	TV-ICD group		S-ICD group
	Shock	ATP	Shock
Idiopathic dilated cardiomyopathy, *n*	7	11	3
Ischemic cardiomyopathy, *n*	9	11	2
Hypertrophic cardiomyopathy, *n*	3	2	1
Brugada syndrome, *n*	1	0	1
LQTS, *n*	0	0	2
ARVD, *n*	1	0	1

LQTS, Long QT syndrome; ARVD, arrhythmogenic right ventricular dysplasia.

for patients with ischemic cardiomyopathy to receive an S-ICD might be due to fair of sustained VT in need of anti-tachycardia pacing (ATP) or incident bradyarrhythmias in need of pacing (17). However, it should be noted that only 15–20% of patients experienced a high rate of monomorphic VT during the first year after the implant with a subsequent risk is 1.8%/year; moreover, the proportions of both monomorphic VT and successful ATP was comparable between patients with

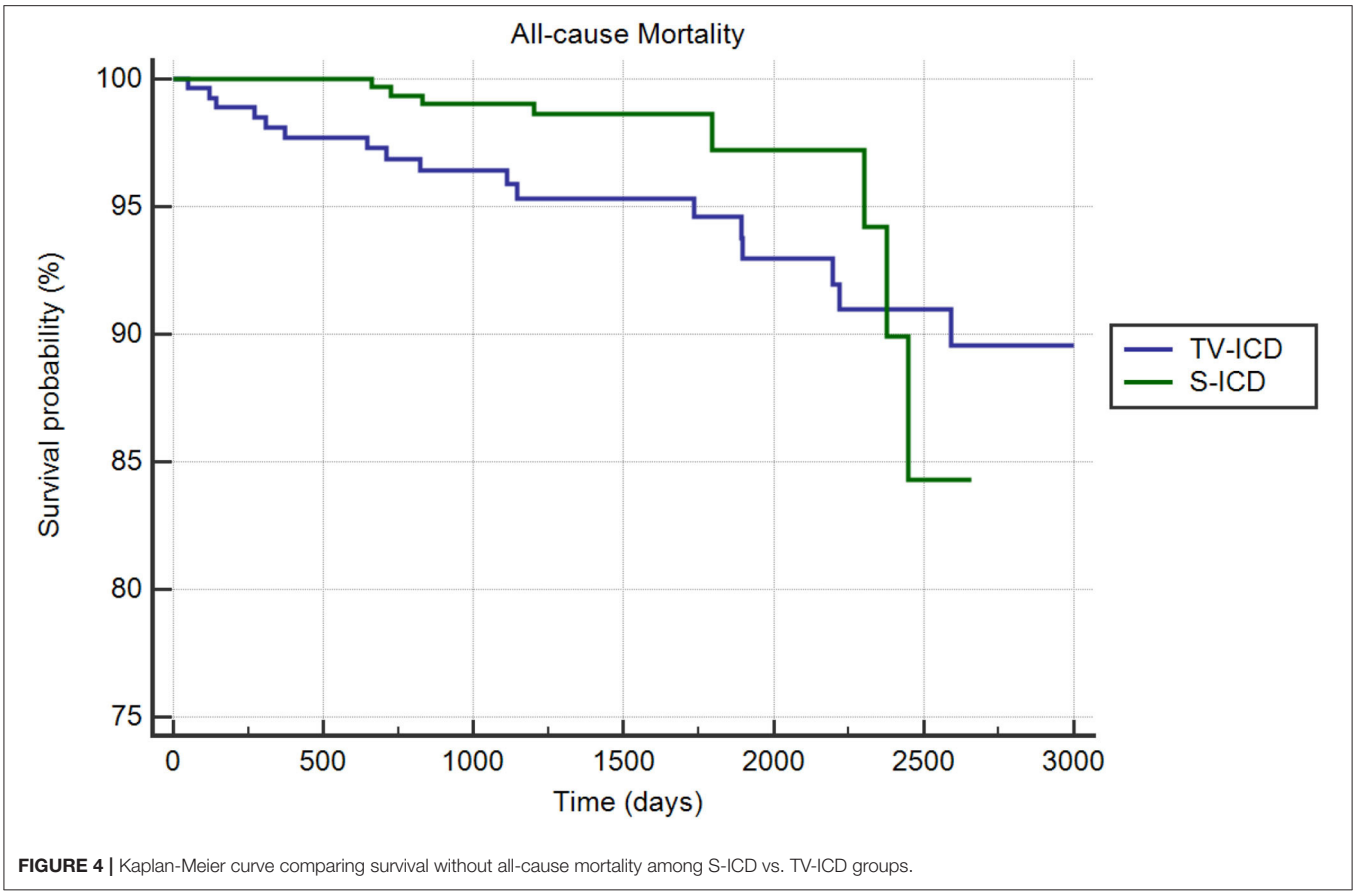

FIGURE 4 | Kaplan-Meier curve comparing survival without all-cause mortality among S-ICD vs. TV-ICD groups.

TABLE 5 | Unadjusted and adjusted odds ratio for S-ICD and the clinical outcomes of interest.

	Unadjusted OR [95% CI], *p*	Adjusted OR [95% CI], *p*
Inappropriate ICD therapies	1.30 [0.43–3.96], 0.64	-
ICD related infections	0.05 [0.007–0.44], 0.006	0.07 [0.009–0.55], 0.01*
ICD related Complications	0.32 [0.12–0.83], 0.01	0.31 [0.12–0.81], 0.01**
Appropriate ICD therapies	0.46 [0.21–0.98], 0.04	0.54 [0.25–1.18], 0.12***
Overall-Mortality	0.89 [0.38–2.09], 0.79	-

**Adjusted for ischemic cardiomyopathy, chronic kidney disease, and previous valve replacement.*
***Adjusted for age and sex.*
****Adjusted for left ventricular ejection fraction, arrhythmogenic right ventricular dysplasia, Ionic channel disorders, diabetes, chronic obstructive pulmonary disease.*

ischemic and non-ischemic cardiomyopathy (18). Finally, no studies have still addressed whether the efficacy of ATP translates into hard outcomes such as mortality benefits, prevention of inappropriate shocks, and risks of pro-arrhythmias (19).

Based on this evidence, the choice to implant an ATP-capable ICD should not exclusively be based on the ischemic or non-ischemic cardiomyopathy, but it should have applied a patient's centered tailoring approach which takes into account the potential mechanisms of ventricular arrhythmias and other patient factors such as susceptibility to systemic infections. Our study population included a large cohort of patients with HCM who were more likely treated with S-ICD; this preferred choice may be justified by the low rate of ATP therapies experienced by patients with HCM, with no difference in the rate of shock therapy compared to those with TV-ICD (20). However, the choice to implant an S-ICD should take into account the clinical features of patients with HCM since older age and symptomatic patients seem to be more likely to benefit from T-ICD pacing for the high incidence of symptomatic bradycardia and conduction disturbances in need of pacing, together with monomorphic ventricular tachycardia, as the predominant rhythm triggering successful ATP therapy (21). Similarly regarding ARVD, TV-ICD should be preferred in older patients with an advanced form of the disease, who more often experienced re-entrant VT that could be interrupted by ATP; in contrast, S-ICD is more indicated among younger patients who more likely experienced VF and are particularly prone to lead-related complications requiring device explantation (22). Recently, the prospective randomized comparison of subcutaneous and transvenous implantable cardioverter-defibrillator therapy (PRAETORIAN) trial (12) showed that, among 849 patients with an indication for ICD therapy but not for pacing therapy, the S-ICD was non-inferior to the T-ICD concerning the cumulative incidence of device-related complications or inappropriate shocks. However, there was a

higher cumulative incidence of device-related complications in the T-ICD group (9.8 vs. 5.9%) and a higher cumulative incidence of inappropriate shocks in the S-ICD group (9.7 vs. 7.3%) at a median duration of follow-up was 49.1 months. Moreover, S-ICD was associated with a lower risk of lead-related complications, which was counter balanced by an increased risk of pocket hematoma.

A recent metanalysis of 13 randomized clinical trials including 9,073 patients (10) showed that the overall risk of clinically relevant complications and inappropriate shocks was not different between patients treated with S-ICD and TV-ICD. On the contrary, the risk of lead-related complications and major procedural complications was higher in the TV-ICD arm. No significant differences were found in the incidence of appropriate shocks and mortality was comparable between the two devices.

Among our study population, the cumulative incidence of inappropriate therapies was lower than previously reported, mainly due to our strategy to optimize the TV-ICD programming at each follow-up visit or based on remote monitoring reporting. In particular, an approach based on the programming of a VF-only zone (23), a cut-off rate greater than 220–240 bpm (24), longer detection intervals (25), activation of lead noise reduction algorithms (26), and enhanced supraventricular tachycardia discriminators (27) was used in our clinical practice. Moreover, the generation of S-ICD systems implanted at our Institution (EMBLEM A209 and EMBLEM-MRI A219) can apply an additional high-pass filter to the sensing methodology, called SmartPass (SP), designed to reduce inappropriate therapies (28). As previously shown in PRETORIAN trial, we did not observe a significant difference in the cumulative incidence of inappropriate therapies between the S-ICD and TV-ICD groups. The main cause of inappropriate therapies was oversensing in S-ICD group and misdetection of supraventricular arrhythmias in the TV-ICD group.

Regarding the complications, we observed a significant reduction of overall ICD-related complications in the S-ICD group, mainly driven by less frequent lead-related complications; in contrast, the device-related complications were higher in the S-ICD group due to some advisory released by Boston Scientifics for generators.[1]

Among our population, we reported a low annual rate of ICD infections, confirming the reduced number of infections in high implantation volume centers (29, 30); as we expected, the TV-ICD group showed higher incidence compared to the S-ICD group. This evidence is of pivotal importance since systemic infections represent an important predictor of death for all causes, regardless of the result of the extraction procedure (31).

Study Limitations

The present is a single-center observational study mainly including ICD recipients, both TV-ICD and S-ICD, not in need of pacing and CRT. As we expected, the baseline clinical characteristics of the two subgroups were different and a regression analysis was performed to identify which variables have impact on the outcomes of interest; however, due to the observational nature of the study, we cannot exclude residual confounding of unmeasured variables. The results of the present study might be influenced by the high experience in ICD implantation and management of our center. The follow-up is relatively short, about 48 months, however, it is the longest among observational studies. No data about pharmacological therapies have been collected at the time of outcomes events.

[1]Available online at: https://www.bostonscientific.com/content/dam/bostonscientific/quality/dlt/reg-code-228/2020Dec_BSC_EmblemPBD_PhysLtr_US_Final.pdf.

CONCLUSIONS

In our clinical practice, the choice to implant S-ICD has been mainly driven by younger age and the presence of ionic channel disease; conversely, ischemic cardiomyopathy reduces the probability to use this technology. There were no significant differences in inappropriate ICD therapies between S-ICD and TV-ICD group; moreover, S-ICD has a lower rate of infectious and non-infectious complications leading to surgical revision or extraction.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Campania - Monaldi Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

VRus designed the study. AR, EA, AP, VT, VB, and SD collected the data. VRug, VRus, and FC performed statistical analysis. VRus wrote the manuscript. AD'O, PG, and GN performed critical revision of article. All authors read and revised the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.879918/full#supplementary-material

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Risk and Protective Factors for Sudden Cardiac Death: An Umbrella Review of Meta-Analyses

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Background: Sudden cardiac death (SCD) is a global public health issue, accounting for 10–20% of deaths in industrialized countries. Identification of modifiable risk factors may reduce SCD incidence.

Methods: This umbrella review systematically evaluates published meta-analyses of observational and randomized controlled trials (RCT) for the association of modifiable risk and protective factors of SCD.

Results: Fifty-five meta-analyses were included in the final analysis, of which 31 analyzed observational studies and 24 analyzed RCTs. Five associations of meta-analyses of observational studies presented convincing evidence, including three risk factors [diabetes mellitus (DM), smoking, and early repolarization pattern (ERP)] and two protective factors [implanted cardiac defibrillator (ICD) and physical activity]. Meta-analyses of RCTs identified five protective factors with a high level of evidence: ICDs, mineralocorticoid receptor antagonist (MRA), beta-blockers, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors in patients with HF. On the contrary, other established, significant protective agents [i.e., amiodarone and statins along with angiotensin-converting enzyme (ACE) inhibitors in heart failure (HF)], did not show credibility. Likewise, risk factors as left ventricular ejection fraction in HF, and left ventricular hypertrophy, non-sustain ventricular tachycardia, history of syncope or aborted SCD in pediatric patients with hypertrophic cardiomyopathy, presented weak or no evidence.

Conclusions: Lifestyle risk factors (physical activity, smoking), comorbidities like DM, and electrocardiographic features like ERP constitute modifiable risk factors of SCD. Alternatively, the use of MRA, beta-blockers, SGLT-2 inhibitors, and ICD in patients with HF are credible protective factors. Further investigation targeted in specific populations will be important for reducing the burden of SCD.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020216363, PROSPERO CRD42020216363.

Keywords: sudden cardiac death, risk factors, protective factors, epidemiology, meta-analysis, umbrella review

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INTRODUCTION

Sudden cardiac death (SCD) constitutes a significant global public health burden, with some estimates of its mortality burden as high as 20% of all deaths in industrialized countries (1–3). SCD refers to any unexpected death within 1 h of the onset of cardiac arrest symptoms.

When the death is not witnessed, the timeline expands to 24 h (4). SCD can be the first presentation of cardiovascular disease, and almost half of all SCD-victims have no previously diagnosed heart condition (1, 5).

In the past 20 years, cardiovascular mortality has decreased significantly in high-income countries (6), especially in groups with higher risk for SCD such as patients with coronary artery disease (CAD) and heart failure (HF) (7). However, recent studies from the U.S. still report a staggering incidence of cardiac arrest with over 350,000 cases out-of-hospital (3) and 290,000 in hospital (8), annually.

Identifying and targeting modifiable risk factors for SCD can improve survival for at-risk patients by preventing the onset of SCD. Yet, risk prediction for SCD is complex. The propensity for sudden death is due to1a combination of intrinsic factors, such as genetic or acquired heart diseases, and transient factors that can trigger an SCD event (7). These factors can be unmodifiable, such as age and gender or modifiable, such as ischemic heart disease (IHD), smoking, low-level physical activity, atrial fibrillation (AF), and type 2 diabetes mellitus (T2DM). Although numerous meta-analyses on risk factors of SCD have been published, there is not yet a complete and succinct summary of the research, that can be applied clinically.

Here we perform an umbrella review to summarize the existing evidence concerning risk and protective factors associated with SCD among published meta-analyses. In accordance with best research practices, we rank the evidence of existing meta-analyses in this topic according to sample size, strength of the association, and existence of diverse biases (9, 10).

METHODS

This umbrella meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (11) reporting guidelines and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (12) (**Appendix 1**). The study protocol was registered in the prospective registry of systematic reviews, PROSPERO (CRD42020216363).

Data Selection, Search Strategy, and Selection Criteria

We performed a systematic search in PubMed, Web of Science, Cochrane review, and Cochrane database of clinical trials through 21st May 2021, to identify systematic reviews with meta-analysis of observational or randomized controlled trials (RCT) examining associations between lifestyle factors, comorbid diseases, medications, echocardiogram (ECHO) abnormalities, electrocardiogram (ECG) abnormalities, and serum biomarkers, with the risk of SCD as a primary or secondary endpoint. Our search strategy was broad to identify all eligible studies using terms related to SCD and meta-analysis (**Appendix 2**). The bibliographies from eligible studies were also reviewed for identification of additional studies.

Two researchers (DK, EC) independently searched articles for eligibility. The full texts of the retrieved articles were further scrutinized for eligibility by the same researchers. Any discrepancies were resolved after consultation with a third researcher (DT).

We included only peer-reviewed systematic reviews which included meta-analyses of RCTs or observational studies with a cohort, case-control, or nested case-control study design, which measured any association between SCD and modifiable risk or protective factors, in any population. In case of the availability of multiple meta-analyses on the same topic, we proceeded with the meta-analysis with the larger number of studies, as previously described (13). All available primary and secondary reported outcomes, for each eligible meta-analysis, were considered for inclusion. Subgroup analyses are presented as reported in the original meta-analyses.

Meta-analyses were excluded if they were: (1) of other study designs than described above (i.e., cross-sectional, letter to the editor); (2) of an individual patient or participant data, pooled analyses that examined a non-systematic selection of observational studies or RCTs, and non-systematic reviews; (3) examining genetic variants as risk factors of SCD; (4) published in other languages than English; (5) provided inadequate data for quantitative synthesis; or (6) presented study-specific effects estimates as mean difference. Reasons for exclusion after full-text assessment were listed in the **Appendix 3**.

Data Extraction and Quality Assessment

From each eligible article, two researchers (DK, DT), independently performed data extraction. Any disagreements were resolved by consensus. For each meta-analysis, the following variables were collected: first author, standard identifier (DOI), journal, study design, year of publication, number of component studies, total sample size, and risk and protective factors assessed. For each primary study, the following variables were collected: first author, year of publication, study design, sample size (exposure and non-exposure), and relative risk estimates [i.e., hazard ratio (HR), odds ratio (OR), risk ratio (RR)] with the corresponding 95% confidence interval (CI). The methodological quality of meta-analyses included was assessed using the AMSTAR2 (Assessment of Multiple Systematic Reviews Tool, available at https://amstar.ca/Amstar-2.php) by two independent researchers (DK, EC) (14).

Data Synthesis and Analysis

For each association, the effect size (ES) of individual studies reported in each meta-analysis was extracted, then the pooled effect sizes and 95% confidence intervals (CIs) were re-calculated, using random-effects models (15). Inter-study heterogeneity was tested with the I^2 statistic (16). Then, small-study effect bias was assessed with the Egger regression asymmetry teste and random-effects summary effect size, to determine whether smaller studies generated larger effect sizes compared with larger

studies (17, 18). Finally, excess significance bias was assessed, to determine whether the observed number of studies with nominally statistically significant results was different from the expected number of studies with statistically significant results (19). The expected number of statistically significant studies per association was computed by summing the statistical power estimates for each component study. The power estimates of each component study depend on the plausible ES for the examined association, which are assumed to be the ES of the largest study (i.e., the smallest standard error) per association. For excess significance bias, a p-value $\leq$ 0.10 was considered statistically significant (19). All analyses were conducted using Stata 17.0 (StataCorp, College Station, TX) and R v.4.0.3 (The R Foundation for Statistical Computing, Auckland, NZ).

Following previous umbrella reviews (20), eligible associations from observational studies were classified into five levels, according to the strength of the evidence of potential risk or protective factors: convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV), and not significant (NS) (eTable 1, **Appendix 3**).

For RCTs, the credibility of evidence was classified according to the summary effect (p-value $<$ 0.01, 0.01 $\leq$ p-value $<$ 0.05, p-value $\geq$ 0.05), 95% prediction interval (excluding the null or not), and presence of large heterogeneity ($I^2 >$ 50%), small study effects ($p <$ 0.10), and excess significance ($p <$ 0.10) (21). An algorithm that assigns GRADE (Grading of Recommendations Assessment, Development, and Evaluation) levels of evidence (GLE) using a modified concrete set of rules was also applied (22, 23). Briefly, four areas were assessed: (1) imprecision, by the number of participants in the pooled analysis (if 100-199 participants, GLE was downgraded by 1 level; if <100 participants, downgraded by 2 levels); (2) risk of bias (RoB) trial quality, by the proportion of RCTs included in the pooled analysis with low RoB for randomization and observer blinding (if > 25% of RCTs had high RoB or RoB not reported, GLE was downgraded by 1 level); (3) inconsistency, by heterogeneity (if $I^2 >$ 75%, downgraded by 1 level); and (4) RoB review quality, by the responses to AMSTAR 2 questionnaire (if moderate quality, downgraded by 1 level; if low or critically low quality, downgraded by 2 levels). Then, reviews were classified as high, moderate, low, or very low, by GLE (eTable 2, **Appendix 3**).

RESULTS

Literature Search

Initially, 2,586 publications were identified. After title and abstract screening, 167 potentially eligible articles were retrieved. Then, 112 articles were excluded after full-text assessment (**Appendix 4** in the **Supplementary Material**). In total, 55 meta-analyses were included in the final analysis, of which 31 evaluated observational studies and reported on 83 associations, and 24 evaluated RCTs and reported on 56 associations (**Figure 1**; eTables 1, 2; eFigure 1 in **Appendix 5**).

Meta-Analyses of Observational Studies

The quality of included meta-analyses of observational studies according to AMSTAR2 was scored as high in 10 meta-analyses, moderate in 11, and low in 10 (**Appendix 5**). The median number of studies included in meta-analyses was 5 (IQR = 3–8), the median number of participants was 23,839 (IQR = 5,426–78,177), and the median number of cases was 514 (IQR = 100–1,417).

In the observational studies meta-analyses, 55 of the 83 examined associations (66%) had a nominally statistically significant effect ($p \leq 0.05$) under the random-effects models and 21 of those (38%) reached a p-value $<10^{-6}$. Thirty associations (36%) had more than 1,000 cases per association. Twenty-one associations (25%) had large heterogeneity ($I^2 >$ 50%), and only 19 associations (23%) had a 95% prediction interval that excluded the null value. In 57 associations (69%), the ES of the largest study had a nominally statistically significant effect ($p \leq 0.05$). Finally, small-study effects were found for 12 associations (15%) and excess significance bias was found for nine associations (11%).

When the classification criteria for credibility of evidence was applied, only five (6.0%) associations presented convincing evidence (**Tables 1**, **3**; eTable 1 in **Appendix 6**, Figure 1 in **Appendix 7**), including three risk factors (early repolarization pattern (ERP) on ECG, T2DM in general population, and smoking) and one protective (physical activity in general population). Only one intervention presented convincing evidence for its association with SCD in meta-analyses of observational studies. This intervention was the implantation of an internal cardiac defibrillator (ICD) in patients with cardiac resynchronization therapy indication (CRT), along with the CRT device. Four additional associations (4.8%) presented highly suggestive evidence for risk factors: AF, T2DM in patients with CAD, T2DM in patients with AF, and hypertension (HTN). Four associations (4.8%) presented suggestive evidence for risk factors: AF in patients with CAD, treatment with macrolides, depression, and overweight (**Tables 1**, **3**). The remaining 42 (51%) statistically significant associations between risk or protective factors and SCD presented weak evidence (eTable 1 in **Appendix 6**), while 28 associations (34%) had no evidence (eTable 1 in **Appendix 6**).

In the prospective analysis, only three risk factors from the main analysis remained at the same class I level. These included T2DM, smoking, and physical activity. However, the five class I factors with convincing evidence in the main analysis remained convincing when associations with >1,000 cases were excluded (**Table 1**; eTable 1 in **Appendix 6**).

Meta-Analyses of Randomized Control Trials

The quality of included meta-analyses according to AMSTAR2 was scored as high in 12 meta-analyses of RCTs, moderate in 4, and low in 8 (**Appendix 5**). The median number of studies included in meta-analyses of RCTs was 5.5 (IQR = 3.5–10), the median number of participants was 9,996 (IQR = 1,695–22,275),

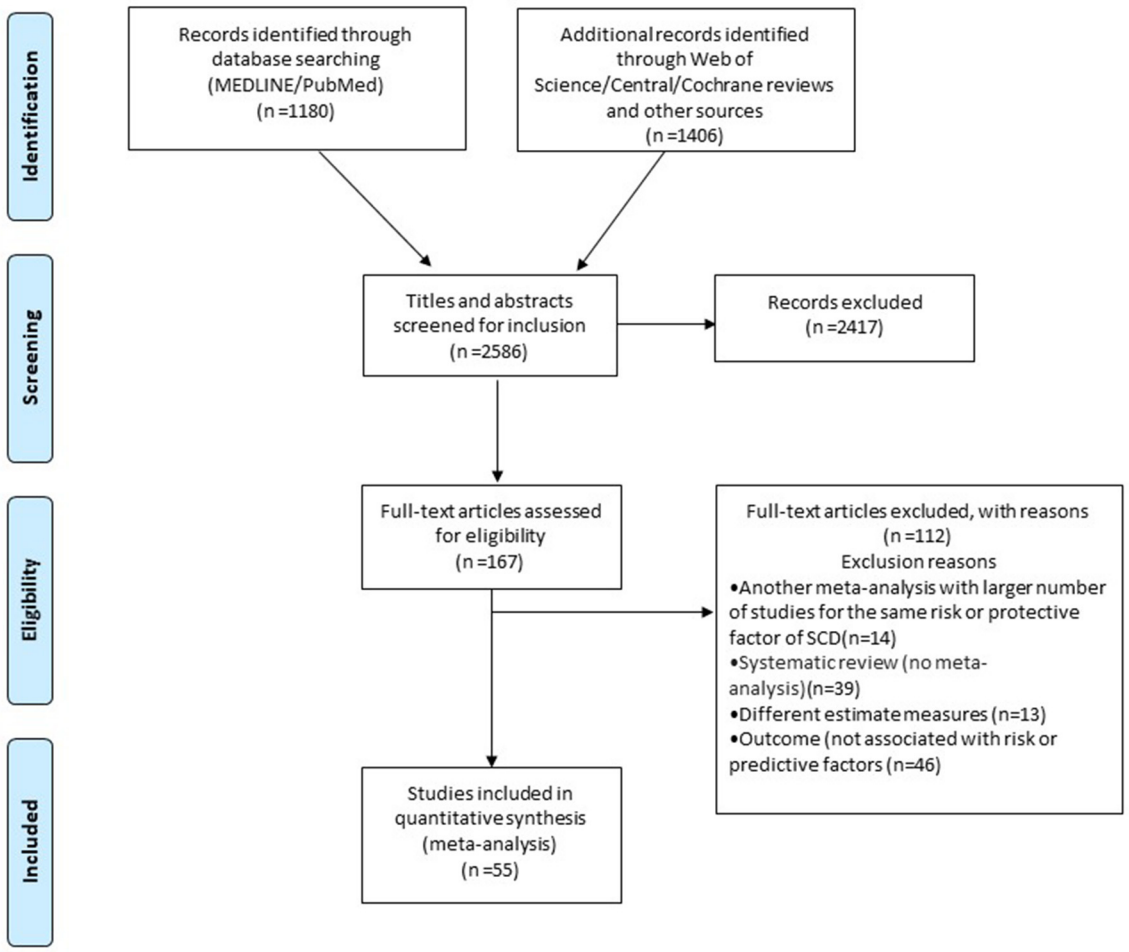

FIGURE 1 | Flowchart of the study selection process (SCD, sudden cardiac death).

and the median number of cases was 378 (IQR = 121–700) (**Table 2**; eTable 2 in **Appendix 6**).

Overall, 31 of the 56 (55%) associations reported a nominally significant summary result at $p < 0.05$ (10 had $p < 0.001$). Only 13 (23.2%) associations had a significant confidence interval, 48 (85.7%) showed no large heterogeneity ($I^2 < 50\%$), six (11%) showed small study effects, and four (7.1%) showed excess significance bias.

When the RCT credibility criteria were applied, five (8.9%) associations between protective factors and SCD presented a high GLE (**Table 2**). These associations included the use of MRA and ICDs in patients with left ventricular systolic dysfunction, the use of b-blockers, MRAs or angiotensin-converting enzyme (ACE) inhibitors in patients with HF, and the use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors in patients with HF or DM. Twelve associations (21%) of protective factors and the risk of SCD presented a moderate GLE such as the use of beta-blockers in patients with HF, the use of ICD in patients with IHD and non-IHD, and the use of cardiac resynchronization therapy defibrillator (CRT-D) in patients with non-IHD (**Tables 2**, **3**; eFigure 1 in **Appendix 7**). The remaining nine statistically significant associations (16%) between protective factors such as amiodarone and omega-3 fatty acids, with SCD presented a low GLE (**Table 2**), while 24 associations (43%) were not statistically significant (eTable 2 in **Appendix 6**).

More specifically, about the use of ICD and CRTs to prevent SCD, meta-analyses of RCTs showed that ICD prevents SCD in patients with HF, IHD, and non-IHD. The evidence of these associations was of high epidemiological credibility. However, CRT-Ds but not CRT-pacemaker (CRT-Ps) showed to protect significantly from SCD in patients with non-IHD.

DISCUSSION

In this study, we reviewed 55 articles concerning the risk and protective factors of SCD. Despite most of the associations being statistically significant, only a minority of them provided convincing evidence. Our meta-analyses of observational studies showed that the presence of ERP on ECG, current smoking, and T2DM were important risk factors, while physical activity was

TABLE 1 | Risk and protective factors of sudden cardiac death, in meta-analyses of observational studies.

Reference	Risk/Protective factor	Exposed/Unexposed as in included MA	Protective/Risk factor or intervention	K	n/N	Metric	ES (95% CI)	*p*-value	PI include null value	I^2	SSE	ESB	LS sign	CE	CES	CES2 (*n* > 1,000)	AMSTAR 2 Quality
General population																	
Cheng (24)	Early repolarization pattern (ERP) on ECG	ERP or not	Risk	19	1,125/ 7,268	OR	4.76 (3.62, 6.26)	6.9×10^{-29}	No	38.4%	No	NP	Yes	I	IV	I	Moderate
Aune (25)	Diabetes mellitus (DM)	DM or not	Risk	14	3,510/ 280,737	RR	2.02 (1.81, 2.25)	4.54×10^{-37}	No	0%	No	NP	Yes	I	I	I	Moderate
Aune (26)	Smoking	Current smoker or not	Risk	4	1,061/ 203,386	RR	2.08 (1.70, 2.53)	4.85×10^{-13}	No	17.5%	No	No	Yes	I	I	I	Moderate
Aune (27)	Physical activity	Physically active or not	Protective	8	1,193/ 136,298	RR	0.52 (0.45, 0.60)	4.77×10^{-18}	No	0%	No	NP	Yes	I	I	I	Critically low
Rattanawong (28)	Atrial fibrillation (AF)	AF or not	Risk	28	3,258/ 75,465	RR	2.04 (1.76, 2.35)	2.83×10^{-22}	No	43%	Yes	Yes	Yes	II	II	II	High
Pan (29)	Hypertension (HTN)	HTN or not	Risk	9	1,211/ 837,795	RR	2.1 (1.71, 2.58)	1.89×10^{-12}	No	56.7%	No	No	Yes	II	II	II	Moderate
Cheng (30)	Macrolides	Used or not	Risk	11	58,810/ 6670,109	RR	2.42 (1.60, 3.63)	2.34×10^{-5}	Yes	85.4%	No	No	Yes	III	NA	III	Moderate
Shi (31)	Depression	Depression or not	Risk	4	2,399/ 83,659	HR	1.98 (1.37, 2.88)	3.1×10^{-4}	Yes	59%	Yes	Yes	Yes	III	IV	III	Critically low
Chen (32)	Body mass index (BMI)	Overweight vs. normal BMI	Risk	9	1,462/ 1188,730	RR	1.21 (1.08, 1.35)	0.001	No	7.7%	No	NP	Yes	III	III	III	Moderate
Heart failure or LV dysfunction population																	
Barra (33)	Implanted Cardiac defibrillator (ICD)	Eligible or not for cardiac resynchronization therapy (CRT)	Intervention	14	1,081/ 5,949	RR	0.33 (0.24, 0.47)	1.59×10^{-10}	No	12.6%	No	NP	Yes	I	IV	I	Critically low
Coronary artery disease population																	
Aune (25)	DM, in patients with coronary artery disease (CAD)	DM or not	Risk	5	2,194/ 45,905	RR	1.64 (1.36, 1.97)	2.15×10^{-7}	Yes	39.0%	Yes	No	Yes	II	II	II	Moderate
Rattanawong (28)	AF, in patients with CAD	AF or not	Risk	4	1,352/ 19,542	RR	1.56 (1.24, 1.96)	1.7×10^{-4}	Yes	34.7%	Yes	No	Yes	III	III	III	High
Hypertrophic cardiomyopathy population																	
Rattanawong (28)	Atrial Fibrillation	Yes vs. No in patients with hypertrophic cardiomyopathy	Risk	4	77/ 1,662	RR	2.05 (1.22, 3.43)	0.006	Yes	25.9%	No	Yes	Yes	IV	III	IV	High quality
Other populations																	
Aune (25)	DM, in patients with AF, CAD, heart failure (HF), or hemodialysis	DM or not	Risk	10	2,713/ 54,735	RR	1.75 (1.51, 2.03)	1.49×10^{-13}	No	38.6%	Yes	Yes	Yes	II	II	II	Moderate

CE, class of evidence; CES, class of evidence sensitivity analysis; CI, confidence interval; ES, effect size; ESB, excess significance bias; HR, hazard ratio; I2, heterogeneity; K, number of studies for each factor; LS, largest study with significant effect; MA, meta-analysis; n, number of cases; N, total number of cohorts per factor; NA, not assessable; NP, not pertinent, because the number of observed studies is less than the expected; NR, not reported; OR, odds ratio; PI, prediction interval; RR, risk ratio; SSE, small study effects.

TABLE 2 | Significant associations of interventions with the risk for sudden cardiac death, in meta-analyses of randomized controlled trials.

Reference	Risk/Protective factor	Exposed/Unexposed as in included MA	K	n/N	Metric	ES (95% CI)	*p*-value	PI include null value	I^2	SSE	ESB	High RoB	GLE	AMSTAR 2 Quality
Heart failure or LV dysfunction population														
Peck et al. (34)	Implantable cardioverter defibrillator (ICD) use, in patients with LV dysfunction	ICD use or not	4	261/4,269	RR	0.40 (0.31, 0.51)	4.21×10^{13}	No	0%	No	No	<25%	High	High
Le (35)	Aldosterone antagonist use, in patients with HF	Use or not	5	456/8,301	RR	0.81 (0.67, 0.98)	0.031	Yes	7.7%	No	NP	<25%	High	High
Bapoje (36)	Mineralocorticoid receptor antagonist (MRA) use, in patients with left ventricular (LV) dysfunction	MRA use or not	6	709/11,654	OR	0.76 (0.65, 0.89)	0.001	No	0%	Yes	No	<25%	High	High
Fernandes (37)	Sodium-glucose cotransporter-2 (SGLT-2) inhibitor use, in patients with diabetes or HF	SGLT-2 use or not	8	187/45,483	OR	0.72 (0.54/0.97)	0.031	Yes	0%	No	NP	<25%	High	High
Kolodziejczak et al. (38)	ICD use, in patients with IHD and non-IHD	ICD use or conventional therapy	7	336/3,959	HR	0.41 (0.31, 0.54)	9.07×10^{11}	No	0%	No	No	>25%	Moderate	High
Gama (39)	ICD use, in patients with HF	ICD use or not	6	1,946/2,197	RR	0.49 (0.40, 0.61)	5.46×10^{11}	No	0%	Yes	NP	>25%	Moderate	High
Peck et al. (34)	ACEi and beta-blocker use, in patients with LV dysfunction	Use or not	10	2,824/36,172	RR	0.89 (0.81, 0.98)	0.014	Yes	31.7%	No	Yes	>25%	Moderate	High
Al-Gobari (40)	Beta-blocker use, in patients with heart failure (HF)	Beta-blocker use or not	26	1,597/24,554	OR	0.69 (0.62, 0.77)	2.79×10^{-2}	No	0%	No	Yes	<25%	Moderate	Moderate
Chatterjee (41)	Beta-blocker use, in patients with HF	Beta-blocker use or comparator	6	787/8,960	OR	0.73 (0.63, 0.85)	3.9×10^{5}	No	0%	No	No	<25%	Moderate	Moderate
Peck et al. (34)	MRA use, in patients with LV dysfunction using ACEi and/or beta-blockers	MRA use or not	3	691/11,032	RR	0.79 (0.68, 0.91)	0.001	Yes	0%	No	No	<25%	Moderate	High
Claro (42)	Amiodarone use, in patients with heart failure	Amiodarone use or not	11	526/4,306	RR	0.79 (0.67, 0.92)	0.004	No	0%	No	NP	>25%	Low	Critically low
Coronary Artery disease population														
Kolodziejczak et al. (38)	ICD use, in patients with ischemic heart disease (IHD)	ICD use or conventional therapy	4	246/2,282	HR	0.39 (0.28, 0.55)	5.95×10^{-8}	No	0%	No	No	>25%	Moderate	High
Fernandes (43)	Trans-endocardial stem cell injection, in patients with chronic IHD	Injection or not	10	7/422	OR	0.19 (0.04, 0.86)	0.031	Yes	0%	Yes	NP	>25%	Moderate	High
Fernandes (43)	Trans-endocardial stem cell injections with other cells, in patients with chronic IHD	Injection or not	4	14/422	OR	0.24 (0.07, 0.89)	0.033	Yes	0%	No	NP	>25%	Moderate	High
Domanski (44)	Angiotensin converting enzyme inhibitor (ACEI) use, in patients with recent MI	ACEi use or not	15	900/15,103	OR	0.80 (0.70, 0.91)	0.001	No	0%	No	No	NR	Low	Critically low
Claro (42)	Amiodarone use, in post myocardial infarction (MI) patients	Amiodarone use or not	6	140/3,377	RR	0.65 (0.46, 0.91)	0.011	Yes	0%	No	NP	>25%	Low	Critically low
Zhao (45)	Omega-3 fatty acid (OFA) use, in high-incidence MI subgroup	OFA use or not	4	305/13,168	RR	0.52	0.027	Yes	33.7%	Yes	No	NR	Low	Critically low

(Continued)

TABLE 2 | Continued

Reference	Risk/Protective factor	Exposed/Unexposed as in included MA	K	n/N	Metric	ES (95% CI)	*p*-value	PI include null value	I^2	SSE	ESB	High RoB	GLE	AMSTAR 2 Quality
Zhao (45)	OFA use, in low-incidence MI subgroup	OFA use or not	4	149/7,829	RR	1.39 (1.01, 1.92)	0.045	Yes	0%	No	NP	NR	Low	Critically low
Khoueiry (46)	OFA use, in patients with recent MI	OFA use or not	5	286/13,126	OR	0.69 (0.55, 0.88)	0.003	Yes	0%	No	NP	NR	Low	Critically low
Non-ischemic cardiomyopathy population														
Peck et al. (34)	ACEi and beta-blocker use, in patients with LV dysfunction without recent MI	Use or not	9	2,461/29,540	RR	0.91 (0.82, 1.00)	0.050	Yes	29.9%	No	No	<25%	High	High
Kolodziejczak et al. (38)	ICD use, in patients with non-ischemic heart disease (non-IHD)	ICD use or conventional therapy	3	90/1,677	HR	0.44 (0.28, 0.69)	3.41×10^{-4}	Yes	0%	No	No	>25%	Moderate	High
Siddiqui, (47)	ICD and cardiac resynchronization therapy with ICD (CRT-D), in patients with non-IHD	CRT-D or medical management	3	90/1,677	OR	0.44 (0.28, 0.70)	0.001	Yes	0%	No	No	>25%	Moderate	High
Hypertensive population														
Hebert (48)	Epithelial sodium channel inhibitors combined with a thiazide diuretic	Use or not	3	100/5,761	OR	0.61 (0.39, 0.95)	0.029	Yes	0%	No	NP	NR	Low	Critically low
High risk population for SCD														
Claro (42)	Amiodarone use, for primary prevention	Amiodarone use or not	17	666/ 8,386	RR	0.76 (0.66, 0.88)	1.98×10^{-4}	No	0%	No	NP	>25%	Low	Critically low
Levantesi (49)	Statin use	Statin use or not	10	688/22,275	OR	0.79 (0.67, 0.94)	0.008	Yes	9.8%	No	No	NR	Low	Critically low
Other categories														
Chen (50)	OFA use, in non-guidelines-adjusted therapy subgroup	OFA use or not	6	308/14,219	RR	0.67 (0.54, 0.84)	0.001	No	0%	Yes	No	<25%	Moderate	Critically low

CE, class of evidence; CI, confidence interval; ES, effect size; ESB, excess significance bias; GLE: GRADE level of evidence; GRADE: GRADE, Grading of Recommendations Assessment, Development and Evaluation; I2, heterogeneity; K, number of studies for each factor; LS, largest study with significant effect; n, number of cases; N, total number of cohort per factor; NA, not assessable; NP, not pertinent, because the number of observed studies is less than the expected; NR, not reported; OR, odds ratio; PI, prediction interval; RoB, risk of bias; RR, risk ratio; SCD: sudden cardiac death; SSE, small study effects.

TABLE 3 | A summary of associations with high epidemiological credibility of risk and protective factors with the risk of postoperative atrial fibrillation.

Population	Level of credibility	Factors associated with sudden cardiac death
General population		
	Meta-analyses including Observational studies	
	Convincing	*Risk factors:* Early repolarization pattern, Diabetes Mellitus, and Smoking *Protective factors:* Physical activity
	High Suggestive	*Risk factors:* Atrial Fibrillation, and hypertension
Heart Failure/Left ventricular dysfunction population	**Meta-analyses including Observational studies**	
	Convincing	*Interventions:* Use of ICD in patients on cardiac resynchronization therapy
	Meta-analyses including RCTs	
	High	*Interventions*: Use of ICD, Sodium-glucose cotransporter-2, and mineralcorticoid receptor antagonists
	Medium	*Interventions*: Use of b-blockers and ACEi
Coronary Artery disease population	**Meta-analyses including Observational studies**	
	Highly Suggestive	*Risk factor:* Diabetes Mellitus
	Meta-analyses including RCTs	
	Medium	*Interventions*: Use of ICD, and trans-endocardial stem cell injection
Non-ischemic Cardiomyopathy population	**Meta-analyses including RCTs**	
	High	*Interventions*: Use of ACEi
	Medium	*Interventions*: Use of ICD, and CRT

ICD, Implanted Cardiac Defibrillator; ACEi, Angiotensin converting enzyme inhibitor.

an important protective factor. In patients with HF, the use of CRT-D compared to CRT-P was the most important protective factor. Sensitivity analyses limited to prospective cohort studies did not alter marginally the main results. Our meta-analyses of RCTs showed that in patients with HF taking MRAs or SGLT-2 inhibitors, and the use of ICDs and CRT-Ds were important protective factors. Furthermore, the association of AF, HTN, and T2DM in patients with cardiovascular comorbidities with the risk of SCD was supported by highly suggestive evidence. Beta-blockers and ICDs were protective factors from SCD with moderate evidence, in certain subpopulations (**Table 3**).

ERP is defined as an elevation of the QRS-ST junction, J-point, and QRS notching in multiple ECG leads, and is high prevalent in middle-aged individuals (51). Although ERP in most cases can be considered benign, it is a marker of increased heterogeneity of ventricular repolarization, which might increase the risk of ventricular fibrillation (24). It is also possible that an ERP pattern can serve as a surrogate ECG marker of certain conditions known to predispose to repolarization heterogeneity, such as myocardial infarction (MI), hypokalemia, and HF. Accordingly, we found that patients with ERP are at increased risk for SCD. However, in one prospective analysis (24), ERP association with SCD was supported only by weak evidence, so future large prospective cohort studies would be of value to clarify the credibility of this association. Other electrocardiographic features, namely, the existence of premature ventricular contractions (PVCs) and microvolt T-wave alternans provided low credibility.

One of the modifiable risk factors of SCD identified in our analysis was smoking. Smoking can lead to increased blood pressure, resting heart rate, and risk of T2DM, AF, and MI, which are all risk factors of SCD (29, 52). The association between smoking and SCD can also be explained by biological mechanisms, as smoking increases the risk of ventricular arrhythmias possibly due to altered ventricular recovery time (53). Furthermore, nicotine has been shown to induce different cardiac arrhythmias in animal models, such as bradycardia, atrioventricular block, and ventricular tachyarrhythmia (54). However, other comparisons between ever, former, or never smokers and a dose-response association between smoking and SCD showed weak evidence, which may be due to the small number of patients ($n < 1{,}000$) in the included primary studies. Smoking as a risk factor is modifiable, and the risk of cardiovascular disease is reduced by 39% as soon as 5 years after cessation (55). Therefore, interventions targeting this risk factor may be able to have a significant impact on SCD incidence.

T2DM increased the risk for SCD by two-fold in our analysis. Several mechanisms have been postulated to explain the association between T2DM and SCD, such as myocardial disease due to atherosclerosis, inflammation-mediated associated with uremia and HTN, potassium imbalances, and arrhythmogenic effects secondary to autonomic neuropathy (56). Interventions to reduce the prevalence of T2DM, such as diet and physical activity modifications, may therefore reduce the risk of SCD indirectly. In fact, physical activity was found in our analysis to be a significant protective factor for SCD. Physical activity is important for controlling metabolic risk factors including obesity, HTN, T2DM (57), CAD (58), and HF (59), all of which are risk factors for SCD.

In patients with HF, the implantation of ICD is the most important protective factor against SCD. We found that more than two-thirds as many patients with a CRT indication are

protected from SCD when they receive ICD compared to only CRT-P, with convincing evidence level. This observation is supported by other meta-analyses of RCTs, which found that ICD reduces the risk of SCD by more than half compared to standard medical treatment, in patients with reduced ejection fraction (EF). These results are consistent both in IHD patients and non-IHD patients (34, 38), with a high GLE and without significant heterogeneity.

More than ten medications have been studied for the risk of SCD, in different patient populations. Androgen deprivation therapy, macrolides, antipsychotics, and Parkinson's drugs, were evaluated in observational studies as risk factors for SCD. All were significant risk factors for SCD but, none showed high epidemiological credibility. However, in the performed sensitivity analysis, when the criterium of more than 1,000 cases per association was omitted, the association of antipsychotics with SCD was upgraded to highly convincing for risperidone and convincing for the antipsychotics' haloperidol, quetiapine, and thioridazine, a finding in line with the literature (60). The risk of SCD is high in psychiatric patients, owing to a large extent to psychotropic drugs. Different mechanisms have been introduced to explain this association (such as the increased torsadogenic effect of a psychotropic drug and the synergic effect of different proarrhythmic drugs) in the coexistence/or not of pre-existing congenital cardiopathies (such as long-QT and Brugada syndrome) (60). Predicting the safety of potential proarrhythmic medicines is a top priority (61). Thus, measures such as the use of pharmacogenetics (i.e., how genes affect the way a person responds to medications) might have relevant clinical implications, particularly for idiosyncratic adverse drug reactions, such as in the case of the use of antipsychotics and other drugs and the risk of SCD (62).

More than six medicines, including amiodarone, beta-blockers, statins, ACE-inhibitors, MRA, SGLT-2, omega-3 fatty acids, and other antihypertensive drugs were tested in meta-analyses including only RCTs. All were found to be statistically protective against SCD, but only SGLT-2 and MRA associations were supported by a high GLE. It is also important to note that these medicines are used for the treatment of heart failure (63) and arrhythmias (7) in a population already at high risk and the generalizability of these findings can be limited.

Concerning imaging-related risk factors for SCD, the presence of LGE in MRI examination was associated with SCD but was supported by weak evidence (64). The lack of strong evidence can be attributed to the small number of patients included in the original studies. When this criterium was omitted from our grading, the level of evidence was raised to convincing in patients with non-IHD. Thus, larger prospective cohort studies can be of value. Similarly, the association of the reduced LVEF with SCD was statistically significant but only supported by weak evidence in the primary analysis and highly supportive only when the criterium of $n > 1{,}000$ patients was omitted. This finding is surprising as low LVEF is the criterion used most commonly during the last decades to find patients eligible for ICD therapy for primary prevention of SCD. The small number of primary studies and the issue of low reproducibility of the measurement of LVEF in clinical settings can possibly explain this finding (7).

In pediatric patients with HCM traditional risk factors, such as extreme LV hypertrophy and non-sustain VT, didn't show significant associations, while others as previous history of syncope or adverse cardiac event (aborted SCD or sustain ventricular tachycardia), were significant, albeit with weak evidence. This finding could be explained by the observational study design, the small sample size, and the critically low quality of the included studies, a fact which was also annotated in the latest published guidelines (65). Hence, larger cohort studies are of great importance for optimizing risk stratification for HCM in children.

Other interesting factors associated with the risk of SCD but not included in previous meta-analyses that fulfill the inclusion criteria of our umbrella review involve risk factors such as gender in young, episodes of supraventricular tachycardias, and COVID-19 infection. Data from observational studies show that the incidence of SCD in young men is lower compared to young women, indicating that SCD due to potentially inherited cardiac diseases is less often in young women (66). Even if this factor is not modifiable, it can lead to further research about young women's protection mechanisms against SCD. SVTs have been reported to be the etiology of sudden cardiac arrest in 5% of all patients with aborted sudden death, including 7 of 13 patients without preexcitation on their baseline ECG (67). There is a subgroup of patients with SVTs with a rapid ventricular rate in which cardiac arrest may be a manifestation even in pediatric patients. Thus, electrophysiology testing must be considered, especially in the pediatric population (68). There is evidence of an increased incidence of ventricular arrhythmias and SCD in COVID-19 patients (69), while a recent meta-analysis found a higher prevalence of SCD during the COVID-19 pandemic compared to the pre-pandemic period (70). Several mechanisms have been proposed to explain the possible association of SARS-CoV-2 infection with increased SCD risk and arrhythmogenesis, including direct myocardial injury, oxygen demand-supply mismatch due to hypoxia, hypercoagulability, and adverse effects of medications for COVID-19 (71). However, reliable data assessing SARS-CoV-2 infection as a potential risk factor for SCD is still missing.

In the current guidelines (7), there is an emphasis on establishing screening and prevention programs for SCD. However, no clear recommendations for population screening have been provided due to a paucity of evidence (7). To the best of our knowledge, this is the first umbrella review providing evidence concerning the associations of modifiable risk and protective factors with the risk of SCD. Our results indicate that people who smoke tobacco and have a sedentary lifestyle, who are diagnosed with DM, AF, or HTN, as well as those who have ERP on their ECG, are at increased risk for SCD. Therefore, these factors should be considered in the design of future studies on SCD prevention. Another implication from the present study is that it identifies several protective factors such as MRA or SGLT-2 inhibitors, and the use of ICD in patients with HF. The use of them should be emphasized whenever possible in patients at high risk of SCD.

There were several modifiable risk factors with only a weak level of evidence (e.g., pre-diabetes, BMI, PVCs, etc.), in the

general population and subpopulations tested. This is likely due to the limited number of available cohorts and the small number of participants available for the subpopulation analysis. Larger cohorts may be helpful for further elucidating the role of these modifiable risk factors, by providing more evidence about these associations.

Our umbrella review provides a broad picture of the non-genetic factors that have been studied for SCD. However, this study has also several limitations. First, in meta-analyses that included observational data, the associations which were supported by high epidemiological credibility can be considered strong evidence, but they cannot imply causality. On the contrary, meta-analyses which include RCTs provide data mostly in patients already at high risk, and therefore is less generalizable to the general population. Thus, our study yields risk factors with proven significant associations to SCD but does not allow conclusions as to their clinical value in primary prevention. Second, grading of meta-analyses which include observational data can provide only warnings concerning the presence of systematic biases and not proof about the nature of these biases (72, 73). Thus, only a description of the results and sources of bias has been made. Third, although a large number of risk and protective factors for SCD were included in this analysis, there may be other important factors not included, as they have not been evaluated in previously published meta-analyses, like the New York Heart Association score. In addition, potential associations of genetic factors with SCD were not assessed, as genetic causality is tested with other analytic approaches -i.e., Mendelian randomization studies- rather than pairwise meta-analysis, which was defined as the unit of analysis in the present review.

CONCLUSIONS

In this umbrella review, we mapped the epidemiological evidence on non-genetic factors associated with SCD as identified in previously published meta-analyses. Even though SCD is a prevalent medical issue, we were only able to identify a small number of risk factors associated with SCD and even fewer with high epidemiological credibility. The association between SCD and the following risk factors were supported by convincing and highly supported evidence: lifestyle risk factors, like the lack of physical activity and smoking; comorbidities, like AF and DM; the use of medications, like MRA or SGLT-2 inhibitors; ECG features, like ERP; and the use of ICD. Further investigation with targeted interventions in these populations is the first step toward a better strategy for SCD prevention.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

EC, DT, and ED designed the study. DK and EC performed a comprehensive screening of the literature, selected the studies included in the meta-analysis, and abstracted the data items. DT and ED performed the statistical analysis. DT and EC drafted the manuscript. EC, DT, DK, LOK, AS, DV, EF, AA, CT, CA, and FB interpreted the results and edited the manuscript critically. All the co-authors have read and accepted this version of the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.848021/full#supplementary-material

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The effect of ionizing radiation through cardiac stereotactic body radiation therapy on myocardial tissue for refractory ventricular arrhythmias: A review

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Cardiac stereotactic body radiation therapy (cSBRT) is a non-invasive treatment modality that has been recently reported as an effective treatment for ventricular arrhythmias refractory to medical therapy and catheter ablation. The approach leverages tools developed and refined in radiation oncology, where experience has been accumulated in the treatment of a wide variety of malignant conditions. However, important differences exist between rapidly dividing malignant tumor cells and fully differentiated myocytes in pathologically remodeled ventricular myocardium, which represent the respective radiation targets. Despite its initial success, little is known about the radiobiology of the anti-arrhythmic effect cSBRT. Pre-clinical data indicates a late fibrotic effect of that appears between 3 and 4 months following cSBRT, which may result in conduction slowing and block. However, there is clear clinical evidence of an anti-arrhythmic effect of cSBRT that precedes the appearance of radiation induced fibrosis for which the mechanism is unclear. In addition, the data to date suggests that even the late anti-arrhythmic effect of cSBRT is not fully attributable to radiation.-induced fibrosis. Pre-clinical data has identified upregulation of proteins expected to result in both increased cell-to-cell coupling and excitability in the early post cSBRT period and demonstrated an associated increase in myocardial conduction velocity. These observations indicate a complex response to radiotherapy and highlight the lack of clarity regarding the different stages of the anti-arrhythmic mechanism of cSBRT. It may be speculated that in the future cSBRT therapy could be planned to deliver both early and late radiation effects titrated to optimize the combined anti-arrhythmic efficacy of the treatment. In addition to these outstanding mechanistic questions, the optimal patient selection, radiation modality, radiation dose and treatment planning strategy are currently being investigated. In this review, we consider the structural and functional effect of radiation on myocardium and the possible anti-arrhythmic mechanisms of

cSBRT. Review of the published data highlights the exciting prospects for the development of knowledge and understanding in this area in which so many outstanding questions exist.

KEYWORDS

cardiac stereotactic body radiation therapy, ventricular tachycardia, cellular response, cardiomyopathy, ablation electrophysiology

Introduction

The use of single fraction, high dose ionizing radiation therapy (RT) in the form cardiac-stereotactic body radiation therapy (cSBRT) has recently been described as a treatment for patients with refractory ventricular arrhythmias (VA). The clinical experience has been reviewed previously (1) and encouraging results have been reported following the use of cSBRT to treat patients in whom control of VA could not be achieved with conventional therapies. While the clinical response has been encouraging, a precise understanding of the anti-arrhythmic mechanism of cSBRT remains incomplete. A number of observations have been consistently reported that indicate a complex response of myocardium to cSBRT and identify areas in which further work will be required to reach a comprehensive understanding of the mode of action of cSBRT.

Conventional radio-frequency (RF) cardiac ablation comprises thermal injury to myocytes resulting in acute coagulative necrosis and associated with acute cell death and consequent myocardial conduction block (2). Other catheter based ablation energies are also associated with acute cell death and secondary conduction block (3, 4). RT, on the other hand, is not expected to be, and has not typically been demonstrated to be, associated with acute formation of conduction block. Despite this, delivery of cSBRT has been successfully used to achieve acute (within 1 day), as well as chronic, suppression of incessant ventricular arrhythmias (5). This raises the question as to how cSBRT results in early arrhythmia suppression and indicates that in contrast to catheter-based ablation technology, other anti-arrhythmic mechanisms may be important. Following cSBRT at doses that have been delivered clinically, development of fibrosis in the timeframe of months following cSBRT has been reported, at which point ongoing suppression of ventricular arrhythmias with cSBRT has also been reported. This suggests that different mechanisms may be responsible for the acute and chronic phases of the myocardial response to cSBRT. In order to understand how cSBRT may exert its anti-arrhythmic effect, an understanding of the tissue response to RT is paramount. In this review, recent experimental and clinical data relating to the effect of RT on myocardium at different time points following RT exposure is reviewed, and the experimental data regarding the functional response of various myocardial structures is considered. Review of this data raises more questions than it provides answers, reflecting the current status of knowledge in this field. This identifies compelling opportunities for future research to develop our understanding of the mechanisms underlying this promising non-invasive treatment strategy in the field of arrhythmia management.

Cellular response to ionizing radiation

Radiation induced cellular changes have been studied widely in the field of oncology. The cellular response to radiation has typically been considered with regard to differentiating cells, and interruption of the cell cycle is an important mechanism through which RT affects malignant cells. This represents an important distinction from the situation when RT is used to treat arrhythmias, in which case it is understood that fully differentiated cells, either anatomically selected on the basis of established ablation strategies (for example atrio-ventricular node (AVN), cavo-tricuspid isthmus (CTI) or pulmonary vein (PV) ostia) or abnormal myocardial substrate in the context of ventricular arrhythmias, are targeted. Despite this key difference, there is a wealth of literature relating to the effect of radiation on cells, much of which remains relevant when considering how RT may affect myocardial tissue. The molecular mechanisms underlying radiation induced cellular death have been recently reviewed (6). A number of responses to RT are recognized, including mitotic catastrophe and cell death, apoptosis, necrosis, cellular senescence and autophagy. Broadly, cell death may be considered as regulated (including apoptosis and other less common forms of regulated cell death) or unregulated (necrosis). Cellular senescence describes a condition of permanent cell cycle arrest, and has been associated with a characteristic senescence associated secretory phenotype (SASP) (7). The role of cellular senescence in already cell-cycle arrested cardiomyocytes is incompletely defined, but senescence and the SASP represent relatively recently appreciated contributors to the development of chronic cardiac conditions, in particular those associated with increasing age, and senescence may comprise part of the myocardial response to RT. Mitotic death may be less relevant to the myocardial response to RT than other forms of cell. Apoptosis is a

highly regulated process and is associated with characteristic morphologic and molecular features. Specifically, cellular markers may identify activation of apoptotic cellular death pathways. Caspase-3 represents a common marker of multiple pathways of activation of apoptotic cell death (6). In contrast to apoptosis, necrosis represents an unregulated form of cell death that may occur in response to RT induced cellular and micro-environment changes. Necrotic tissue has characteristic morphological features including increased cellular volume, membrane rupture and release of intracellular contents (6). In addition to effecting direct cellular damage, RT may induce secondary cell death. Experimental data from the cancer literature indicates that doses of greater than 10Gy induce severe vascular damage within tumors resulting in hypoperfusion and likely secondary cell death through ischemia, effects which have been observed as early as 24 hours following irradiation (8). It is recognized that neovascularization within tumors renders the blood supply more radiosensitive than surrounding normal tissue (9). RT induced vasculitis represents a potential mechanism through which cSBRT may mediate an ablative effect in myocardium. Secondary effects of RT exposure may also include augmentation of an immune response, which has been suggested in tumor biology. Whether or not a secondary immune response to cSBRT is relevant remains uncertain. It is plausible that there would exist differences in the radiosensitivity of pathological myocardial substrate when compared to adjacent healthy tissue, although evidence to demonstrate this has not been established. Data from experimental and clinical studies following cSBRT have identified features indicating a role for necrosis, apoptosis and vascular injury in the myocardial response to cSBRT and are discussed below.

Ionizing radiation induced cardiovascular disease

Data from patients undergoing thoracic irradiation for malignancy established the potential for RT to cause cardiovascular damage (10). RT may cause early toxicity such as pericardial inflammation or delayed toxicity affecting the pericardium, valves, conduction system or myocardium (11). The mechanisms underlying RT induced cardiovascular disease (CVD) are relevant when considering the mechanism through which cSBRT may mediate an ablative or anti-arrhythmic effect. Mechanisms through which RT may induce CVD include endothelial damage, through direct DNA damage and oxidative stress, which may result in a greater risk of atherosclerotic plaque rupture. Microvascular obstruction may also occur, which contributes to the development of capillary loss, ischemia, myocardial cell death and subsequent myocardial fibrosis. In addition to promoting vascular effects with a secondary impact on myocardium, direct effects on the myocardium are recognized. Oxidative stress on the cell membrane following RT exposure is a key mechanism underlying the development of myocardial inflammation and subsequent progression to fibrosis, which most commonly manifests as restrictive cardiomyopathy, likely reflecting progressive myocardial fibrosis (12). The generation of reactive oxygen species (ROS) following RT affects mitochondrial function, which represent the primary cellular site of oxidative metabolism (10). RT induced mitochondrial dysfunction promote cellular aging and apoptosis (13). RT induced mitochondrial dysfunction may promote the development of myocardial cellular senescence, and the associated senescence-associated secretory phenotype (SASP) (7). The impact of RT in promoting the SASP in the heart remains incompletely characterized, is likely to be complex and specific to different cell types within the myocardium, but is likely to be relevant to the myocardial response to RT. The QUANTEC project has sought to evaluate the current state of knowledge of the biologic effect of radiation doses on normal tissue (14) and provided data specifically relevant to cardiac toxicity (14). Although the data from the oncologic experience reflects heterogeneous radiation doses and dosing regimes, which in general have been delivered with the aim of minimizing the myocardial dose, the mechanism for myocardial toxicity has been consistently identified as the late development of myocardial fibrosis. This appears to be mediated through vascular as well as direct myocardial effects following an initial inflammatory response to RT.

Effect of cardiac stereotactic body radiation therapy on myocardial tissue

As the therapeutic potential for cSBRT in the treatment of arrhythmias has become apparent, there has been greater interest in the mechanisms by which high-dose radiation affects myocardium. While data collected from the collateral irradiation of myocardium in cancer patients provides an invaluable foundation for the study of the myocardial response to RT, this data has been collected from studies in which the cardiac dose has been deliberately minimized. More recently, pre-clinical studies and a smaller number of clinical reports have attempted to assess the acute and chronic effect of high-dose single fraction cSBRT on different heart structures. These data are also confounded by the use of different radiation sources and modes of delivery, however the reports are considered according to the time course at which tissue and electrophysiologic function was assessed following irradiation. Radiation sources are generally described as γ-radiation, β-radiation, proton beam and heavy (Carbon) ion beam. It is appreciated that the different forms of radiation have different properties and different energies meaning that their effects on tissue are not comparable but the

purpose is to review patterns of damage to cardiac tissue and learn from this.

Acute effect of cSBRT on myocardium

A small number of studies have considered the ability of RT to induce acute effects on myocardium, which may be considered as effects seen within hours of irradiation. Lehmann et al. applied heavy ion radiation to the atrio-ventricular node of Langendorff-perfused porcine hearts (15). No acute AV conduction disturbance followed 70Gy irradiation, AV prolongation (in a heart demonstrating pre-existing Mobitz II second degree AV block) followed 90Gy irradiation, and complete AV block followed 160Gy irradiation (more than seven times the most commonly reported cSBRT dose). In this study no macroscopically visible damage was seen following irradiation and histological analysis did not reveal evidence of apoptosis or necrosis, in addition there was no evidence of increased expression of protein markers of apoptosis in the irradiated area. Hypereosinophilia was noted in the in the field irradiated with 160 Gy. Phosphorylated histone 2AX (a marker of double stranded DNA damage) was strongly positive in the irradiated region. Pérez-Castellano et al. delivered β-radiation (high-energy electrons) at a dose of 60Gy through a balloon catheter within the pulmonary vein (PV) trunk of *in-vivo* porcine hearts (16). Acute histological assessment of the acutely irradiated PV sleeve demonstrated endothelial damage, disruption of the elastic intima and myocardial sleeve necrosis. PV isolation was not achieved in this experiment. An example of the acute effects of β-radiation in this experiment is shown in Figure 1 (16).

These data indicate that acute conduction block within the specialized conduction system may be achieved with extremely high doses of heavy ion radiation, and that this was achieved without evidence of tissue necrosis or apoptosis. *In-vivo*, high dose β-radiation was associated with acute endothelial damage and myocardial necrosis, without resulting in acute conduction disturbance across the irradiated atrio-venous junction. These data do indicate an important difference between the response of tissue to RT compared to that of RF energy, following which electrophysiologic effects on both myocardial tissue and specialized conduction system tissue are seen acutely.

Chronic effect of cSBRT on myocardium

Sharma et al. considered the impact of γ-irradiation on porcine atrial structures (17). Tissue was examined at various times (25 to 196 days) after exposure to 32–80Gy doses and demonstrated transmural loss of myocyte architecture and increased fibrin, inflammatory changes (monocyte infiltration) and discrete areas of transmural fibrosis.

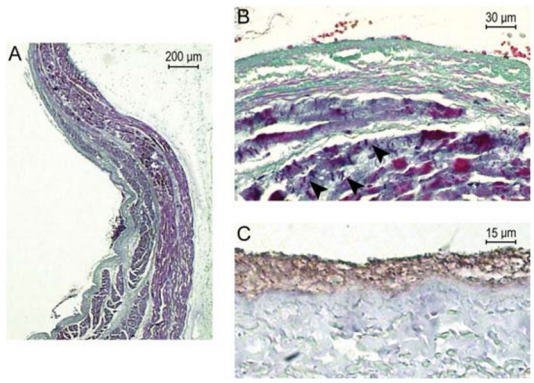

FIGURE 1
Reproduced with permission from Pérez-Castellano et al. (16). Acute pathological effects of PV β-radiation. This pig was euthanized just after radiation. **(A)** Longitudinal section of the right PV at the level of the radiated area (Masson's trichrome stain). At the luminal side of the vein (left), a laminar fibrin thrombus is adhered to the intima along a large area of endothelial denudation. A thick PV sleeve (purple) can be appreciated under the PV adventitia, which gets thinner as it enters the vein. There is some collagenous connective tissue among PV sleeve fascicles. **(B)** Previous preparation at higher magnification where PV sleeve myocardiocytes can be observed displaying marked fuchsinophilia and contraction bands (arrowheads), which are signs of impending necrosis. The absence of nuclei at the intima suggests endothelial denudation. At the lumen, there are several red blood cells included in fibrin. **(C)** CD-31 stain to best appreciate the absence of endothelial cells between the fibrin thrombus (brown) and the vein wall (gray).

Amino et al. studied the effect of heavy ion irradiation on recently infarcted leporine ventricular myocardium (18). Myocardium was irradiated two weeks following experimental MI and tissue assessment was undertaken two weeks post tissue irradiation. Compared to control animals, there was no increase in the amount of fibrosis identified. Immunohistochemistry demonstrated a 76% increase in expression of the gap junction protein Connexin-43 (Cx43) which was observed in the peri-infarct zone and remote healthy tissue, as well as changes in the distribution pattern, such that lateralization of Cx43 was observed. The group subsequently demonstrated that the increased expression of Cx43 was the result of myocardial (as opposed to fibroblast) expression and that the increased expression was likely to reflect functional gap junctions (19).

At 3 months following 25–55Gy γ-irradiation of the porcine AV node, macroscopically visible fibrosis was evident and corresponding dense fibrosis evident microscopically, with lesion volume demonstrating a strong radiation dose-response relationship (20). Following 35–40Gy γ-irradiation of the porcine AV node associated with complete AV block, loss of cellular architecture, necrosis and extensive fibrin deposition as well as fibrosis within the AV node was demonstrated (21). At 3 months following proton beam irradiation of the porcine

AV node at doses of 40 – 55Gy, Suzuki et al. demonstrated heterogeneous lesions comprising mixed fibrotic changes and necrotic tissue at the targeted region, in a study in which varying degress of AV block were induced (22).

Following 60Gy β-radiation delivery 2–3 months prior in a porcine atrial model, mild neointimal hyperplasia was seen, the elastic intima was thickened and fibrosis of the PV sleeve was seen (16). There was evidence of necrosis and vacuolization in remaining myocardial tissue and inflammatory changes (mononuclear leukocyte infiltration). In addition, some calcification was noted.

In 25–50Gy β-radiation delivered *via* an intra-cardiac catheter created bidirectional CTI conduction block in a canine model (23). At 3 months, the tissue demonstrated endothelial thickening but no disruption. Transmural loss of myocyte architecture was seen, along with markers of cell death (myolysis and vacuolization) and well demarcated, transmural fibrosis.

Blanck et al. undertook a dose-finding study to assess the effect of 17.5–35Gy doses at 6 months following γ-irradiation of porcine right superior PV antrum (24). Following 17.5Gy, fatty tissue necrosis was seen, without significant fibrosis. Fatty tissue necrosis was also seen following doses of 20Gy and above, and in addition fibrosis was present, which demonstrated a dose-dependent intensity and reached transmurality following 35Gy. Subsequent work from the same group undertook a dose finding and feasibility study, this time using doses 22.5–40Gy applied to the porcine left atrial-PV junction. In this study, fatty tissue necrosis was seen following doses of 22.5Gy and higher, and fibrosis was seen following doses above 30Gy. Complete circumferential fibrosis was seen following a 40Gy dose. Of note, in this study 37.5Gy was associated with a fatal broncho-mediastinal fistula and 40Gy was associated with complete AV block secondary to AV node fibrosis (demonstrated histologically) (25). Zei et al. have also demonstrated the induction of circumferential transmural fibrosis at the right superior PV antrum when examined at 6 months following 25 and 35Gy γ-irradiation. In these specimens, there was evidence of persistent myocyte necrosis with other markers of cell damage (vacuolar degeneration with pyknotic nuclei), which was more marked in the subject receiving 35Gy compared to the one receiving 25Gy (26). Mild persistent chronic inflammation and minimal hemorrhage within the lesions was noted. In addition, this study specifically identified severe vasculitis with medial destruction, fibrinoid necrosis and luminal thrombi within the intramyocardial vessels.

Suzuki et al. considered the time course of the development of proton beam induced radiation changes in healthy porcine ventricular myocardium (22). At 12 weeks after irradiation, homogeneous necrotic tissue was seen in the lesion core and necrotic tissue and hemorrhage in the lesion border. At subsequent time points assessed (16-, 24-, and 40-weeks post irradiation), the fibrotic changes became predominant. In addition, immunohistochemical analysis demonstrated the time course of markers of apoptosis following irradiation. Caspase-3 was identified at 12 and 16 weeks but was no longer seen at 24 weeks.

Following heavy ion beam irradiation with 40Gy radiation, previously healthy porcine ventricular tissue was examined at 3 and 6 months. Targeted myocardium demonstrated hemorrhage, inflammation and early fibrosis at 3 months. In addition, caspase-3, a marker of cellular apoptosis, was present at 3 months. At 6 months, there was less marked hemorrhage and inflammation with marked fibrosis and myocyte disarray, and markers for caspase-3 were negative by this point (27). Examples of ventricular myocardial histological response to irradiation is show in Figure 2 [reproduced from Lehman et al. (27)].

Chang et al. assessed canine left atrial tissue at 6-weeks and 4-months following 33Gy γ-radiation delivered to a target area encompassing the pulmonary veins and posterior left atrial wall (28). Tissue was examined under light microscopy following Hematoxylin and eosin and Masson's trichrome staining. Immunohistochemical analysis for Cx43 was also undertaken. No gross lesions were appreciated at 6-weeks, however vacuolization, diffuse hemorrhage and inflammatory cell infiltration were appreciated. In addition, dilated capillaries were observed. At 4-months, atrial tissue demonstrated massive hemorrhage and extensive interstitial fibrosis. Of note, in this study a border-zone around the margin of the targeted area was appreciated which demonstrated a mixture of viable myocytes and fibrosis amongst significant hemorrhage. In this study, at 4-months Cx43 expression was downregulated at 4-months following 33 Gy γ-radiation.

Dose dependent upregulation of Cx43 was demonstrated up to a year following heavy ion irradiation using doses between 10–15Gy in healthy leporine ventricular myocardium (but not at 5Gy doses), without evidence of myocardial fibrosis (19).

Clinical data

Data from clinical specimens has been reported from a small number of cases at various time points following RT exposure. In all cases, the substrate has been targeted with 25Gy γ-radiation. In the first series of clinical cSBRT, one patient died from a stroke 3 weeks post cSBRT and histological analysis of this patient's heart was presented (29). This patient had an ischemic cardiomyopathy and note was made of prominent ectatic blood vessels at the interface of dense scar and normal tissue, without evidence of an acute vasculitis or edema. No inflammation, hemorrhage or necrosis was observed. The timing of the sample relative the cSBRT raise the possibility that the scar observed in this case was exclusively the result of the underlying cardiomyopathy. It is not clear if the observed vascular changes were related to the cardiomyopathy or represented a reaction to the RT. Krug et al. reported the histological findings from a patient

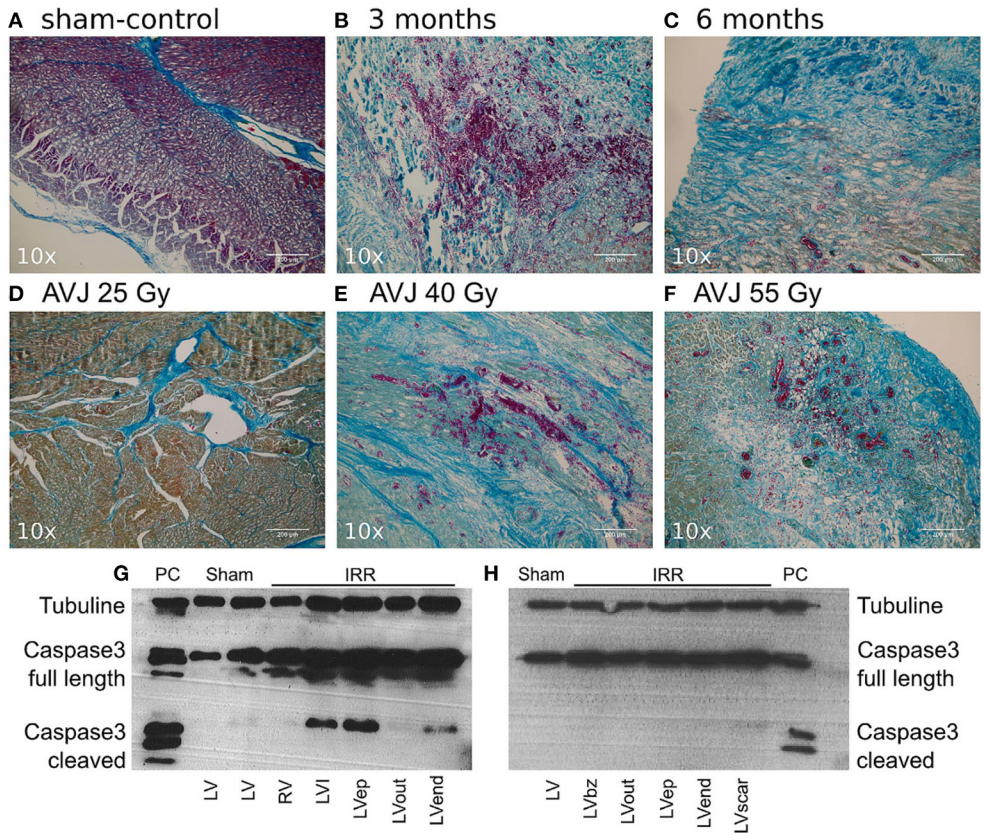

FIGURE 2
(Reproduced from Lehmann et al. (27) under Creative Commons CC YB License) Mallory Trichrome Staining of Ablation Lesions, and Apoptosis Outcomes. **(A)** Sham-control **(B)** Target tissue 3 month after 40 Gy carbon ion irradiation with marked hemorrhage, inflammation, and early stage fibrosis, **(C)** Target tissue 6 months after carbon ion irradiation, showing later stage fibrosis. **(D–F)** Comparison of myocardial lesion outcomes for 25, 40, and 55 Gy of carbon ions 6 months after irradiation for the atrioventricular junction ablation group. **(G)** Western blot for cleaved caspase-3 a marker for apoptosis; signals for cleaved caspase-3 were positive in myocardium 3 months after irradiation, whereas no signals were observed 6 months after irradiation **(H)**. Bz, borderzone; ep, Epicardium; IRR, Irradiated tissue; LV, Left ventricle; PC, positive control; HaCaT (Lysats of HaCaT cells 5 days after irradiation with 10 Gy of X-ray), I, infield; Out, Outfield; RV, Right ventricle.

with dilated mixed ischemic and non-ischemic cardiomyopathy who died 57 days post cSBRT (30). This patient underwent cSBRT for electrical storm. Within days of cSBRT, ventricular arrhythmias reduced to the point of allowing tapering of AADs, although these were subsequently re-introduced. The patient subsequently died from cardiac circulatory failure in the context of pulmonary embolus and infection. Histological analysis of the patient's heart demonstrated extensive areas of myocardial fibrosis, without clear differences between the treated and untreated regions. This report is notable for demonstration of a clear anti-arrhythmic effect of cSBRT without evidence of fibrosis formation at around 2 months post cSBRT in the context of a mixed cardiomyopathy. Kiani et al. presented the first series of histopathological specimens from patients treated with cSBRT who subsequently underwent cardiac transplantation (31). This series included 4 patients with NICM at 12–250 days post cSBRT, including one patient who had undergone 2 cSBRT treatments and included histological and ultra-structural assessments. A variety of histopathological changes were seen in the different specimens. Three cases (examined at 12, 250 and 211 days post cSBRT) demonstrated central myocyte drop out, indicating myocardial necrosis, surrounded by a rim of fibrosis. One specimen (12 days post cSBRT) demonstrated subendocardial fibrosis only without the central liquefaction noted in the other specimens. At day 12 post cSBRT, hemorrhage was seen in one sample but not the other. In addition, vascular changes were noted, including myointimal thickening and endothelial damage were seen. At 12 days post cSBRT, electron microscopy of specimens from 2 patients showed degenerative changes in myocytes. These changes included irregular and convoluted intercalated disc regions, contractile elements were absent and myofibrils were disrupted and disorganized. Mitochondria were edematous and demonstrated loss of cisternae. These observations at 12 days post cSBRT indicate acute RT induced cellular injury. Of note, there was evidence of RT-induced fibrosis in all samples, including 2 obtained at 12 days post

cSBRT. Kautzner et al. assessed specimens obtained from patients who died at 3, 6 and 9 months following cSBRT (32). The substrate in this group was NICM in the patient who died at 3 months and ICM in the patients who died at 6 and 9 months. Images from this study are reproduced in Figure 3 demonstrating these histologic changes (32). On review of the pathologic specimens they identified evidence of myocytolysis at 3 months, with progressive development of fibrosis at the subsequent time points. In each specimen they noted sharp transition to viable myocardium at the edge of the targeted area. Intracellular immunoreactivity to caspase-3 was assessed in each case, and found to be positive at 3 months, less strongly positive at 6 months and absent at 9 months. These data indicate apoptosis plays a role in the early response to RT in human myocardium. Zhang et al. reported histological data from four patients at 17, 209, 251, and 478 days post cSBRT. In this report myocardium was stained with Masson's trichrome and fibrosis quantitatively assessed. In these specimens, there were only minor differences in degree of fibrosis in the RT targeted region when compared to matched untreated areas (receiving <5Gy), and these regions demonstrated significantly less fibrosis than seen in areas targeted with catheter ablation. Additional human data comes from indirect assessment of cSBRT treated myocardium in which repeat electro-anatomic mapping (EAM) followed by catheter ablation was undertaken. Gianni et al. reported 3 cases in which repeat EAM at between 6 and 12 months demonstrated preserved viability within the treated region at this time point. These data support the inference that across the time frames assessed, the anti-arrhythmic effect demonstrated in these patients was not attributable to fibrosis alone. When interpreting clinical data, it is acknowledged that in general significant heterogeneity exists between the substrate and time point at which specimens were assessed, and differentiation between substrate progression and effects of cSBRT are on occasion difficult to differentiate. Despite these caveats, dense transmural fibrosis has not been consistently identified even in the late phase following RT in human specimens following 25Gy cSBRT, despite clear demonstration of a late anti-arrhythmic effect. These observations support the concept that fibrosis alone cannot explain the clinical timeline and magnitude of reduced VT burden observed after RT. Further clinical data will be important in establishing the relative contributions of a late fibrotic effect and other anti-arrhythmic mechanisms to the efficacy of cSBRT.

Functional effect of cSBRT

A number of studies have assessed the feasibility of using radiation to achieve conduction block in the specialized conduction system of the heart, with the AV node commonly chosen as the target. Acute AV conduction block in Langendorff perfused porcine hearts was induced with very high dose heavy ion beam irradiation (15). Heavy ion beam irradiation of the porcine AV node *in-vivo* resulted in AV block following doses of 40Gy and 55Gy, but not following 25Gy (27). This developed up to 17 weeks following irradiation. The same group have demonstrated induction of chronic AV block with γ-irradiation (20). In this study, doses of 25Gy and upwards resulted in complete AV block, which appeared at a median time of 11.2 weeks after irradiation. Refaat et al. applied γ-radiation at doses of 35–40Gy to the porcine AV node and observed complete AV block in all subjects, which appeared between 2- and 7-months following irradiation (21). Suzuki et al. induced complete AV block following *in-vivo* irradiation of the porcine AV node with proton beam radiation at doses of 40Gy and 55Gy, as well 2:1 AV block in one subject receiving 40Gy irradiation (22).

Other studies have considered the possibility of using external radiation to target common atrial locations that would be relevant to treating common atrial arrhythmias. 40Gy γ-irradiation of the CTI in a porcine model was associated with bidirectional conduction block at 30-days post irradiation, while conduction block was not observed with doses of 25Gy. At other dose levels conduction slowing across the CTI was demonstrated without conduction block (17). In the same study complete AV block was induced following 70Gy γ-irradiation and diminished amplitude of left atrial potentials at 35 days following irradiation with dose between 38–80Gy. Guerra et al. demonstrated bidirectional CTI conduction block in a canine model following delivery of 25–50Gy β-radiation delivered via an intra-cardiac catheter, which was demonstrated at between one- and four-weeks post irradiation.

β-radiation at a dose of 60Gy through a balloon catheter within the pulmonary vein (PV) trunk resulted in diminished PV amplitude and elevated pacing threshold without conduction block in or out of the vein at 81 days post irradiation (16).

At 6 months following 17.5–35Gy γ-irradiation of the right superior PV, pulmonary vein isolation was not achieved in a porcine model, likely due to incomplete circumferential transmural ablation in this study (24). However, in a subsequent study circumferential transmural fibrosis was achieved with a dose of 40Gy, which resulted in electrical isolation of the right superior PV (25). Of note, in addition to PV isolation, there was AV node fibrosis resulting in complete AV block. In those animals in whom PV isolation was not observed, there was a dose-dependent reduction in PV electrogram amplitude. Zei et al. demonstrated electrical right superior pulmonary vein isolation at 3–6 months following γ-irradiation at doses of 25–35 Gy, electrical isolation in some subjects (with partial effect in the remainder) following 20Gy and no or partial effect in subjects receiving 15Gy. Combined pulmonary vein and posterior left atrial wall isolation was achieved in 3 of 4 animals at 4-months following 33Gy γ-irradiation in a canine model. Conduction block was not apparent in two animals assessed at 6-weeks post cSBRT using the same protocol (28).

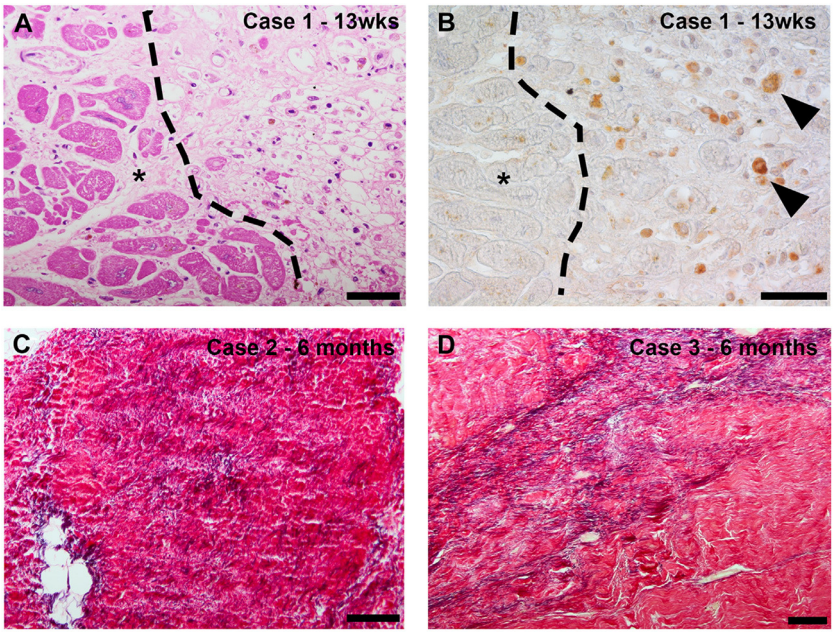

FIGURE 3
(Reproduced with permission from Kautzner et al. (32)–case numbers and details are described in referenced article): Case 1 (13 weeks after stereotactic body radiotherapy [SBRT]): routine histologic evaluation revealed myocytolysis corresponding to a previously irradiated region with a sharp transition to viable myocardium (*) **(A)**. Detection of active caspase-3 as a marker of apoptosis revealed intracellular immunoreactivity in the cytoplasm of rounded cells that morphologically corresponded to macrophages. * marks viable myocardium **(B)**. Case 2 (6 months after SBRT): histologic staining of the irradiated area revealed fibrotic region containing densely packed fibers, including a relatively high elastic component **(C).** Case 3 (9 months after SBRT): histologic staining of the irradiated region revealed myocardial scarring with marked elastosis **(D)**.

Previously healthy porcine ventricular myocardium underwent *in-vivo* proton beam irradiation and systolic function was assessed over time (34). At 16 weeks, fibrosis was seen in regions receiving 20–30Gy doses, and in the lesions core, which received >30Gy necrotic tissue was seen, with vacuolar degeneration and myocytolysis present. This study demonstrated a dose dependent effect on LV systolic function and LV end-diastolic volume–a greater volume of myocaridum treated with cSBRT in a range to cause necrosis and subsequent fibrosis was associated with a reduction in LV systolic function. Dusi et al. provide further evidence of the potential impact of cSBRT on myocardial function in the first reported case of proton-beam radiation cSBRT for VA. In this report there was a local decrease in longitudinal strain noted in the targeted region at 1 month post cSBRT, supporting an early local mechanical effect of cSBRT, as well as effective suppression of previously incessant VA (35). These observations are of particular relevance when consideration is given to the potential for a substrate-based delivery of cSBRT, as recently reported by Qian et al. (36), during which extensive regions may be considered for targeting. The demonstrable impact on LV function following delivery of cSBRT to a large anatomic area support the paramount importance of a precise target definition and focused energy delivery for cSBRT.

Data from a small number of patients has been reported assessing surface ECG data from patients undergoing cSBRT. Zhang et al. report a non-significant trend toward QRS shortening among 19 patients who underwent cSBRT, including 4 of whom demonstrated a robust 25ms shortening of the QRS duration at 6-weeks post cSBRT (33). A reduction in late potentials on high-resolution signal averaged ECG from a single patient was also noted by Amino et al. at 6-weeks post-cSBRT (37), an effect which persisted out to 6-months. The mechanism underlying these observations, as well as their clinical relevance remains uncertain. These data are consistent with reduction in volume of late activated myocardium, changes in myocardial CV or a combination of these and other mechanisms.

cSBRT in experimental models of ventricular substrate

In a leporine model of recent MI, heavy ion beam irradiation resulted in changes in ventricular conduction velocity in both control tissue and in the peri-infarct border zone at 2 weeks following irradiation. These may be summarized as demonstrating an increase in transverse CV following irradiation in both control and peri-infarct tissue, and in

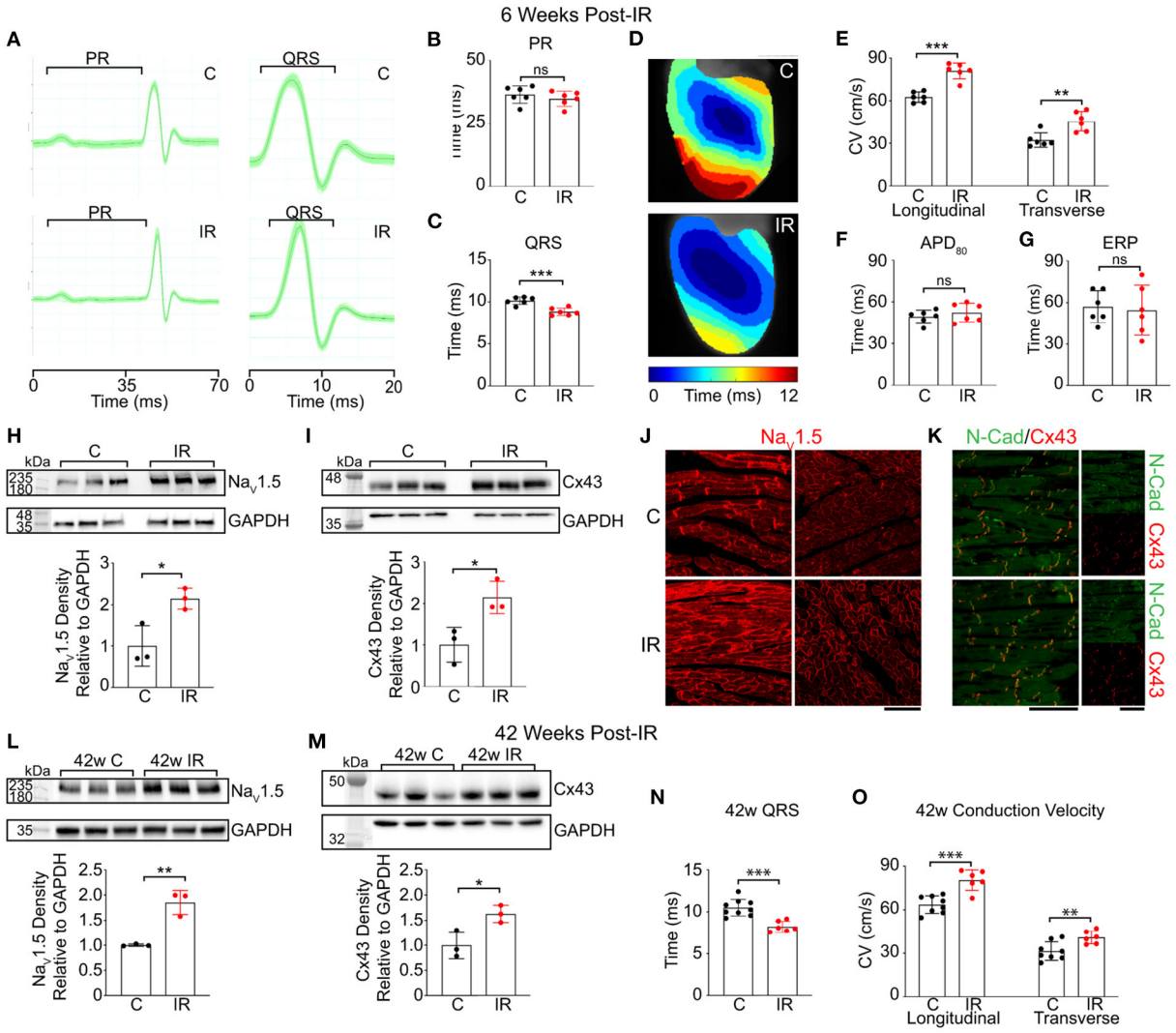

FIGURE 4
Reproduced from Zhang et al. (33) under Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/) Cardiac RT persistently increases adult murine ventricular conduction. **(A)** Representative ECGs from control (top) and IR mice (bottom) highlighting PR and QRS intervals. **(B,C)** Effect of radiation on PR ($P = 0.39$) and QRS (**$P = 0.00043$) intervals in control (black) vs. IR (red) mice ($n = 6$ biologically independent animals per condition). **(D)** Representative ventricular activation maps from control and IR mice. Scale bars =3 mm. **(E)** Effect of RT on ventricular CV ($n = 6$ biologically independent animals per condition; ***$P = 0.00005$; **$P = 0.0034$). **(F,G)** APD80 ($P = 0.39$) and ERP ($P = 0.78$) in control versus IR mice ($n = 6$ biologically independent animals per condition). **(H,I)** Western blots of NaV1.5 (*$P = 0.022$) and Cx43 (*$P = 0.025$) in control and IR ventricles ($n = 3$ biologically independent samples per condition). **(J)** Immunostaining of control (top) and IR (bottom) myocardium for NaV1.5 and **(K)** co-stained for Cx43 (red) and N-Cadherin (green). Scale bars= 70 μm. Experiment was replicated 3 times in biologically independent specimens and produced similar results. **(L,M)** Western blots of NaV1.5 (**$P = 0.0034$) and Cx43 (*$P = 0.027$) after 42 weeks post-IR ($n = 3$ biologically independent samples per condition). **(N)** Effect of RT on QRS intervals in control vs. IR mice after 42 weeks (***$P = 0.00027$; C, $n = 9$; IR, $n = 6$). **(O)** Left ventricular CVs in control ($n = 9$ biologically independent animals) vs. IR (n = 6 biologically independent animals) mice at 42 weeks post-IR (***$P = 0.00042$; **$P = 0.0092$). All P values determined by two-way unpaired t test. Bar graphs are represented as mean ± SD.

addition an increase in longitudinal CV in peri-infarct tissue, reversing the CV slowing seen in peri-infarct tissue following MI without irradiation. Therefore, as well affecting total activation time of the ventricle, irradiation affected the ventricular anisotropic conduction properties in both healthy and peri-infarct tissue. In addition, refractoriness was prolonged in healthy tissue following irradiation. In this study, irradiation resulted in an overall decrease in the susceptibility to inducible ventricular arrhythmias (18).

In a canine model of recent MI, 15Gy of heavy ion beam irradiation resulted in reversal of MI-induced diminished expression of Cx43 seen in the peri-infarct border zone at 1

year. Of note, this was also associated with reduced surface ECG evidence of delayed ventricular activation, reduced susceptibility to induced ventricular arrhythmias as well as greater recovery of LV systolic function (as assessed by echocardiographic fractional shortening) without effect on diastolic function at 1 year post irradiation (38).

At 4 weeks following experimental MI, proton beam irradiation was applied to porcine ventricular tissue (targeting CMR identified infarct) at doses of 30–40Gy (39). In this study, no differences in the histological appearance of tissue from treated and untreated areas was noted at 8 weeks. At 15 weeks, progressive interstitial fibrosis was seen in the peri-infarct zone as well as in targeted healthy tissue, along with signs of inflammation (mononuclear cells). By 6 months, tissue in the peri-infarct zone receiving >30Gy was largely homogenized, with widespread myocytolysis and vacuolar degeneration as well as fibrosis. A reduced proportion of surviving cardiomyocytes and an increase in the proportion of collagen was demonstrated at 6 months post irradiation in treated areas when compared to untreated peri-infarct tissue. Of note, with radiation constrained to the scar in this model there was no adverse impact on LV systolic function.

Zhang et al. considered the early effects of RT on conduction velocity (33). At 2 weeks post experimental MI in a murine model, 25Gy γ-radiation was applied to the whole heart. At 6 weeks post irradiation myocardial CV was assessed using optical mapping, and a significant increase in both longitudinal and transverse CV was identified in both normal tissue and peri-infarct border zone, without clear change in the CV anisotropy ratio. At this time point, no increase in fibrosis was detected on histological assessment, although immunohistochemical analysis identified an increase in voltage gated sodium channel ($Na_V1.5$) and Cx43 proteins, without change in their pattern of distribution. Further data is presented using gain and loss of function knock-out mice (without infarct), to indicate that activation of the Notch signaling pathway is involved in regulation of RT induced changes in CV and protein expression, and that upregulation of $Na_V1.5$ persisted out to a year following transient Notch activation, while Cx43 in this experiment was not increased at this time point. These data are sumarized in Figure 4 (33). This data, alongside the work from Amino et al. (19, 38), indicates a potential mechanism for the early anti-arrhythmic effect of cSBRT that has been consistently observed in clinical studies. There are a number of plausible mechanisms through which increasing CV could effect an anti-arrhythmic effect including changes in reentrant wavelength and conduction safety factor, but these remain speculative at present. In addition to demonstrating an increase in CV following RT, Zhang et al. used a dose-escalation approach to demonstrate that this electrophysiological response was present following single fractions doses as low as 15Gy (33). Given the potential importance of this change in CV in mediating the desired anti-arrhythmic effect, this result raises the possibility delivering an effective treatment at lower RT lower dose, with the potential for reduced toxicity if this was the case. This observation motivates further research to establish the minimum dose required to achieve the anti-arrhythmic effect of cSBRT, in order to minimize the toxicity associated with this treatment while maintaining the efficacy. Of note, both of the studies in which an acute increase in conduction velocity was observed used models of early MI, representing an important difference from the typical clinical situation of VA in the context of chronically remodeled ventricular tissue. Note is made of the improvement in LV function observed in the canine study (38) which raises the possibility of a broader effect on the healing process beyond the specific conduction properties of tissue, which may be relevant to the observations made. If this was the case, it may affect the likelihood of these observations being seen in the chronic remodeled myocardium typically treated in the clinical setting, but there is no data assessing this currently available. As yet, no clinical data regarding early changes in conduction velocity in humans has been presented and the early biological effect of RT on human myocardium remains undefined.

Conclusion

cSBRT represents a promising non-invasive modality that has recently emerged for the treatment of refractory VA. The myocardial response to RT is complex and likely to be cell-type specific. In addition, amongst similar cell types, the radio-sensitivity of tissue may be different in healthy vs. unhealthy myocardium. Acute and sub-acute cellular changes following cSBRT including those of cellular necrosis and apoptosis have been identified in experimental and clinical reports. Vascular effects, including vasculitis and capillary thrombosis, as well as acute mitochondrial damage have been reported in the acute phase following cSBRT. These changes precede the development of myocardial fibrosis, which has most commonly been seen beyond 3 months from cSBRT. Furthermore, in several clinical reports, no discernible histopathological changes were identified in the treated myocardium despite a reduction in the arrhythmia burden of the patients following cSBRT. The cancer community are increasingly aware of radiation induced damage to normal tissue in patients receiving RT for cancers; especially dose to cardiac substructures. There are many ongoing pre-clinical and clinical studies in this area providing much more data which may give further useful insights into mechanisms of damage.

In experimental conditions, acute conduction block within specialized conduction tissue may be achieved, in some cases with doses well in excess of those that have been used to achieve arrhythmia suppression clinically. In contrast to the mechanism through which arrhythmia suppression is achieved with traditional catheter-based technologies, acute conduction block does not appear to be the mechanism underlying the

early anti-arrhythmic of cSBRT. Experimental studies have indicated the possibility of acute increases in CV in experimental models of early MI and suggested that RT induced electrical reprogramming of myocardial gap junction and sodium channel expression may persist up to a year after RT exposure. The relevance of these observations to the early, and indeed late, anti-arrhythmic effects of cSBRT remain uncertain but represent an intriguing area for future investigation. Clinical data assessing the CV in human myocardium following cSBRT has not been reported. The role of late-stage fibrosis in the homogenization of arrhythmogenic myocardial substrate may represent a more familiar mechanism through which arrhythmias are inhibited, but even data confirming this are so far limited.

The structural and functional myocardial response to RT exposure through cSBRT is likely to be specific to the cell type targeted, the dose and radiation source of the RT delivered and the time-point at which tissue is assessed. There exists a large knowledge gap regarding many of the topics discussed in this review which represents an exciting opportunity for future research. As experience grows with the wider use of cSBRT, a greater understanding of the tissue response will likely develop and this may contribute to further insights into the mechanisms through which cSBRT provides acute and chronic arrhythmia suppression. In the future, with the benefit of a greater understanding of the many outstanding issues discussed in this review, it is envisaged that cSBRT therapy could be planned to optimally titrate both early and late radiation effects to optimize the combined anti-arrhythmic efficacy of the treatment, minimize radiation associated toxicity and thus achieve the best patient outcomes.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Increased bystander intervention when volunteer responders attend out-of-hospital cardiac arrest

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Aim: The primary aim was to investigate the association between alarm acceptance compared to no-acceptance by volunteer responders, bystander intervention, and survival in out-of-hospital cardiac arrest.

Materials and methods: This retrospective observational study included all suspected out-of-hospital cardiac arrests (OHCAs) with activation of volunteer responders in the Capital Region of Denmark (1 November 2018 to 14 May 2019), the Central Denmark Region (1 November 2018 to 31 December 2020), and the Northern Denmark Region (14 February 2020 to 31 December 2020). All OHCAs unwitnessed by Emergency Medical Services (EMS) were analyzed on the basis on alarm acceptance and arrival before EMS. The primary outcomes were bystander cardio-pulmonary resuscitation (CPR), bystander defibrillation and secondary outcome was 30-day survival. A questionnaire sent to all volunteer responders was used with respect to their arrival status.

Results: We identified 1,877 OHCAs with volunteer responder activation eligible for inclusion and 1,725 (91.9%) of these had at least one volunteer responder accepting the alarm (accepted). Of these, 1,355 (79%) reported arrival status whereof 883 (65%) arrived before EMS. When volunteer responders accepted the alarm and arrived before EMS, we found increased

proportions and adjusted odds ratio for bystander CPR {94 vs. 83%, 4.31 [95% CI (2.43–7.67)] and bystander defibrillation [13 vs. 9%, 3.16 (1.60–6.25)]} compared to cases where no volunteer responders accepted the alarm.

Conclusion: We observed a fourfold increased odds ratio for bystander CPR and a threefold increased odds ratio for bystander defibrillation when volunteer responders accepted the alarm and arrived before EMS.

KEYWORDS

out-of-hospital cardiac arrest, volunteer responders, bystander interventions, cardiopulmonary resuscitation, defibrillation

Introduction

During the last decade, a strategy of activating volunteer responders to increase bystander cardiopulmonary resuscitation (CPR) and early defibrillation with automated external defibrillators (AEDs) has been implemented world-wide with positive results and increasing interest from both the general public and professionals (1–11). Globally, survival following out-of-hospital cardiac arrest (OHCA) ranges from 2 to 11% with great variations (12, 13). Experiences from US casinos and Copenhagen Airport have reported survival rates between 74 and 100% within the subgroup of OHCAs with initial shockable heart rhythm (14, 15). These findings imply a large potential to increase survival if defibrillation can be achieved within minutes from OHCA and support the continued development and implementation of bystander engaging initiatives such as volunteer responder programs (16), as recommended by both the American Heart Association and the European Resuscitation Council (17, 18). However, there are currently great variations in design and reporting within volunteer responder systems worldwide and knowledge regarding factors that influence whether volunteer responders accept the alarm are scarce. Likewise, little is currently known about the relation between alarm acceptance and the volunteer responder arriving and assisting at the site of OHCA. Information in these areas is important to further understand and improve volunteer responder systems. In this study, we aimed to investigate bystander interventions and 30-day survival when volunteer responders accepted the alarm compared to OHCAs where no volunteer responders accepted the alarm. Our primary analysis was in the group where volunteer responders reported arriving before Emergency Medical Services (EMS). Secondary analysis was done where volunteer responders reported arriving at the scene of OHCA and finally we compared OHCAs where at least one volunteer responder accepted the alarm compared with OHCAs where no volunteer responders accepted the alarm (irrespective of when or if they arrived at the scene and before EMS). These secondary analyses were included to compare our volunteer responder programs to other international programs with less complete data and/or missing data about volunteers' time of arrival. We hypothesized that when a volunteer responder accepted the alarm and arrived before EMS compared to not it was associated with increased bystander interventions (CPR and defibrillation) and 30-day survival. Furthermore, we hypothesized that a larger proportion of alarms not accepted occurred during nighttime and in rural areas.

Materials and methods

Study setting

This observational study with prospective data collection included OHCAs with activation of volunteer responders in the Capital Region of Denmark (1 November 2018 to 14 May 2019), the Central Denmark Region (1 November 2018 to 31 December 2020), and the Northern Denmark Region (14 February 2020 to 31 December 2020). Due to an ongoing randomized controlled trial, data collection for the Capital Region does not include patients after 14 May 2019. All three included regions consist of both urban, suburban, and rural areas and covers approximately 23,554 km^2 (≈55% of Denmark) and inhabits 3.75 million people (≈64% of the total population).

Emergency Medical Services

All included regions are served by a two-tiered EMS system consisting of an ambulance and a physician-staffed unit which are dispatched in case of suspected OHCA. The three regions have separate and independent dispatch centers but follow the same standardized protocol in the event of suspected OHCA. In addition, emergency dispatchers perform telephone-guided CPR and assistance with information on accessing the nearest available AED. In Denmark, a national AED registry was established in 2007 and now contains >21,000 publicly available registered AEDs. The AED registry is linked to all dispatch centers with information on opening hours,

accessibility, and global position system location. All EMS dispatchers in Denmark can activate volunteer responders in case of suspected OHCA to assist with CPR and acquisition of a nearby AED. Volunteer responders can be activated simultaneously with the ambulance but usually the activation occurs 30−60 s later as the dispatcher needs to make sure that the surroundings are safe for volunteer responders to attend (6). In this study, all interventions before the arrival of EMS are referred to as bystander interventions. It is not possible to differentiate between interventions performed by random bystanders and volunteer responders.

The Danish volunteer responder program

The program was first implemented in the Capital Region of Denmark in September 2017 with other regions gradually following resulting in full national coverage by May 2020. The program is based on volunteers willing to assist in case of OHCA. The purpose of the program is to improve bystander intervention prior to the arrival of EMS to ultimately increase the chances of survival (19). In case of a nearby OHCA, volunteers are activated *via* a smartphone application, and when activated, the volunteer responder can either accept or reject the alarm. When the alarm has been accepted, the volunteer responder is guided either directly to the site of OHCA or *via* an AED registered in the national AED registry. The nearest 20 volunteer responders within 1,800 m of the potential OHCA are activated. We have previously demonstrated that approximately 50% of the volunteer responders react to the alarm whereof roughly 50% accept the alarm (overall acceptance rate 25−30%) (6, 20). All volunteer responders must be ≥18 years of age to register with the program. Previous experience or certified CPR training are not required to register but are highly recommended. After 90 min from dispatch, volunteer responders are asked to complete a questionnaire about their participation and experiences related to their mission. Emergency dispatchers do not activate the volunteer responder system in OHCAs involving suicide, trauma, children <8 years or if OHCA surroundings are deemed unsafe. Previous publications describe the program in more detail (6, 20).

Study population, groups, and design

All presumed OHCAs, assessed by emergency dispatchers, with volunteer responder activation from the Central, the Capital and North regions of Denmark were identified. Confirmed OHCA was defined as OHCA registered in the Danish Cardiac Arrest Registry, thus we excluded cases (non-OHCAs) not found in the Danish Cardiac Arrest Registry. Further, we excluded OHCAs witnessed by EMS and OHCAs with volunteer responder activation but with no one within range (<1,800 m) of the OHCA. The study population was divided into two groups: one group where at least one volunteer responder accepted the alarm (referred to as "accepted") and one group where no volunteer responder accepted the alarm (referred to as "not-accepted"). The "not-accepted" group thus includes both rejected and unseen/unanswered alarms. Further, the primary analysis was in the group where volunteer responders reported arriving before EMS in the subsequent questionnaire sent to them. Secondary analysis included OHCAs where at least one volunteer responder accepted the alarm and arrived at the site of OHCA (irrespective of EMS arrival) and OHCAs where at least one accepted the alarm (irrespective of their reported arrival status) both compared to OHCA where no volunteer responders accepted the alarm. This was done in order to compare our data with different volunteer responder programs where arrival status of the volunteer responders is unavailable for scientific reporting. Finally, as Supplementary data we provided a comparison of patients according to initial shockable rhythm.

Study parameters and data sources

Variables related to the OHCA originate from the Danish Cardiac Arrest Registry which includes time and date of OHCA, latitude and longitude of OHCA, home or public location, age, sex, witnessed status, initial shockable heart rhythm [ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT)], bystander CPR, bystander defibrillation, EMS response time, EMS defibrillation, ROSC, and 30-day survival. Information regarding volunteer responders originated from the Volunteer Responder Application Server (local register) and includes geographical locations, app-interactions when accepting or declining alarms, sex, and age. Population density estimates at the OHCA site were based on the municipal population density and were stratified according to the EUROSTAT degree of urbanization system (DEGURBA) producing a three-layered population density stratification (low, intermediate, and high) (21).

Study outcomes

The primary outcomes for this study were bystander CPR, bystander defibrillation, and secondary outcome was 30-day survival.

Statistical analysis

Categorical variables were presented as proportions and percentages and continuous variables were presented as medians with interquartile range (IQR). A logistic regression analysis was performed to investigate association between exposure (volunteer responders accepting the alarm and their

arrival status) and primary outcome variables (bystander CPR, defibrillation, and 30-day survival). Furthermore, we performed a multivariable logistic regression analysis to adjust for identified confounders. We used Direct Acyclic Graphs to determine potential confounders affecting both the exposure and outcomes, **Supplementary Figures 1–3**. Only time of day (of the OHCA) and the degree of urbanization were deemed confounders which we adjusted for in the logistic regression analysis. Statistical analysis was carried out in SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC, United States) and RStudio version 1.2.1335 (22).

Ethical and legal approval

Data were obtained and stored according to the Danish Data Protection Agency (P-2021-670 and P-2021-82). According to Danish Law register studies do not require ethical approval. The study was approved by the Danish Safety Authority (3-3013-2721/1). At registration, volunteer responders give permission to be contacted by the research team if necessary. Volunteer responders consent not to disclosure any private information in relation to OHCA alarms and resuscitation attempts. Volunteer responders can withdraw from the program at any time and simultaneously withdraw their consent.

Results

We initially identified 3,142 presumed OHCAs, assessed by emergency dispatchers, with volunteer responder activation within the study period. Of these, 1,082 were verified non-OHCA, but presumably other genesis, and 24 were witnessed by ambulance staff and thus excluded from further analysis. This resulted in a study population of 1,877 OHCAs with volunteer responder activation, **Figure 1**. Of these, 1,725 (91.9%) OHCAs had at least one volunteer responder accepting the alarm (classified as accepted). Of these, 1,392 (80%) answered the question about arrival at the scene whereof 1,388 (99,7%) reported successful arrival at scene. Further, 1,355 (79%) answered the question about arrival before EMS whereof 883 (65%) reported arriving before EMS. In 152 OHCAs (8.1%) no volunteer responders accepted the alarm (classified as not accepted).

Cardiac arrest characteristics

We found no difference in baseline characteristics such as sex and age and likewise, no difference was found in initial shockable heart rhythm (VF or pVT) and proportion of bystander witnessed arrests between the accepted and not-accepted groups, **Table 1**.

A longer median EMS response time (9.00 vs. 7.00 min) and longer distance from volunteer responder to OHCA site (720 vs. 527 m) were found in the not-accepted group. A larger proportion of OHCAs in the accept group occurred in public locations (18.1 vs. 11.2%) and in areas of high population density (38.7 vs. 14.5%) compared to the not-accepted group. More OHCAs where at least one volunteer responder accepted the alarm occurred during working hours (8.00 a.m.−03.59 p.m.) with no difference during evening (04.00 p.m.−11.59 p.m.) and fewer during night-time (00.00−07.59 a.m.). Still, we found more than 4 times as many incidents of accepted as not-accepted alarms during nighttime (295 vs. 61 incidents).

Bystander interventions and outcome

In our primary analysis we observed that significant more received bystander CPR [94 vs. 83%, odds ratio (OR) 3.37 95% Confidence Interval (95% CI) (2.02−5.60)] and bystander defibrillation [13 vs. 9%, 3.19 (1.64−6.19)] when a volunteer responder accepted the alarm and arrived before EMS compared to OHCAs where no volunteer responders accepted the alarm, respectively, **Figure 2**. After adjusting for confounders, bystander CPR [4.31 (2.43−7.67)] and defibrillation [3.16 (1.60−6.25)] remained significant. However, we observed no difference in 30-day survival, **Figure 2**. In the secondary analysis, we observed that significant more received bystander CPR [90 vs. 83%, 1.77 (1.12−2.79)] and bystander defibrillation [14 vs. 7%, 2.27 (1.17−4.38)] when a volunteer responder accepted the alarm and arrived at the scene of OHCA compared to cases where no volunteer responders accepted the alarm, respectively, **Figure 3A**. When adjusting for confounders odds ratio of bystander CPR increased [2.17 (1.33−3.54)] while the odds ratio of bystander defibrillation remained similar [2.20 (1.12−4.30)]. In the other secondary analysis of all OHCAs (irrespective of arrival status of the volunteer responders) we identified a significant association between volunteer responder acceptance of the alarm and both bystander CPR [90 vs. 83%, 1.78 (1.12−2.79)] and bystander defibrillation [13 vs. 7%, 2.15 (1.12−4.15)], with a borderline significant association in 30-day survival [15 vs. 9%, 1.71 (0.97−3.02)]. After adjusting for confounders, bystander CPR [2.06 (1.28–3.32)], and bystander defibrillation [2.04 (1.05–3.96)] were significantly associated with volunteer responder acceptance of the alarm, whereas difference in 30-day survival [1.61 (0.90–2.86)] was non-significant, **Figure 3B**.

Patients presenting with and initial shockable rhythm had higher survival rates (39%) when at least one volunteer responder accepted the alarm compared to cases where no one accepted the alarm (29%), **Supplementary Table 1**. However, these results were not statistically significant, $p = 0.36$.

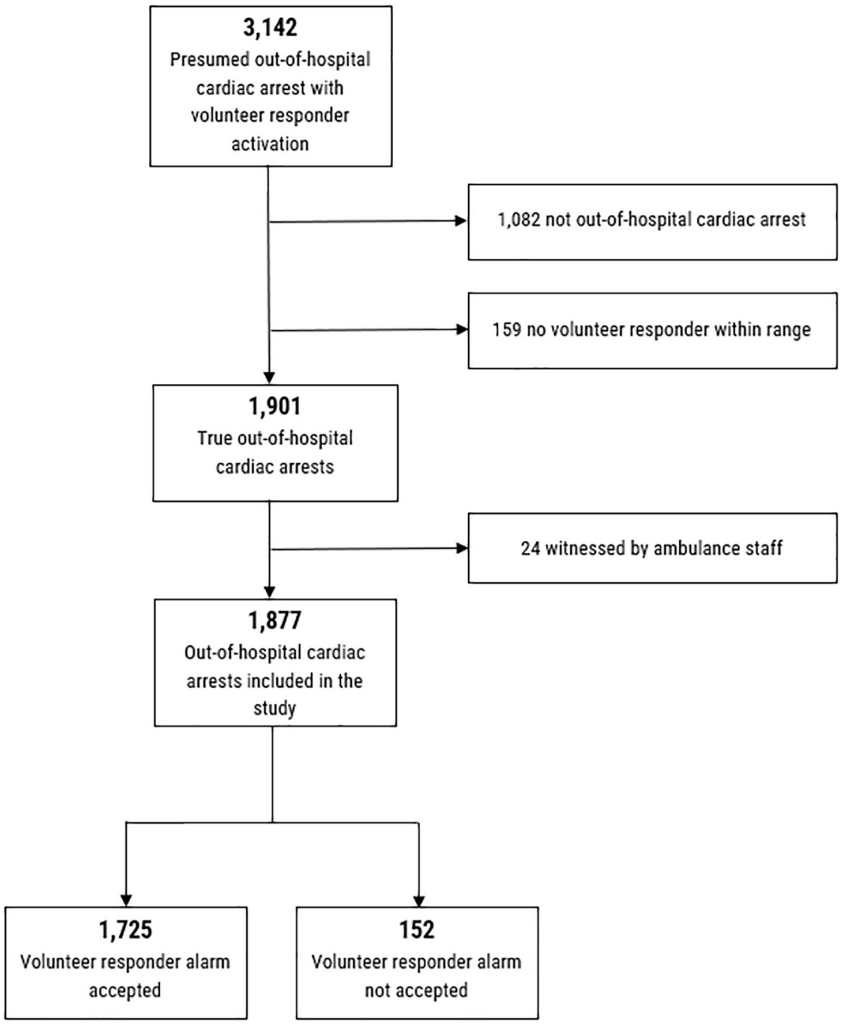

FIGURE 1
Flowchart of included patients.

Discussion

This prospective observational study investigated whether alarm acceptance by volunteer responders in the case of OHCA was associated with increased bystander intervention and improved patient outcome and the circumstances related to the OHCA. In 9 out of 10 OHCAs we found that at least one volunteer responder accepted the alarm, with fewest alarms accepted (29.1%) in rural areas and during nighttime (17.1%) compared to urban areas (38.7%) and during daytime (48%). The adjusted odds ratio of bystander CPR and defibrillation increased fourfold and threefold, respectively, when a volunteer responder accepted the alarm and arrived before EMS compared with cases where no volunteer responders accepted the alarm. Similar, we found increased odds ratios of bystander CPR and defibrillation when volunteer responders reported arriving at scene of OHCA. Finally, when looking at all OHCAs irrespective of the volunteer responder's arrival status we still observed increased odds ratios of bystander CPR and defibrillation when at least one volunteer responder accepted the alarm compared to OHCAs where no one accepted the alarm.

Positive association with bystander intervention

Previous studies have shown that volunteer responder programs hold the potential to increase bystander CPR and defibrillation (5–7, 23). However, only few studies have compared the direct association between alarm acceptance and outcome. One recent study from the UK by Smith et al. found increased bystander CPR with volunteer responder acceptance compared with no volunteer responder involvement in one group (London; 70.6 vs. 65.6%) but lower bystander CPR rate

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TABLE 1 Characteristics of population with out-of-hospital cardiac arrest and volunteer responder activation based on accept or no accept of alarm.

	Accepted (n = 1725)	Not-accepted (n = 152)	Missing (n)
Age, years (IQR)	73 (63−81)	73 (63−80)	47
Male sex, *n* (%)	1121 (66.7%)	100 (67.1%)	47
Witnessed arrest, *n* (%)	905 (52.6%)	81 (53.3%)	3
Initial shockable rhythm (VF/pVT), *n* (%)	486 (28.3%)	36 (23.7%)	9
Median EMS response time, min. (IQR)	7.00 (5.00−10.00)	9.00 (6.00−12.00)	53
Distance between volunteer responders and OHCA, m (IQR)	527 (298−855)	720 (384−1422)	0
Volunteer responder answered question about arrival at scene, *n* (%)	1,392 (80)	0	485
Reported arriving at OHCA site*, *n* (%)	1388 (99.7%)	0	0
Volunteer responders answered question about arrival prior to EMS, *n* (%)	1,355 (79)	0	522
Arrival prior to EMS**, *n* (%)	883 (65.3%)	0	0
Public OHCA location, *n* (%)	312 (18.1%)	17 (11.2%)	1
Population density at OHCA site, *n* (%)			1
Low	501 (29.1%)	74 (48.7%)	
Intermediate	556 (32.3%)	56 (36.8%)	
High	667 (38.7%)	22 (14.5%)	
Weekend, *n* (%)	474 (27.5%)	43 (27.6%)	0
Median number of activated volunteer responders based on population density, *n* (IQR)			0
Low	12 (5−20)	1 (1−3)	
Intermediate	20 (10−20)	6 (2−13.5)	
High	20 (20−20)	15 (10−20)	
Time of the day, *n* (%)			0
08.00–15.59	828 (48.0%)	54 (35.5%)	
16.00–23.59	602 (34.9%)	37 (24.3%)	
00.00–07.59	295 (17.1%)	61 (40.1%)	
EMS defibrillation, *n* (%)	498 (28.9%)	47 (30.9%)	0
Bystander CPR, *n* (%)	1543 (89.6%)	126 (82.9%)	3
Volunteer responders answering question about type of CPR performed, *n* (%)	606 (35%)	0	1,119
Reported performing compressions and ventilation, *n* (%)	213 (35)	0	
Reported performing compressions alone, *n* (%)	362 (60)	0	
Reported performing ventilations alone, *n* (%)	31 (5)	0	
Bystander defibrillation, *n* (%)	227 (13.2%)	10 (6.6%)	1
ROSC at hospital arrival, *n* (%)	471 (27.4%)	30 (19.9%)	7
30-day survival, *n* (%)	253 (15.1%)	14 (9.4%)	50

OHCA, out-of-hospital cardiac arrest; VF/pVT, ventricular fibrillation/pulseless ventricular tachycardia; EMS, emergency medical services; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation. Values are median (Q1, Q3), *n* or *n* (%). *At least one volunteer responder arrives at site. **At least one volunteer responder arrives at site prior to EMS.

in a second group (East Midlands 60 vs. 74.9%). Smith et al. also found increased bystander defibrillation (9.8 vs. 8.5%) with volunteer responder acceptance (10). The proportions from London are comparable to, but lower than our findings. This difference could be related to the very high number of accepted alarms we observe in our study with alarms acceptance in 91.9% of OHCAs with volunteer responder activation compared to respective 16% in London and 15% in East Midlands. We observed markedly increased probability of both bystander CPR and defibrillation when one volunteer responder accepted the alarm and arrived before EMS. Dispatcher assisted CPR, which is a part of the OHCA protocol in Denmark, is deemed to be one of the reasons that we still find a high proportion of bystander CPR in the not-accepted group. A high bystander engagement is also part of the culture in Denmark with high rates of bystander CPR even before implementation of the volunteer responder program (24).

A recent Dutch study by Stieglis et al. from 2020 found that 17% of all OHCAs with initial shockable rhythm were defibrillated by volunteer responders (25). Comparably, we observed bystander defibrillation in 13.2% of all OHCAs where at least one volunteer responder accepted the alarm which is twice the proportion we find with alarm not accepted (6.6%). The proportion of bystander defibrillated OHCAs increased even further when volunteer responders reported arrival at OHCA site (14%) and arrival prior to EMS (18%).

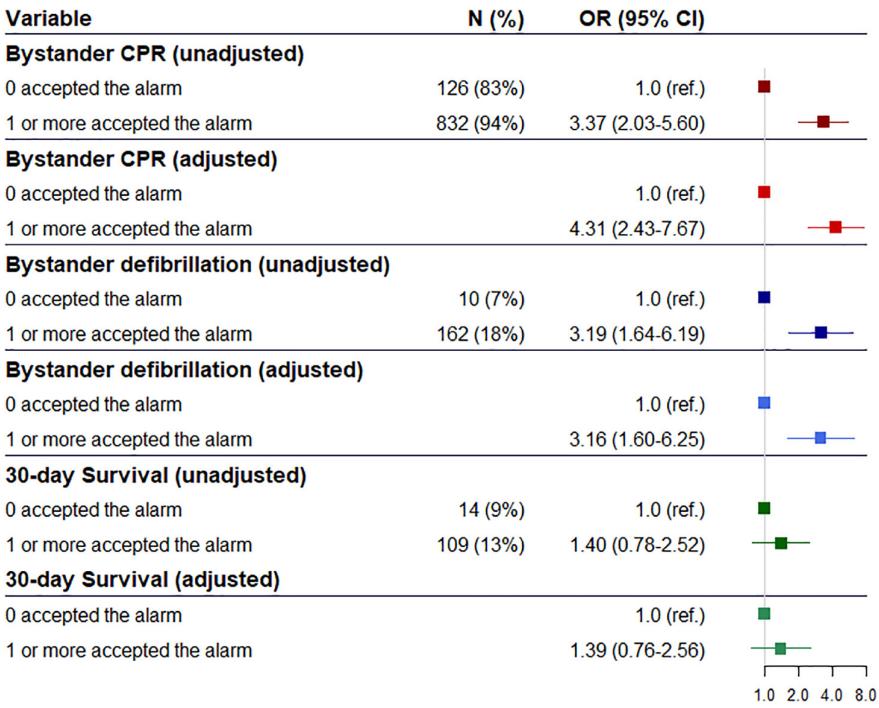


FIGURE 2
Odds ratio and adjusted odds ratio of association between alarm acceptance and bystander cardiopulmonary, bystander defibrillation and 30-day survival where at least one volunteer responder accepted the alarm and arrived before the ambulance compared to cases where no volunteer responders accepted the alarm.

Unfortunately, we were not able to differentiate between whether CPR and defibrillation was performed by random bystanders at site or alerted volunteer responders. As public arrests were more frequent in the accept group this may have contributed to the higher occurrence of bystander intervention, as public location of arrest in itself is associated with bystander intervention as these arrests are more likely to be witnessed (26–28). As we did not find any difference in proportion of bystander witnessed arrests between our two groups why this most likely does not explain the difference in bystander CPR. It could still be a contributing factor to the difference in bystander defibrillation as publicly available AEDs generally are more accessibly in public locations (29–31).

Time and place

An OHCA alarm was more likely to be accepted in areas of high population density. This is most likely due to availability as more volunteer responders were activated in areas of high population density, **Table 1**. Indeed, the 2020 study by Stieglis et al. found an association between the density of volunteer responders and the likelihood of bystander defibrillation and that this correlation was stronger in less densely populated areas where they found few volunteer responders (25).

The fact that we find a longer EMS response time in the not-accepted group could also be a result of rurality of the OHCA location as OHCAs in rural areas also were more frequent in this group. A volunteer responder study by Andelius et al. from 2020 found an association between longer EMS response time and increased bystander interventions (6). This strongly suggests a big potential to improve bystander intervention in rural areas by utilizing the potential of volunteer responder systems.

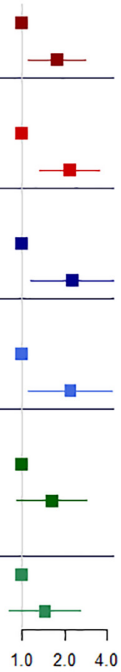
We also observed significant diurnal variations in alarm acceptance with significantly higher proportions of alarms being accepted during daytime/evening and higher proportions of not-accepted alarms during nighttime (32). However, we still found more than 4 times as many incidents of accepted as not-accepted alarms during nighttime. As OHCAs during nighttime are generally known to be associated with worse outcome (33, 34) an increased focus on volunteer responder alarm acceptance could prove beneficial (32, 35).

Is there a potential to increase survival?

This study found a difference in 30-day survival (15.1% when at least one volunteer responder accepted the alarm vs. 9.4% where none accepted the alarm) which was statistically insignificant after adjusting for confounders [1.61 CI (0.90–2.86)]. Further, when looking only at patients presenting with

A

Variable	N (%)	OR (95% CI)
Bystander CPR (unadjusted)		
0 accepted the alarm	126 (83%)	1.0 (ref.)
1 or more accepted the alarm	1,241 (90%)	1.77 (1.12-2.79)
Bystander CPR (adjusted)		
0 accepted the alarm		1.0 (ref.)
1 or more accepted the alarm		2.17 (1.33-3.54)
Bystander defibrillation (unadjusted)		
0 accepted the alarm	10 (7%)	1.0 (ref.)
1 or more accepted the alarm	191 (14%)	2.27 (1.17-4.38)
Bystander defibrillation (adjusted)		
0 accepted the alarm		1.0 (ref.)
1 or more accepted the alarm		2.20 (1.12-4.30)
30-day Survival (unadjusted)		
0 accepted the alarm	14 (9%)	1.0 (ref.)
1 or more accepted the alarm	194 (14%)	1.62 (0.92-2.87)
30-day Survival (adjusted)		
0 accepted the alarm		1.0 (ref.)
1 or more accepted the alarm		1.45 (0.81-2.61)



B

Variable	N (%)	OR (95% CI)
Bystander CPR (unadjusted)		
0 accepted the alarm	126 (83%)	1.0 (ref.)
1 or more accepted the alarm	1,543 (90%)	1.78 (1.12-2.79)
Bystander CPR (adjusted)		
0 accepted the alarm		1.0 (ref.)
1 or more accepted the alarm		2.06 (1.28-3.32)
Bystander defibrillation (unadjusted)		
0 accepted the alarm	10 (7%)	1.0 (ref.)
1 or more accepted the alarm	227 (13%)	2.15 (1.12-4.15)
Bystander defibrillation (adjusted)		
0 accepted the alarm		1.0 (ref.)
1 or more accepted the alarm		2.04 (1.05-3.96)
30-day Survival (unadjusted)		
0 accepted the alarm	14 (9%)	1.0 (ref.)
1 or more accepted the alarm	253 (15%)	1.71 (0.97-3.02)
30-day Survival (adjusted)		
0 accepted the alarm		1.0 (ref.)
1 or more accepted the alarm		1.61 (0.90-2.86)

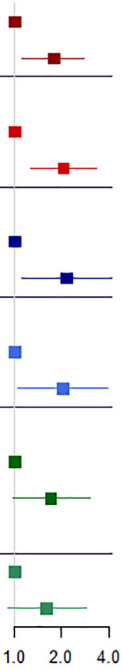


FIGURE 3
(A) Odds ratio and adjusted odds ratio of association between arrival at out-of-hospital cardiac arrest (OHCA) site of volunteer responder and bystander cardiopulmonary resuscitation and bystander defibrillation with alarm not accepted as reference. **(B)** Odds ratio and adjusted odds ratio of association between alarm acceptance and bystander cardiopulmonary, bystander defibrillation and 30-day survival with alarm not accepted as reference.

an initial shockable rhythm survival increased non-significantly to 39% when at least one volunteer responder accepted the alarm compared to cases where no one accepted the alarm (29%, $p = 0.36$). This difference might indicate a potential to improve survival and that the statistical insignificance could be a result of lack of power, due to the limited number of OHCAs in the study where no volunteer responders accepted the alarm. However, the 30-day survival presented in this study is comparable to the overall survival rate after OHCA in Denmark in 2020 (14%) (13). Yet another study by Stieglis et al. from 2021 demonstrated increased 30-day survival in residential locations after implementing a volunteer responder program (7).

The UK GoodSAM system also demonstrated a difference in 30-day survival between the alarmed and not-alarmed group [London; 17.6 vs. 10.3%, 3.15 95% CI (1.19–8.36)] but interestingly, also found a difference between the groups of alarm accepted and not-accepted [3.06 95% CI (1.0.–9.03)] (10).

Currently, available studies demonstrating differences in 30-day survival are all observational studies and presenting small absolute numbers of survivors. This increases the risk of confounding and misinterpretation. Furthermore, most available studies compare volunteer responder activation with no activation which is problematic as it further increases risk of inducing both bias and confounding to the analysis as several factors related to the circumstances of the OHCA differ. To fully understand the effect of volunteer responder systems, randomized controlled trials are warranted and currently being conducted in the US/Canada (PulsePoint Study; NCT04806958) and Denmark (HeartRunner Trial; NCT03835403) (36).

Implications of more detailed data

As demonstrated by the findings in this study, data reporting and selection of variables in volunteer responder programs have a big impact on results and the interpretation hereof. We found a clear tendency toward higher odds for bystander CPR and defibrillation in the cases where volunteer responders arrived at site and further with arrival before the EMS compared to only reporting data with respect to whether the volunteer responders accepted the alarm or not. This demonstrates why it is difficult to compare studies with different exposure and outcome variables (37) and supports the importance of having detailed data available for correct interpretation. A greater uniformity with international consensus on reported measurement variables could improve translation and sharing of knowledge (38).

Strengths and limitations

Within the variables "arrival at site" and "arrival prior to EMS" we saw a large number of missing values as some volunteer responders have not completed the survey which should be taken into consideration. This study is limited as it is an observational study why we can only investigate associations and not causal effects. The EUROSAT degree of urbanization system (DEGURBA) (21) was used to stratify population density. This was the best tool available but arguably has some limitations such as very broadly defined subcategories which could run the risk of overlooking finer details on the population map.

Conclusion

We observed a fourfold increased odds ratio for bystander CPR and threefold increased odds ratio for bystander defibrillation in OHCAs where volunteer responders accepted the alarm and arrived before EMS compared to cases where no volunteer responders accepted the alarm. We saw no difference in 30-day survival when volunteer responders accepted the alarm.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to fredrik.folke@regionh.dk.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CN: study conception and design, analysis and interpretation of data, and writing the manuscript. LA, CH, UV, EC, and CT-P: interpretation of data and revision of manuscript. AE: statistical review, analysis and interpretation of data, and revision of manuscript. FF and MG: study conception and design, analysis and interpretation of data, and revision of manuscript. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1030843/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Directed acyclic graph showing the included variables and possible confounders for bystander cardiopulmonary resuscitation as outcome.

SUPPLEMENTARY FIGURE 2
Directed acyclic graph showing the included variables and possible confounders for bystander defibrillation as outcome.

SUPPLEMENTARY FIGURE 3
Directed acyclic graph showing the included variables and possible confounders for 30-day survival as outcome.

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Management of hemodynamically stable wide QRS complex tachycardia in patients with implantable cardioverter defibrillators

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Management of hemodynamically stable, incessant wide QRS complex tachycardia (WCT) in patients who already have an implantable cardioverter defibrillator (ICD) is challenging. First-line treatment is performed by medical staff who have no knowledge on programmed ICD therapy settings and there is always some concern for unexpected ICD shock. In these patients, a structured approach is necessary from presentation to therapy. The present review provides a systematic approach in four distinct phases to guide any physician involved in the management of these patients: PHASE I: assessment of hemodynamic status and use of the magnet to temporarily suspend ICD therapies, especially shocks; identification of possible arrhythmia triggers; risk stratification in case of electrical storm (ES). PHASE II: The preparation phase includes reversal of potential arrhythmia "triggers", mild patient sedation, and patient monitoring for therapy delivery. Based on resource availability and competences, the most adequate therapeutic approach is chosen. This choice depends on whether a device specialist is readily available or not. In the case of ES in a "high-risk" patient an accelerated patient management protocol is advocated, which considers urgent ventricular tachycardia transcatheter ablation with or without mechanical cardiocirculatory support. PHASE III: Therapeutic phase is based on the use of intravenous anti-arrhythmic drugs mostly indicated in this clinical context are presented. Device interrogation is very important in this phase when sustained monomorphic VT diagnosis is confirmed, then ICD ATP algorithms, based on underlying VT cycle

length, are proposed. In high-risk patients with intractable ES, intensive patient management considers MCS and transcatheter ablation. PHASE IV: The patient is hospitalized for further diagnostics and management aimed at preventing arrhythmia recurrences.

KEYWORDS

wide QRS complex tachycardia, ICD programming, anti-tachycardia pacing, ICD therapies, treatment of ventricular tachycardia

1. Introduction

Based on data from a survey performed in the UK (1), the prevalence of ventricular arrhythmias is between 0.25 and 0.5% and higher in patients older than 65 years of age. A minority of cases with wide QRS complex tachycardia (WCT), do not have ventricular tachycardia (VT), but rather a supraventricular tachycardia (SVT). Of these patients only a minority also have an implantable cardioverter defibrillator (ICD). Patients that do have an ICD, are by definition, at higher arrhythmic risk, because they have an underlying arrhythmic heart disease. Cardiac arrhythmic diseases implicate, most frequently the presence of underlying structural heart disease (SHD) or, less frequently, an inherited primary arrhythmia syndromes (IPAS), namely long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), early repolarization syndrome (ERS), or idiopathic ventricular fibrillation (IVF).

In a single-center experience, cumulative incidence of any form of appropriate ICD therapy at 10 years for secondary prevention indication patients was 65% (2). In an another single-center contribution, the rate of ventricular arrhythmic episodes that occurred at 2 years follow-up was roughly 20% in patients with primary prevention indication compared to 37% in patients with an ICD in secondary prevention (3).

As may be extrapolated from the epidemiological data, the prevalence of an incessant, hemodynamically stable WCT in ICD patients is an uncommon event (roughly 0.5–1.0%/year). Preparing the staff through the implementation of some fairly simple measures could be of great assistance for adequate and regular management. The fact that the patient who presents has an ICD, and despite this, presents with sustained WCT, may be a source of concern that the ICD may deliver shocks unexpectedly.

General management of WCT in the emergency setting has been addressed in the most recent European practical guidelines on the management of supraventricular tachycardia (4). WCT may be supraventricular or sustained monomorphic ventricular tachycardia (VT). Although hemodynamically stable VT may not present immediately with signs and symptoms of organ hypoperfusion, the clinical situation may deteriorate suddenly and rapidly, especially in "high-risk" patients with electrical storm (ES). ES is defined as the occurrence of 3 or more distinct episodes of VT within 24 h (5) or incessant VT for more than 12 h (6). In ICD patients who present with a sustained WCT, patient management differs in three ways:

(1) The ICD may deliver unnecessary or inappropriate shock and therefore a magnet may be utilized temporarily to withhold anti-tachycardia therapies.
(2) If no shocks have been delivered, 1 or more of these conditions may be present.
    (a) The arrhythmia cycle length (CL) is below that of the therapy window.
    (b) The WCT is supraventricular and discriminating algorithms have adequately detected and interpreted the arrhythmia.
    (c) Only anti-tachycardia pacing therapies (ATPs) without shocks were programmed in the slower VT window and the device is now in "ATP time out" mode, i.e., a programmable maximum time duration during which ATP was permitted to continue.
(3) Manual programming of ATP bursts, scans and/or ramps to terminate WCT may be programmed, without the need for deep sedation and electrical cardioversion.

This review discusses the diagnosis and treatment by proposing a structured approach for the optimal management of hemodynamically stable sustained WCT in ICD patients. The document is structured in four parts. In the first part,

Abbreviations: AF, atrial fibrillation; AT, atrial tachycardia; ATP, anti-tachycardia pacing; AV, atrio-ventricular; AVNRT, atrio-ventricular nodal reentry tachycardia; AVRT, atrioventricular reentry tachycardia; BrS, Brugada syndrome; CAD, coronary artery disease; CL, cycle length; CPR, cardio-pulmonary resuscitation; CPVT, catecholminergic polymorphic ventricular tachycardia; CRT-D, cardiac resynchronization ICD; DC ICD, dual-chamber ICD; EP, electrophysiological; ERS, early repolarization syndrome; ES, electrical storm; FVT, fast ventricular tachycardia; ICD, implantable cardioverter defibrillator; IPAS, inherited primary arrhythmia syndrome; IVF, idiopathic ventricular fibrillation; LQTS, long QT syndrome; LVEF, left ventricular ejection fraction; MCS, mechanical cardiocirculatory support; PLSGB, percutaneous left stellate ganglion block; POCUS, point of care ultrasonography; PoliVT, polymorphic ventricular tachycardia; S-ICD, subcutaneous ICD; SC ICD, single-chamber ICD; SHD, structural heart disease; SQTS, short QT syndrome; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

the most relevant measures needed upon presentation of the patient are discussed, namely measures to avoid the delivery of unnecessary/inappropriate shocks, careful interpretation of the ECG, identification of eventual triggers, and patient risk stratification when presentation is ES. Management of patients who present with ES and a "high risk" profile should follow an accelerated management algorithm consisting in pre-alerting a tertiary center. In the second part, preparatory measures are presented, including contacting the anesthesiologist and, if available, the ICD specialist. In the third part, after evaluation, and especially based on whether an ICD specialist is available, the chosen therapeutic approach is applied. In the last part, further diagnostic and therapeutic measures that are usually indicated during the hospitalization of these patients are discussed.

2. PHASE I: Presentation of the ICD patient with hemodynamically stable WCT

2.1. Early assessment and inhibition of ICD therapies

Upon arrival in the emergency room (ER) or in the intensive care unit (ICU), the patient is immediately placed under continuous monitoring of heart rate, rhythm, and blood pressure. The patient's hemodynamic status is then assessed. Hemodynamically stability is established in the absence of life-threatening features; specifically, hemodynamic shock (systolic blood pressure < 80 mmHg with signs of peripheral hypoperfusion), syncope, severe heart failure (pulmonary edema or increased jugular venous pressure) and myocardial ischemia (chest pain in patient with known coronary artery disease) are excluded (7). In case one of these conditions are present, measures for rapid conversion to sinus rhythm are indicated consisting in synchronized electrical external cardioversion (5, 7). In patients with ICDs, some caution should be taken in the positioning of external defibrillation patches or when applying external defibrillation chest paddles as discussed below.

After confirming that the patient is hemodynamically stable, an external magnet may be applied on top of the ICD pulse generator to avoid inappropriate/unnecessary therapies. This is especially important in patients who have already experienced 1 or more ICD shocks upon presentation. While the ICD generator can is usually positioned in left subclavicular sub-cutaneous or sub-pectoral positions, the sub-cutaneous ICD (S-ICD) is located along the left midaxillary line. The S-ICD is an extra-vascular "shock box" most often indicated in young adult patients with either IPAS or a form of dilative cardiomyopathy in the absence of a pacing indication for bradycardia (8, 9). This type of ICD has shown reduction of long-term device-related complications (9–11) in different IPAS patient series. In pediatric patients with ICDs, the ICD generator is often located in the upper abdominal quadrants. **Figure 1** illustrates different ICD types, namely a transvenous single-chamber ICD, epicardial single chamber ICD, S-ICD and the anatomic position of the ICD can for each type. Magnet application deactivates tachycardia detection and/or anti-tachycardia therapy without influencing bradycardia pacing. Although in most ICDs and CRT-Ds, the pacing mode, sensor function, pacing polarity and intervals remain unchanged, some ICD devices behave differently. Most importantly, in Microport (former Sorin) ICDs, pacing mode, sensor function, pacing polarity and intervals do change during magnet response. Pacing output is increased to 6V @ 1 ms for each chamber, the sensor (R-function) is disabled. If the device is in "Mode switch" pacing is performed according to permanently programmed mode independently of underlying rhythm, and, in CRT-D devices, AV delay does not change, but VV delay is set to 0 ms. Several contributions have extensively described magnet response of ICDs [(12–14); refer to the "Appendix" for further details].

2.2. Twelve-lead ECG interpretation algorithms

Once the patient is monitored, a 12-lead surface electrocardiogram is performed (**Figure 2**). Different ECG diagnostic algorithms have been proposed for the diagnosis of WCT. Some of these algorithms are simple, others are more complex. The most comprehensive and accurate algorithm is, in fact, based on a systematic and structured approach (15) which integrates clinical features (patient history and comparison of a previous ECG for example) (16–18), pathognomonic ECG features for the diagnosis of VT (18), and morphological features of VT in the precordial leads (19) and in a VR (20) (**Figures 2**, **3**).

2.3. Laboratory tests and echocardiography

At the same time, a routine blood test is performed including determinations of potassium, sodium, magnesium levels, high-sensitive Troponin, creatinchinase (total and MB), creatinine, glomerular filtration rate, hemoglobin, hematocrit, CRP, D-dimers, BNP, and white blood cell count, thyroid-stimulating hormone. Electrolytic alterations, myocardial injury, renal impairment, anemia, hypovolemia, heart failure, inflammation or infection may all act as triggers, especially in the presence of a vulnerable myocardial substrate (**Figure 4**).

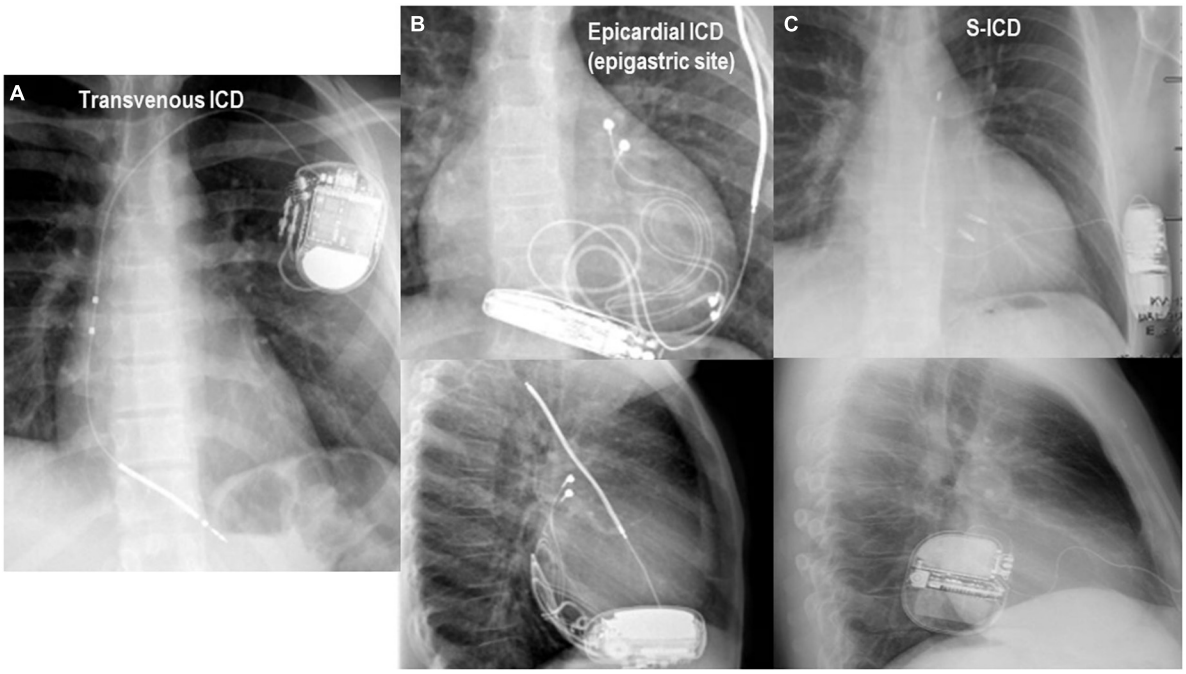

FIGURE 1
Chest X-ray in anterior-posterior and lateral projections are important for the identification of the type of implantable cardioverter defibrillator (ICD) and for the application of the magnet which should be fixed on top of the ICD can for disabling therapies. **(A)** Panel shows the typical position of a transvenous ICD immediately below the left clavicula. **(B)** Panel shows the radiologic antero-posterior and lateral projections in an 8 year-old girl with an epicardial ICD and the can located in the epigastric area. In panel **(C)**, the typical position of the S-ICD system is appreciated.

Depending on the clinical phase, point of care ultrasonography (POCUS), provides further assistance for the identification of potential mechanical triggers (pericardial effusion, signs of acute pulmonary hypertension, etc.) and/or characterization of cardiac chambers, contractility of both ventricles as well as anatomy and function of cardiac valves (21).

2.4. Electrical storm: Identification of the "high-risk" patient

It is important to establish whether the current episode of sustained hemodynamically stable WCT is ES, since this situation entails elevated intra-hospital morbidity and mortality, especially in clinically compromised patients. ES is often an arrhythmic situation associated with compromised left ventricular systolic function, with heart failure symptoms, and other comorbidities (22, 23). One study found that in CRT-D patients as well, ES was associated with non-ischemic heart disease, ICD secondary prevention indication, and with persistent heart failure symptoms and low LVEF despite CRT (24). Unfavorable prognosis following ES is determined by low LVEF, ICD secondary prevention indication, advanced NYHA class, and the presence of comorbidities such as chronic obstructive lung disease (25, 26). Therefore, if the patient presents a "high risk" profile, an accelerated management protocol should be activated, that includes pre-alerting a tertiary clinic for eventual urgent therapeutic measures such as transcatheter ablation with or without mechanical cardiocirculatory support (MCS) bridging (see parts "4.4.3 Left ventricle unloading" and "4.4.4 Radiofrequency catheter ablation").

3. PHASE 2: Preparation for therapy

For patient clinical stabilization, several non-anti-arrhythmic measures are taken according to the clinical picture as well as the laboratory results. These include, correction of electrolytes and/or volume depletion, and mild sedation. Sometimes, as is the case with first-aid measures, these may determine interruption of the arrhythmia.

Once the patient is monitored and stabilized, the anesthesiologist/intensive care teams and, depending on available resources, the ICD clinic are notified for the organization of the therapeutic plan. Anti-arrhythmic treatment then follows and mainly depends on the availability of a device specialist for device check and, eventually, delivery of anti-tachycardia ICD-based therapies.

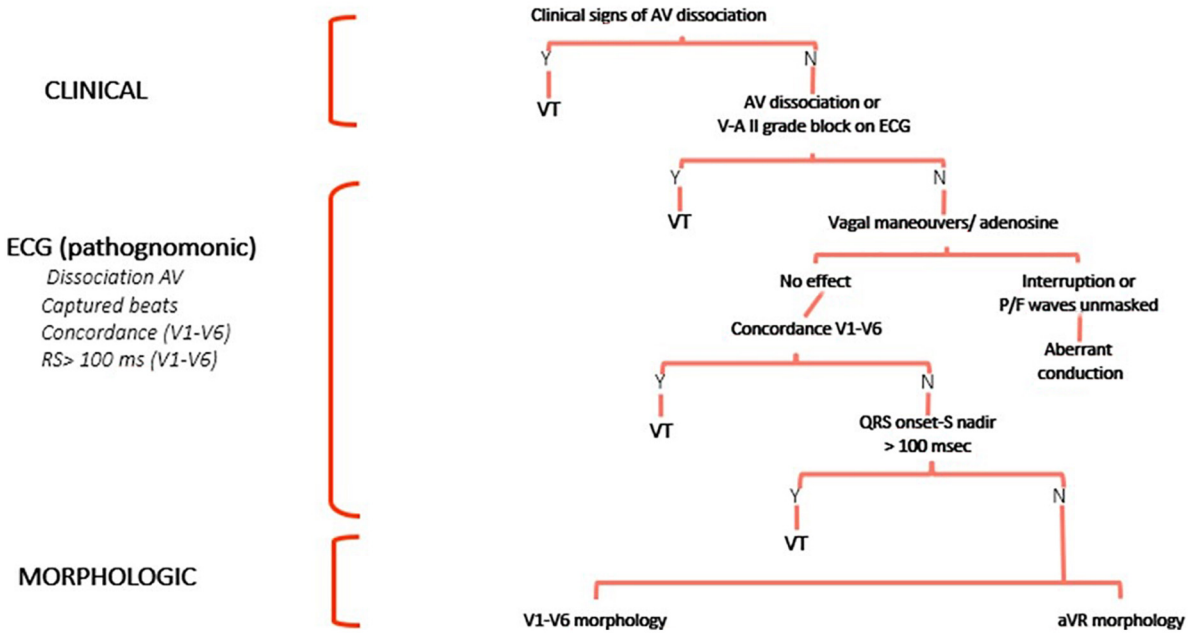

FIGURE 2
Proposed systematic and structured diagnostic tree for the ECG diagnosis of wide QRS complex tachycardia (WCT). AV, atrio-ventricular; V-A II grade block: retrograde "P" wave is present after the end of the QRS complex with a 2:1 sequence; VT, ventricular tachycardia.

While the same preparatory measures should be followed for the "high-risk" patient with ES, these should be implemented rapidly.

4. PHASE 3: Anti-arrhythmic therapies

4.1. Conversion to sinus rhythm when device-based therapies cannot be delivered

Patient treatment depends on the type of ICD and whether a device specialist is readily available. In the event that the device model is an S-ICD, and/or that a device specialist is not readily available, then a stable WCT should be treated according to the proposed management algorithm of the Guidelines (4, 5). In patients with SHD, if there is a low suspicion of reentry SVT or after vagal manoeuvers and adenosine have failed, intravenous amiodarone is the drug of first choice. For the management of hemodynamically stable ES either endovenous amiodarone or non-selective beta-blocker are recommended. In this setting, propranolol is superior to metoprolol (27). Endovenous procainide is also effective for suppression of stable VT, but should not interact with sotalol or amiodarone and is not always available. Less commonly, as second line treatment, the use of endovenous lidocaine (4, 5, 7) (**Figure 5**) may be considered. **Table 1** summarizes the main therapeutical measures indicated in patients with WCT who have underlying SHD.

The management of IPAS deserves specific consideration, because this group includes a wide spectrum of different arrhythmic diseases. For the arrhythmic management of these patients, immediate contact with a specialized tertiary is highly recommended.

In long-QT syndrome (LQTS) stopping QT-prolonging drugs is of pivotal importance. Potassium supplement and spironolactone have been proposed for LQTS2. Class Ia Mexiletine and class Ic Flecainide have been proposed for LQTs3 (enhanced sodium channel function) (28, 29). Available data suggest the efficacy of Quinidine therapy in short-QT syndrome, by prolonging the QTc interval (30–32). Drug efficacy of Quinidine is maintained in the long-term (33). Class Ic Quinidine as well as isoprotenerol or temporary atrial overdrive pacing in patient with dual-chamber ICD may interrupt an incessant or recurring VT in Brugada Syndrome and early repolarization syndrome. These measures prevent premature ventricular beats during bradycardia and reduce early after-depolarization (34). Moreover, aggressive control of temperature is a significant part of the comprehensive management for patients with Brugada syndrome (34–37). Betablockers, sedation as well as flecainide have been

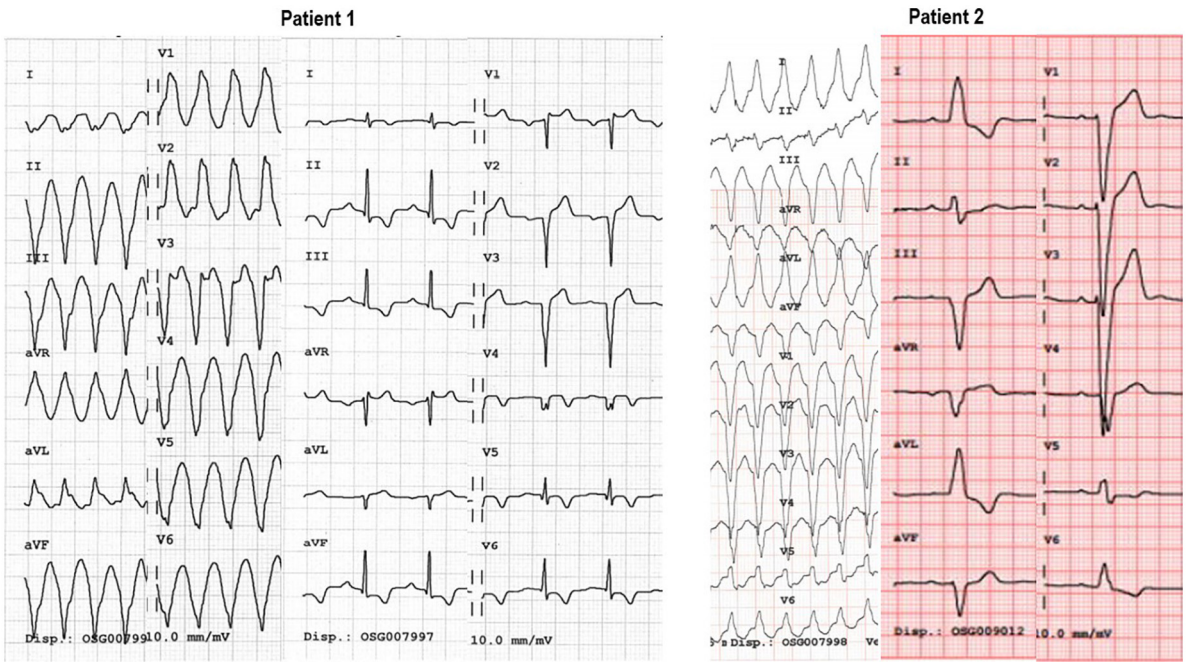

FIGURE 3
In this 49 year old patient (Patient 1) with a previous antero-septal infarct several years before, WCT at 190 bpm, QRS axis is deviated to the right; atypical RBBB morphology and the presence of a monophasic R wave in aVR indicate VT. The ECG at rest in sinus rhythm, shows the absence of an R wave from V1-V6 indicative of antero-septal transmural necrosis. Patient 2 presents with a WCT at 180 bpm, with a normal QRS axis and typical LBBB pattern in the precordial leads (QS in V1, monophasic R-wave in V6). QRS morphology in sinus rhythm is the same as the one during tachycardia. Intravenous adenosine, allowed to diagnose atrial tachycardia conducting with LBBB.

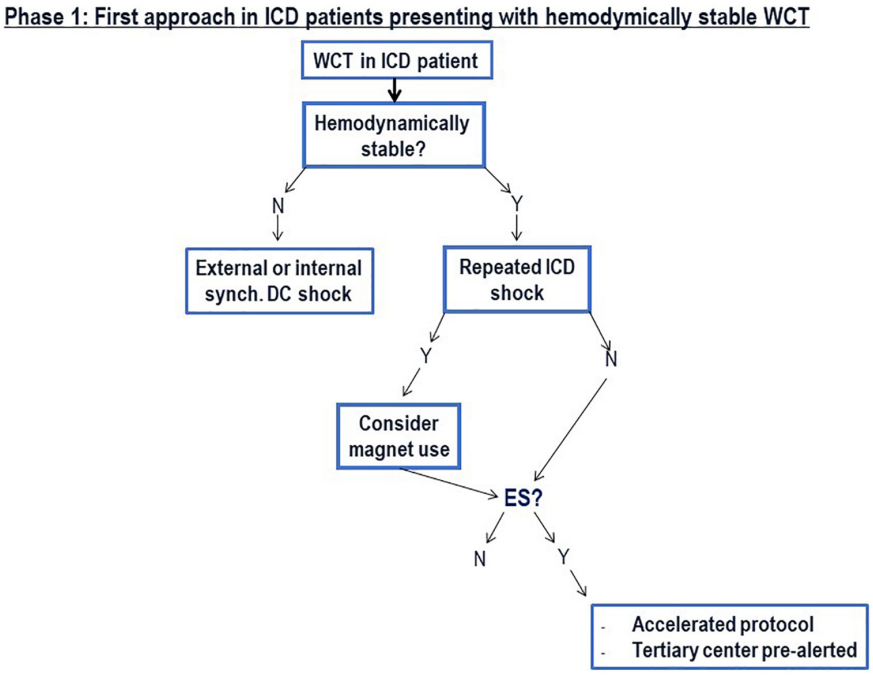

FIGURE 4
The different steps of the first phase are summarized.

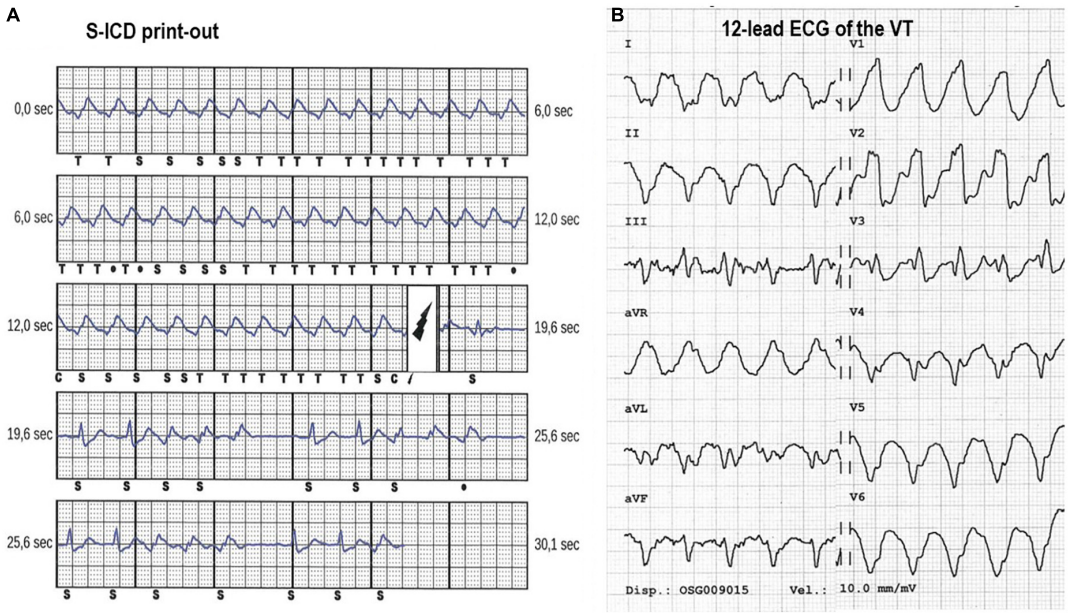

FIGURE 5
(A) Panel shows the print-out of the S-ICD electrogram of a 46 year old patient with dilatative cardiomyopathy. The ventricular tachycardia at 160 bpm with shock therapies set at 200 bpm. The device electrogram (EGM) shows how there is double-counting of the QRS due to T-wave oversensing and a 80 Joules shock is delivered with successful interruption of the arrhythmia. **(B)** Panel shows the ECG of the VT. The patient experienced repeated shocks following gastroenteritis with hypokalemia without loss of consciousness. The arrhythmia was successfully controlled by hydration, intravenous KCl, and intravenous 150 mg of amiodarone (the patient was already under chronic treatment with amiodarone).

implemented for patients with catecholaminergic polymorphic ventricular tachycardia (38–40).

Should the patient require external electrical cardioversion because of onset of hemodynamically instability, because other measures have failed, or because this is the preferred approach, then caution should be taken in the positioning of the defibrillation patches and/or paddles (41). Positioning of the patches should be either in apex-anterior or apex-posterior positions in such a way that the defibrillation current vector is distant from the defibrillator generator. In patients with an S-ICD, the patches should be placed anteriorly along the right parasternal line and dorsally left of the thoracic spine.

High-energy synchronous shock should be delivered. If patches are not effective, suspect inadequate contact or vector and switch to manual cardioversion with the paddles. Conversion to sinus rhythm of WCT through external electrical cardioversion is safe and effective if applied correctly.

4.2. Conversion to sinus rhythm by device-based therapies

The availability of a device specialist allows ICD interrogation. The presence of a transvenous ICD during a hemodynamically stable WCT has several implications. First, confirmation of the diagnosis of the WCT may be achieved; second, delivering atrial or ventricular pacing burst or ramps may effectively terminate the arrhythmia; third, effective ATP algorithms may then be programmed to treat future recurring arrhythmic events. Importantly, S-ICD is a "shock-only" ICD device and cannot deliver ATP.

4.2.1. Fundamental concepts and clinical data on non-shock-based ICD treatment of arrhythmias

Whether the origin of the sustained WCT is supraventricular or ventricular, the underlying mechanism is most likely reentry. Being able to terminate a reentry arrhythmia by delivering a train of impulses is based on the concept that effective entrainment, i.e., the train of impulses has entered the excitable gap of the reentry circuit and "unpins" the reentry rotor through entrainment, creates another pacing-induced and sustained rotor, which is interrupted when pacing is stopped. While in theory this principle is quite effective to terminate slower supraventricular and ventricular arrhythmias, its effectiveness is limited for higher frequency VT and for atrial fibrillation (multiple rotors and wave fronts) (42–44).

Clinical data concerning the termination of SVT using ICD-based pacing algorithms is limited to experience and knowledge derived from electrophysiological studies. Reentry atrial tachycardia (AT), atrioventricular node reentry tachycardia (AVNRT), and atrioventricular reentry tachycardia (AVRT) are

TABLE 1 Therapeutic measures used for conversion to sinus rhythm and for ventricular rate control during hemodynamically stable wide QRS complex tachycardia.

Measures	Dosages	Remarks and precautions
Vagal manoeuvers	/	"Modified" vagal manoeuver is more effective to interrupt AVNRT or AVRT
Adenosine i.v.	6–18 mg	No evidence of pre-excitation at baseline ECG Suspect of AVNRT or orthodromic AVRT
Amiodarone i.v.	300 mg push, followed by 150 mg push 1–2 g/24 h	During ES in SHD
Procainide i.v.	10 mg/kg in 20'	Stable monomorphic VT Caution in pts under amiodarone or sotalol Watch for hypotension and QRS prolongation Limited availability
Propranolol p.os.	40 mg/6 h	ES/VT with stable blood pressure
Metoprolol i.v.	5 mg push every 5', to max of 15 mg	ES/VT with stable blood pressure
Lidocaine i.v.	1 mg/kg push 1–2 mg/min	2° line therapy in stable monomorphic VT

Listed anti-arrhythmic drugs are those indicated in patients with structural heart disease (SHD). AVNRT, atrio-ventricular node re-entry tachycardia; AVRT, atrio-ventricular re-entry tachycardia; ES, electrical storm; SHD, structural heart disease; VT, ventricular tachycardia.

amenable to effective atrial burst pacing because the arrhythmia cycle length (CL) is not too short and it is easier to penetrate into the circuit for entrainment by using bursts that are 15–20% shorter than the SVT CL.

Importantly, short bursts of ventricular pacing at a programmable shorter cycle length than the arrhythmia may effectively terminate VT (45, 46). Different ATP modalities may be programmed, including fixed rate burst and ramp pacing ATPs. Ramp designates a sequence of programmed pulses in which each pulse is delivered at a progressively slightly shorter interval than the previous one.

Anti-tachycardia pacing in the VT window (<185 bpm) are usually programmed in secondary prevention patients with previous known stable monomorphic VT (47, 48). The first sequences are usually bursts with pulse increments between each scan, followed by several trials of ramps with progressively shortening of CL between pulses. The study by Schaumann et al. (49) tested an empiric ATP sequence scheme in patients implanted with an ICD in whom no stable VT was inducible during an EP study. In this study, most of the patients were implanted in secondary prevention and in more than half of the patients ICD therapies were programmed in the VT window (<185 bpm). The empiric ATP algorithm consisted in three trials of autodecremental ramps with 8–10 pulses, 8 ms decrement between each pulse, starting with CL of 81% of the detected VT. The minimal interval between pulses was set at 200 ms. The effectiveness of this ATP scheme to terminate VT was 90%, while 5% of patients experienced acceleration following ATP delivery.

Concerning ATP delivery for the treatment of fast ventricular tachycardia (FVT > 185 bpm), several large multicenter clinical trials have shown the safety and the effectiveness of programming 1 ATP of eight pulses, at 85–88% of VT CL (50, 51), in primary prevention, including CRT patients with non-ischemic heart disease etiology (52) and in secondary prevention patients (53), showing a significant reduction of any ICD shock. Shock reduction in these studies was not only determined by the effects of a standard ATP algorithm for the treatment of FVT, but this ATP algorithm was programmed in combination with long detection intervals as well as SVT discrimination features.

Later multicenter studies have demonstrated the relative value of ATP for VT and FVT termination, regardless of indication and underlying heart disease (46, 53). Some additional studies have further demonstrated that delivering a single biventricular ATP burst in patients with CRT-D and ischemic etiology (46) may effectively interrupt FVT and reduce shocks.

4.2.2. Anti-tachycardia pacing delivery in the emergency setting

As the device is being interrogated during the arrhythmia, it is important to have identified the type of device (S-ICD, transvenous single-, dual-chamber, or CRT-D device) and to have knowledge of the device electrophysiological (EP) features (**Table 2**). Apart from single chamber ICD devices, some other manufactures do not offer the possibility to stimulate the atrium. This is the case of MicroPort devices. In patients who present such devices, they should be treated like S-ICD recipients.

The possibility to deliver rapid burst pulses manually (Abbott and Biotronik ICDs) from both the atrium and the ventricle, allows to rapidly activate ATPs and may avoid excessive stimulation, thus reducing the risk of arrhythmia acceleration or degeneration in AF for the atrium or VF in the ventricle, respectively. Although there are no data to support this, in experienced hands this feature is preferred. **Figure 6** proposes a decision tree for the WCT management in ICD patients considering different ICD models, ATP algorithms and VT cycle length. **Table 3** proposes a step-wise approach for the programming of ATPs based on VT rate.

4.2.2.1. Burst pacing from the atrium to terminate SVT

During reentry supraventricular tachycardia, delivering burst pacing manually or through programmed burst algorithms, by starting with 80–85% CL is recommended.

By keeping the same interval, therapy effectiveness may be obtained by lengthening the train of pulses and increasing energy output. If the arrhythmia persists, shorten CL < 80%. In these cases, if the SVT degenerates in AF the ventricular response is usually lower and partial clinical benefit may result, and therefore there is less concern about the effects of acceleration at the level of the atrium.

4.2.2.2. Anti-tachycardia pacing delivery for VT < 185 bpm

Even though the ATP scheme proposed by Schaumann (45) is highly effective, current ICD programming guidelines recommend to begin by delivering 8–10 pulses at 75–85% CL and progressively to lengthen pulses and shorten CL until 75% (43, 44). If after 4–5 trials of ATP the arrhythmia persists unchanged, then delivery of ramps according to the Schaumann scheme (10 pulses, 81% ramp, with 8 ms decrement between pulses) ensues, ensuring that a minimum CL interval between pulses ≥ 200 ms is programmed.

4.2.2.3. Anti-tachycardia pacing delivery for VT ≥ 185 bpm

During sustained FVT (≥185 bpm), consider starting with eight pulses, at 85–88% CL; if ineffective, strengthen by increasing pulse number to 10–12 and, lastly, program scans with 5% decrement, respectively. Programming ramps is not recommended for FVT, and decrementing should be made with caution especially in VT with high rates. In patients with ischemic etiology and CRT-D devices with biventricular burst capability (Medtronic, Biotronik, and Boston Scientific CRT-D devices), consider delivering biventricular bursts following the same sequence of attempts (54).

4.3. Anti-tachycardia pacing do not interrupt supraventricular tachycardia

When vagal maneuvers as well as repeated ATPs do not allow termination of WCT, further treatment depends on the persistence of hemodynamic stability, and the severity of underlying heart disease. When aberrant SVT is suspected, and no structural heart disease known, procainamide can be used (4, 5).

4.4. Anti-tachycardia pacing do not interrupt ventricular tachycardia

4.4.1. First-line management

When repeated ATPs do not terminate VT or there is immediate VT recurrence, further treatment depends on the persistence of hemodynamic stability, on VT cycle length, and the severity of underlying heart disease. If there is concern for accelerating the VT or for degeneration in VF, the best choice is to consider electrical external cardioversion, after having repeated ATP attempts with the patient under sedation. Actually, repeated ATPs may cause shortening of the CL and morphology change of the VT as well as induce VT. Further management depends on hemodynamic conditions, the characteristics of the new VT (CL and stability), and on programmed ICD settings. If the new, more rapid VT is still below the set ICD therapy window and the patient remains stable, then ATP delivery should be repeated by considering the CL of the new VT. If the accelerated VT falls within the therapy window then the ICD will intervene as programmed. Degeneration in VF will trigger ICD shock (**Figure 7**).

Alternatively, if the patient remains stable, further mild sedation with midazolam may be performed and beta-blocker can be administered before delivering ATPs once again (**Table 1**). The latter is particularly indicated in cases of incessant slow VT and mild to moderate compromised left ventricular systolic function.

4.4.2. Sympathetic drive management

The autonomic nervous system plays a major role in the pathophysiology of arrhythmias potentially leading to sudden cardiac death. Sympathetic hyperactivity plays a critical role in VT onset and maintenance, thus modulation of neuro-axial efferent cardiac neurotransmission may be a target (55, 56). In case of hemodynamic instability and refractory or recurrent VT despite ATP, electrical cardioversion and antiarrhythmic drugs as well as deep sedation may be attempted to reduce the sympathetic drive. Recent experiences reported high efficacy of conversion to sinus rhythm of incessant VT in selected patients by performing percutaneous left stellate ganglion blockade (PLSGB) (57, 58).

4.4.3. Left ventricle unloading

In patients with a "high risk" profile who present with sustained hemodynamically stable WCT, especially when ES, acute decompensation and cardiogenic shock may occur rapidly, especially if the first therapeutic measures are ineffective to control the arrhythmia (59). In such patients, required measures should be undertaken to consider and prepare for MCS (60). The hemodynamic support obtained from a chosen MCS is an effective rescue treatment for cardiogenic shock secondary to VT refractory to medical therapy and sedation. LV unloading by MCS in this setting improves end-organ perfusion and may contribute to sinus rhythm conversion (61, 62). MCS may provide hemodynamic support for VT ablation when a bailout transcatheter ablation procedure is needed to treat refractory VT. Moreover, MCS and catheter ablation have shown a synergic role to achieve electric and hemodynamic stabilization (63).

Various MCS techniques have been studied and used in clinical practice in secondary and tertiary centers.

TABLE 2 Available implantable cardioverter defibrillator (ICD) device features for each manufacturer for stimulation of the atrium and/or the ventricle during tachycardia.

Manufactures	Function on the programmer	Atrial therapy*§	Manual burst method in atrium (A) and ventricle (V)	Commanded bursts/Programmed PES in atrium (A) and ventricle (V)	Biventricular bursts**	Comments
Abbott	NIPS	√	√(A) √(V)	√(A) √(V)	X	
Biotronik	A: NIPS V: DFT (EPS/ATP)	√	√(A) √(V)	√(A) √(V)	√	
Boston Scientific	EP tests	√	√(A) X(V)	√(A) √(V)	√	For termination of atrial arrhythmias high rate pacing (50 Hz) may be delivered
Medtronic	EP study	√	X	√(A) √(V)	√	
MicroPort	X	X	X	X	X	ATPs from the V according to standard procedure under "Tachycardia" heading

A, atrial chamber; V, right ventricular chamber; √, feature is available in recent generation ICD models. X, feature is not available.
*Dual-chamber and CRT-D models.
**Recent generation CRT devices (Medtronic, Biotronik, and Boston Scientific) fixed bursts and programmed electrical stimulation may be performed using biventricular stimulation.
§PM-dependent ensure that back-up pacing is activated.

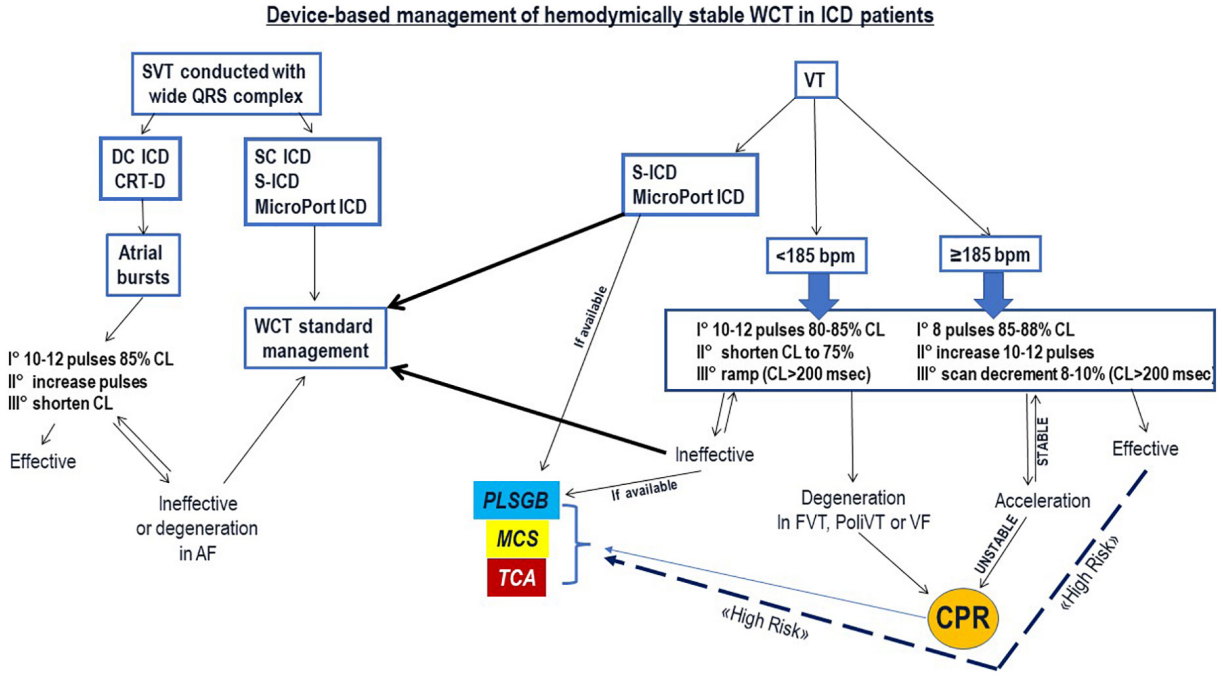

FIGURE 6
The figure proposes a device-based management algorithm for the treatment of wide QRS complex tachycardia (WCT) in ICD patients, based on the type of ICD, specific ICD features according manufacturer, and stimulation therapies delivery from the atrium (in case of supraventricular tachycardia) or from the ventricle (in case of ventricular tachycardia). AF, atrial fibrillation; CL, cycle length; CPR, cardio-pulmonary resuscitation; CRT-D: cardiac resynchronization ICD; DC ICD, dual-chamber ICD; FVT, fast ventricular tachycardia; MCS, mechanical cardio-circulatory support; PLSGB, percutaneous left stellate ganglion block; PoliVT, polymorphic ventricular tachycardia; S-ICD, subcutaneous ICD; SC ICD, single-chamber ICD; SVT, supraventricular tachycardia; TCA, transcatheter ablation; VT, ventricular tachycardia.

Intra-aortic balloon pump (IABP) is the most widely used device in low-output states. IABP decreases LV pressures and increases stroke volume, however, IABP has been recently downgraded in various guidelines (63). Percutaneous axial blood flow pump such as the Impella are increasingly used. Impella devices entrain blood from the LV and pump it into the aorta, thus unloading the LV (64). Lastly, extracorporeal membrane oxygenation

TABLE 3 Proposed step-wise approach for the programming of anti-tachycardia pacing therapies (ATPs) based on the rate of the ventricular tachycardia.

	VT < 185 bpm	FVT ≥ 185 bpm
Burst	8–10 pulses at 75–85% VT CL	Eight pulses at 85–88% VT CL
Scans	Decrement scans by 5% until 75%	I° increment pulses to 10–12 II° decrement scans by 5% until 78%, and for each scan with CL shortened increase pulses to 10–12, before further shortening*
Ramps	I° 10 pulses, 81% VT CL, 8 msec decrement* II° 10 pulses, 75% VT CL, 8 msec decrement* III° 10 pulses, 75% VT CL, 10-12 msec decrement*	Ramps are not recommended in FVT

*Minimum CL between pulses > 200 msec. CL, arrhythmia cycle length; FVT, fast ventricular tachycardia; VT: ventricular tachycardia.

extracorporeal membrane oxygenation (ECMO) is a portable modification of a cardiopulmonary bypass providing cardiopulmonary support for patients with refractory shock with or without multi-organ failure (63). Large randomized clinical trials comparing different devices and different timing strategies are lacking.

4.4.4. Radiofrequency catheter ablation

Catheter ablation is an important treatment option in tertiary centers for the management of incessant VT or ES. Urgent catheter ablation is recommended in "high-risk" patients with scar-related incessant VT or ES with or without MCS support (65). Moreover, catheter ablation is recommended in patients with ischemic heart disease and recurrent effective ICD shocks due to sustained VT (66, 67). Most monomorphic VT have an origin or myocardial substrate that can be targeted for ablation. Catheter ablation risks and outcomes depend on the presence and type of structural heart disease as well as the mechanism, location, epicardial exit and acute setting of the VT (60). Catheter ablation by advanced strategies has been effectively applied to a various patient populations in the acute management of ES (65). However, catheter ablation of VT may results in various local and systemic complications, including stroke, valve damage, cardiac tamponade or AV block with a procedure-related mortality ranging from 0 to 3% (60). Moreover, urgent catheter ablation of VT is system-demanding because it requires experienced operators and

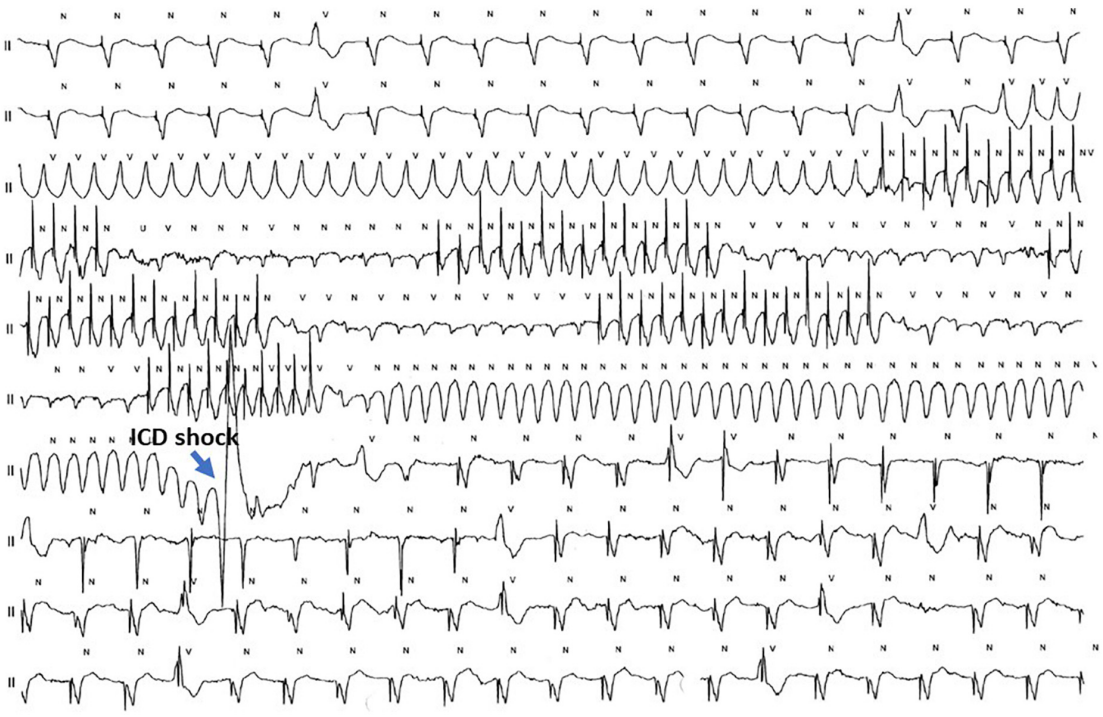

FIGURE 7
Telemetry of a 77 year-old CRT-D male patient with a dilated post-infarct heart disease, severely depressed left ventricular ejection fraction, chronic obstructive lung disease, and renal impairment who presents with electrical storm ("high-risk" profile). On the recording, the initial rhythm is a normal pacing rhythm in VDD modality with some single monomorphic premature ventricular beats (PVBs). A fast ventricular tachycardia (FVT) is triggered by the PVB. The first ATP burst of 14 pulses causes degeneration of the VT into a low-amplitude polymorphic FVT refractory to two ATP burst attempts. A 3rd ramp ATP causes degeneration into ventricular flutter which is terminated after a single ICD shock. This patient was stabilized with endovenous amiodarone and underwent transcatheter ablation on the next day.

advanced mapping and ablation equipment and staff support as well the need for on-call electrophysiological laboratory staff, anesthesiologists and surgical back-up. Therefore, the ablation management strategy is possible only in tertiary centers.

5. PHASE 4: Hospitalization and follow-up

After an ICD patient experiences sustained WCT which has been treated effectively, hospitalization ensues for completing diagnostics and implementing therapeutic measures for preventing recurrences. Further diagnostic evaluations aiming better myocardial substrate characterization include transthoracic echocardiography and/or cardiac magnetic resonance imaging. For better characterization of the arrhythmic substrate, particularly in the presence of frequent premature ventricular beats and episodes of non-sustained ventricular tachycardia, a 24–48 h 12 lead Holter electrocardiogram is useful for morphologic characterization and for the confirmation of medical therapy effectiveness (34).

Coronary artery angiography has a limited role for patients with hemodynamically stable WCT with a few exceptions. Urgent coronary angiography and, if indicated, revascularization are recommended for incessant VT or unstable patients when myocardial ischemia cannot be excluded or coronary artery disease (CAD) is suspected (34). Non-urgent coronary angiography is recommended in stable patients with or without dilated heart disease with an intermediate risk of CAD (34).

Long-term medical treatment is usually based on associating amiodarone with progressive up-titration of beta-blocker therapy (**Table 4**) in patients with SHD. In cases of recurrences, regardless of arrhythmia mechanism, and once reversible causes have been treated and corrected, transcatheter ablation is indicated. For recurring VT, several randomized controlled trials have demonstrated that trancatheter ablation is effective in preventing VT recurrences (68), especially if performed early on (69, 70).

Planning a diagnostic and therapeutic follow-up program is of fundamental importance for the prevention and long-term management of arrhythmic recurrences. Different medical figures, including the family doctor, the general cardiologist as well as the heart failure and arrhythmia specialists, should play a concerted role in the follow-up of these patients.

TABLE 4 Anti-arrhythmic measures used for the prevention of WCT recurrences when the diagnosis is ventricular tachycardia.

Anti-arrhythmic drug	Dosages	Remarks and precautions
Beta-blocker therapy (metoprolol, bisoprolol, or carvedilol)*	Up-titration to maximum tolerated dose	Prevents VT and SCD in patients with SHD through modest anti-arrhythmic effect
Sotalol	Starting dose: 40-80 mg BID Target dose: 120-160 mg BID	Monitor ECG (SR, QRS duration, and QT interval) Monitor renal function Contraindicated in advanced HF disease
Amiodarone	200–400 mg daily	Monitor multi-organ side-effects As with sotalol monitor ECG parameters
Mexiletine	200–400 mg TID	2° line treatment in combination with amiodarone Caution in pts with SHD
Flecainide	50–100 mg BID	In ARVD

*Patients with SHD besides up-titration of beta-blocker therapy, optimization of heart failure medication should be performed by ensuring that the therapeutic scheme is complete (includes ARNI, an anti-aldosteronic agent, and SGLTII agent) with adequate dosages. ARVD, arrhythmogenic right ventricular dysplasia; BID, twice a day; SCD, sudden cardiac death; SHD, structural heart disease; SR, sinus rhythm; TID, three times daily; VT, ventricular tachycardia.

6. Summary and conclusion

A structured and coordinated strategy is recommended for the management of every cardiovascular emergency, including hemodynamically stable WCT in ICD patients. As a first approach, basic knowledge of how to manage the ICD in this situation is important, by quickly recognizing ICD type and manufacturer, followed by application of the magnet to prevent unnecessary or inappropriate ICD shocks in a conscious patient. Differential ECG diagnosis is fundamental for further patient management as is rapid identification of potentially reversible arrhythmic triggers. Patients who present with ES, with severe underlying heart disease, heart failure symptoms, and comorbidities are "high risk" patients and should be channeled toward an accelerated management protocol that includes pre-alerting a tertiary center.

After these initial measures have been taken and the patient is stable, under mild sedation, anesthesiological and cardiological support are required for further management and appropriate anti-arrhythmic drug treatment may be delivered. Involvement of a device specialist and the ICD clinic, when available, is absolutely indicated. ICD device interrogation confirms diagnosis, and when a transvenous ICD is involved, ATP therapies may be delivered. When sustained VT is the diagnosis, specific ATP algorithms should be delivered according to VT cycle length, with particular attention in delivering ATPs that are not too aggressive to avoid conversion to VT with shorter CL or degeneration into VF, especially in the high risk patient. The proposed ATP algorithms are extrapolated from clinical studies and are empiric. These would merit evaluation through prospective multicenter studies, specifically

evaluating the safety and effectiveness of delivering ATP in patients who present with lasting incessant VT (71). If the arrhythmia is refractory to the various measures performed in the ER or the ICU further management is indicated through invasive procedures, specifically urgent transcatheter ablation (less commonly urgent coronary angiography) with or without bridging with MCS.

Clinical management of ICD patients presenting with hemodynamically stable WCT depends on a coordinated multidisciplinary effort which consists in defining the best strategy on a patient-to-patient basis. Prompt recognition of the type of ICD, of arrhythmic triggers, and of patients' general status are key for the optimal management of these challenging clinical scenarios.

Author contributions

FR, MC, and FK contributed to the conception and design of the manuscript to its final form. AT, HB, and LS contributed to the preparation of the tables, the figures, the reference list and by reviewing for content. All authors have contributed by reviewing the manuscript critically and approving the final version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Appendix

Specific responses of some ICDs when a magnetic field is detected

Specific aspects concerning application of an external magnet over an ICD can:

1. In Abbott and Boston Scientific ICDs magnet response is programmable and nominally programmed for inhibition of detection and therapies (Abbott) and only therapies in Boston Scientific transvenous ICD devices (while detection remains active). For other manufactures, magnet response is not programmable.
2. Different ICD models often release an acoustic signal when in contact with an electromagnetic interference, such as application of a magnet. The acoustic signal *does not* mean that the ICD will imminently deliver a shock.
3. Characteristics of acoustic signals are important to recognize for ICDs in which magnet response is programmable, namely for some Abbott and Boston Scientific models. In recent generation Abbott ICDs (Avant, Gallant, Entrant, and Neutrino) magnet mode initiation is indicated by emission of a 4 s tone (magnet mode termination by a 6 s higher tone). For most Boston Scientific transvenous ICDs a constant tone indicates "Monitor Only", unless the magnet response has been programmed "Off/Ignore". For Boston Scientific S-ICD, 60 s duration beeping confirms deactivation of detection and therapy. For older Boston Scientific ICD models, namely PRIZM, PRIZM 2, and VITALITY the acoustic signal changes from beep to continuous (therapies deactivated), while from continuous to beep signifies that the therapies are re-activated. In these older models, magnet repositioning causes switches in magnet response between "Off" and "Monitor + Therapy."
4. In Microport (former Sorin) ICDs, pacing mode, sensor function, pacing polarity and intervals do change during magnet response. Specifically, pacing output is increased to 6V @ 1 ms for each chamber, the sensor (R-function) is disabled, if the device is in "Mode switch" pacing is performed according to permanently programmed mode independently of underlying rhythm, and, in CRT-D devices, AV delay does not change, but VV delay is set to 0 ms.
5. For some ICD devices, detection ± therapy inhibition duration do not always follow magnet application. For Microport ICDs, therapy Inhibition may extend up to 2.5 min after magnet removal if a charge occurred just before magnet application. For Biotronik ICDs, after 8 h of continuous magnet application, tachy-detection/therapies are automatically re-enabled.

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Case report: Lamin A/C gene mutation in patient with drug-induced type 1 Brugada syndrome at high arrhythmic risk

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We report the case of drug-induced type 1 Brugada syndrome at high arrhythmic risk associated with Lamin A/C gene mutation.

KEYWORDS

arrhythmias, Brugada syndrome, Lamin A/C mutation, flecainide challenge test, electroanatomical mapping, programmed ventricular stimulation, induced type 1 Brugada pattern

Introduction

The sudden cardiac death (SCD) risk stratification in drug-induced type 1 Brugada syndrome is still challenging. Current guidelines do not support the role of programmed ventricular stimulation (PVS) in this subset of patients. The genetic testing for SCN5A gene is the only recommended for probands with BrS (1); however, many other genes modulating the arrhythmic risk have been described in patients clinically affected by BrS (2). We report the case of drug-induced type 1 Brugada syndrome at high arrhythmic risk associated with Lamin A/C gene mutation.

Case presentation

We report the case of asymptomatic 42-year-old male with evidence of 1 mm J-point elevation in V2–V3 and a saddleback shaped ST elevation V3 on basal electrocardiogram (ECG). His family history was positive for sudden cardiac death (father died at 64 years old) and dilatative cardiomyopathy (sister, onset at 40 years old). The patient had no personal relevant medical history.

Transthoracic echocardiography (TTE) showed no cardiac abnormalities. The sodium channel blocker test using flecainide 2 mg/kg over 10 minutes revealed a diagnostic type I Brugada ECG (Figure 1). For SCD risk stratification, an endocardial three-dimensional (3D) map of the right ventricle was constructed using a high-resolution mapping system (RhythmiaHdx™ Mapping System, Boston Scientific

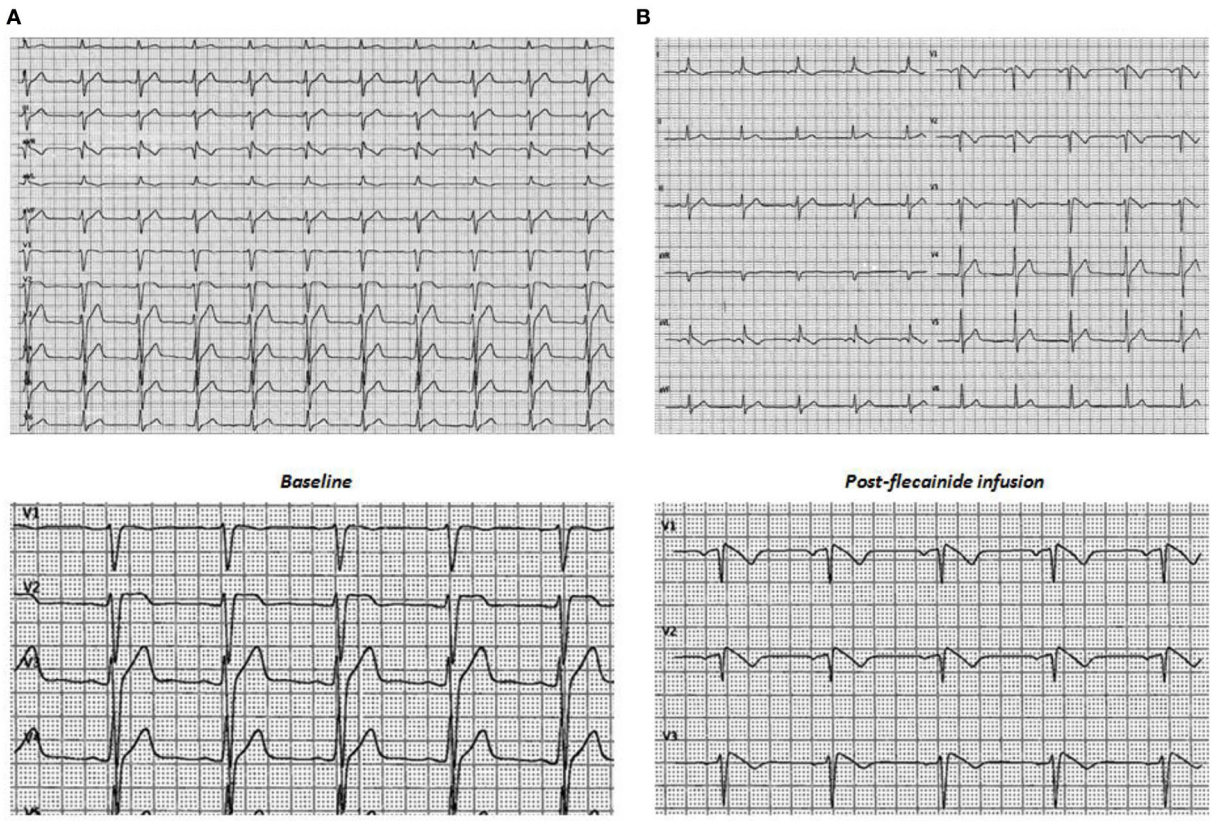

FIGURE 1
Basal **(A)** and post-flecainide infusion **(B)** twelve-lead electrocardiographic recordings.

Corporation) and the programmed ventricular stimulation (PVS) at two ventricular sites, right ventricular apex (RVA) and right ventricular outflow tract (RVOT), with up to three premature extrastimuli was performed.

At unipolar (cut-off: 5.5–8.3 mV) and bipolar (cut-off: 0.2–1 mV; 0.5–1.5 mV) voltage mapping in sinus rhythm no abnormalities were shown; the propagation map instead showed systolic late potentials in the antero-superior region of RVOT, where depolarization slowed significantly (Figure 2; Supplementary Video 1).

The PVS from RVOT with a paced drive train at cycle length of 500 ms followed by two extrastimulus at 220 and 200 ms respectively revealed the induction of a sustained polymorphic ventricular tachycardia (PVT) symptomatic for syncope and treated by external DC-shock (Figure 3A). During the arrhythmic event, the early diastolic potentials were recorded by the high-density diagnostic catheter (IntellaMap Orion™, Boston Scientific Corporation, US) placed in RVOT (Figure 3B). Subcutaneous ICD implantation was performed in order to prevent the sudden cardiac death. At 6 months follow-up, the patient did not experience arrhythmic events. The molecular genetic analysis showed a c.1718C>T heterozygous variation on exon 11 of Lamin A (p. Ser573Leu). Family members were genetically screened and the probands' sister and daughter showed the same LMNA mutation in absence of ECG abnormalities.

Discussion

We described the LMNA Ser573Leu missense mutation in asymptomatic drug-induced type 1 Brugada patient at increased arrhythimic risk for family history of sudden death and polymorphic VT induction at PVS. This missense mutation causes the substitution of a hydrophilic aminoacid (Serin) to a hydrophobic one (Leucine) in the highly conserved globular carboxyl tail of the Lamin A isoform, involved in the lateral assembly of protofilaments and mediating the Lamin network formation and may lead to change in the protein secondary structure, given the difference in polarity, electrical charge and dimension of the two peptides (3).

The LMNA Ser573Leu missense mutation was found in heterozygous individuals affected by dilatative cardiomyopathy, hypertrophic cardiomyopathy and atrio-ventricular block,

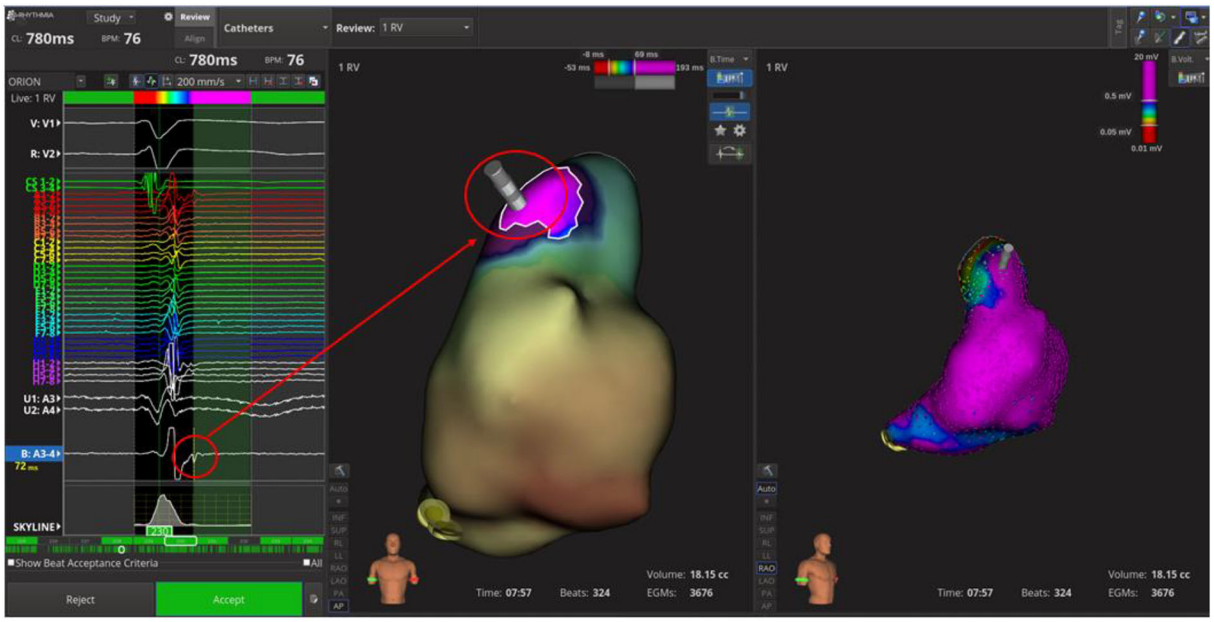

FIGURE 2
Time-domain electroanatomical map. In the antero-superior region of right ventricle outflow tract; the systolic late potentials were shown.

familiar partial subtype 2 lipodystrophy, limb girdle muscular dystrophy, Charcot-Marie-Tooth disease, Emery-Dreifuss muscular dystrophy (3, 4).

Our case report firstly described its association with BrS and supports the hypothesis of a possible alteration of sodium ionic currents (INa) in cells carrying LMNA gene mutations. Salvarani et al. demonstrated a direct interaction between Lamin A/C protein and SCN5A gene promoter with a significative *in vitro* reduction in SCN5A expression in induced pluripotent stem cells K219T LMNA-mutated derived cardiomyocytes (5). Recenlty, Armaroli et al. described a case of 31-year-old man, carrying a heterozygous mutation in exon 4 of Lamin A/C (p.R216C), with spontaneous type 1 Brugada ECG pattern who experienced at-rest cardiac arrest (6). Based on this evidence, we suggest to perform the genetic testing for LMNA gene in all probands with BrS.

The present case offers us the opportunity to discuss the role of PVS in drug-induced type 1 Brugada syndrome. The 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (1) stated that PVS may be considered in asymptomatic patients with a spontaneous type I BrS; however, no indication was given for those with drug-induced type 1 BrS. The relatively low arrhythmic risk of this subgroup, it does not mean zero risk. In the IBRYD study including 226 drug-induced type 1 BrS patients, 4.9% of them experienced a primary outcome event (appropriate ICD therapy or SCD) during a median follow-up of 106 months (7). In a recent meta-analysis including 4.099 patients with a mean follow-up of 4.5 years, the pooled annual incidence of major arrhythmic events (MAE) was 0.65% in symptomatic and 0.21% in asymptomatic drug induced type 1 BrS patients; the incidence of MAE between symptomatic drug-induced and asymptomatic spontaneous Type 1 was similar (8). The PVS failed to stratify the high-risk drug-induced BrS patients, showing a low positive predictive value (8.9% in asymptomatic; 9.6% in symptomatic); however. it may be considered a good tool to identify those at low arrhythmic risk, showing a high negative predictive value (95% in asymptomatic; 100% in symptomatic). Recently, the electroanatomical mapping has been considered an additional tool for SCD risk stratification among BrS patients (9); in particular an extensive RVOT electroanatomical abnormalities identify asymptomatic BrS patients at high risk (10). In order to better characterize the BrS electrophysiological substrate, we usually propose the ventricular endocardial electroanatomical mapping for all BrS patients followed at our center.

Since the drug-induced type 1 BrS might be part of laminopathies spectrum, a patients' centered approach including LMNA genetic testing, high density electro-anatomic mapping and PVS should be applied for the sudden cardiac death risk stratification.

Conclusion

Drug-induced type 1 BrS might be part of the laminopathies spectrum. The LMNA gene screening, the high density electro-anatomic mapping and the programmed ventricular stimulation

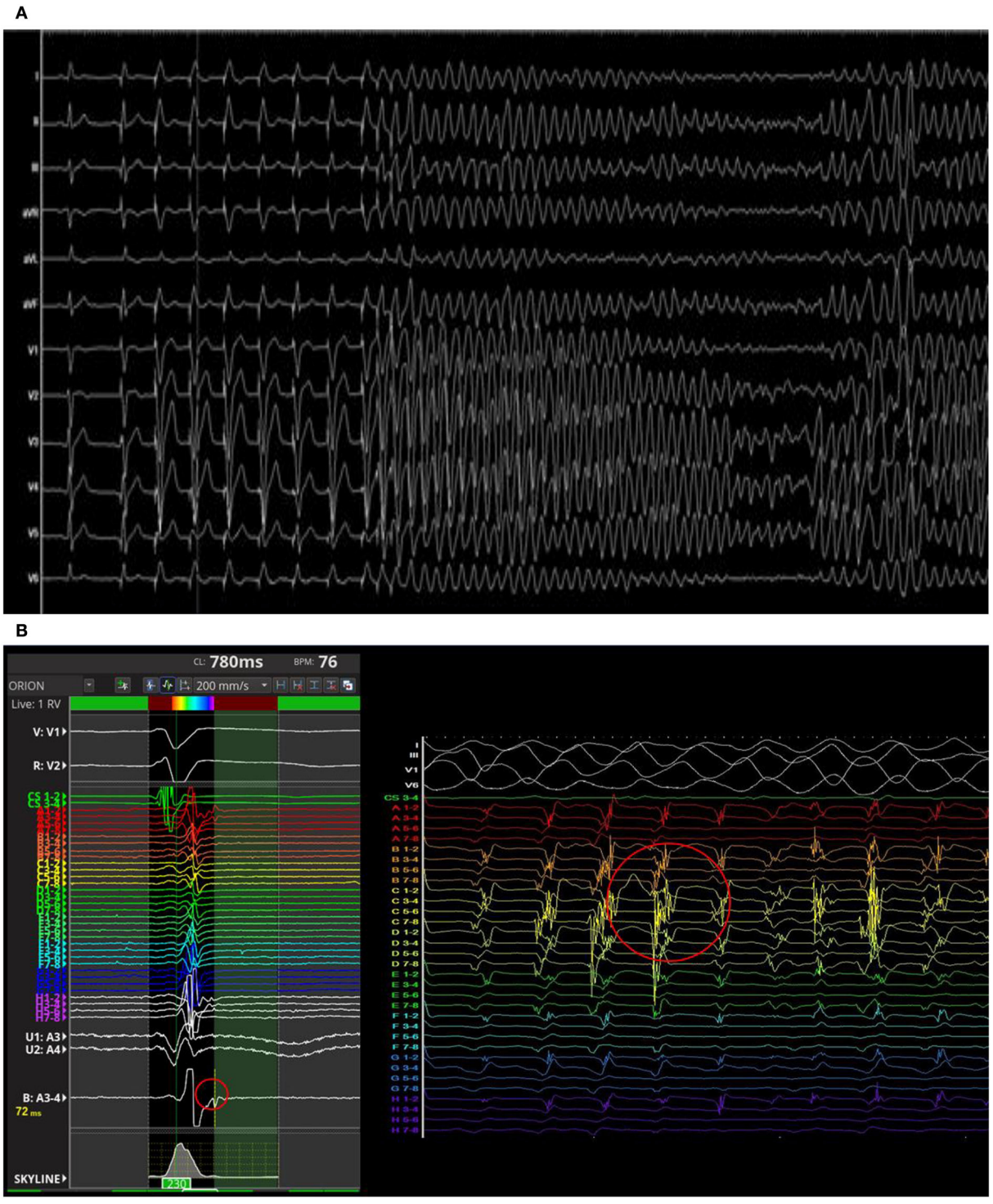

FIGURE 3
Polymorphic ventricular tachycardia induced by programmed ventricular stimulation from right ventricular outflow tract (RVOT) **(A)**. The early diastolic potentials were recorded by the mapping catheter placed in RVOT **(B)**.

should be considered in the patients' centered care of drug-induced type 1 BrS.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by University of Campania Luigi Vanvitelli ID: 07082021. The patients/participants provided their written informed consent to participate in this study.

Author contributions

VR: study concept and writing of the manuscript. PG and AR: critical revision of the manuscript for intellectual content. MM, VM, GP, AC, VR, and NP: acquisition of data and figures. All authors cared for the patient and contributed to the writing of the report. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.1099508/full#supplementary-material

SUPPLEMENTARY VIDEO 1
Activation map during sinus rhythm. The antero-superior region of right ventricle outflow tract shows a delayed activation.

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aMplitude spectral area of ventricular fibrillation and amiOdarone Study in patients with out-of-hospital cArdIaC arrest. The MOSAIC study

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Objective: Antiarrhythmic drugs are recommended for out of hospital cardiac arrest (OHCA) with shock-refractory ventricular fibrillation (VF). Amplitude Spectral Area (AMSA) of VF is a quantitative waveform measure that describes the amplitude-weighted mean frequency of VF, it correlates with intramyocardial adenosine triphosphate (ATP) concentration, it is a predictor of shock efficacy and an emerging indicator to guide defibrillation and resuscitation efforts. How AMSA might be influenced by amiodarone administration is unknown.

Methods: In this international multicentre observational study, all OHCAs receiving at least one shock were included. AMSA values were calculated by retrospectively analysing the pre-shock ECG interval of 2 s. Multivariable models were run and a propensity score based on the probability of receiving amiodarone was created to compare two randomly matched samples.

Results: 2,077 shocks were included: 1,407 in the amiodarone group and 670 in the non-amiodarone group. AMSA values were lower in the amiodarone group [8.8 (6–12.7) mV·Hz vs. 9.8 (6–14) mV·Hz, $p = 0.035$]. In two randomly matched propensity score-based groups of 261 shocks, AMSA was lower in the amiodarone group [8.2 (5.8–13.5) mV·Hz vs. 9.6 (5.6–11.6), $p = 0.042$]. AMSA was a predictor of shock success in both groups but the predictive power was lower in the amiodarone group [Area Under the Curve (AUC) non-amiodarone group 0.812, 95%CI: 0.78–0.841 vs. AUC amiodarone group 0.706, 95%CI: 0.68–0.73; $p < 0.001$].

Conclusions: Amiodarone administration was independently associated with the probability of recording lower values of AMSA. In patients who have received amiodarone during cardiac arrest the predictive value of AMSA for shock success is significantly lower, but still statistically significant.

KEYWORDS

cardiac arrest, AMSA, ventricular fibrillation, defibrillation, amidoarone

1. Introduction

Ventricular Fibrillation (VF) is one of the rhythms in adult out-of-hospital cardiac arrest (OHCA) (1). Correct treatments are prompt defibrillation and cardiopulmonary resuscitation (CPR) (2, 3). Data supporting the use of antiarrhythmic drugs after three ineffective shocks is sparse (4). Their effects on improving the rate of return of spontaneous circulation (ROSC) and survival to hospital admission are weak (5, 6). None of them has shown increased long-term or survival to discharge with good neurological outcomes. Amiodarone may improve short-term outcome (ROSC and survival at hospital admission) (7, 8), but this might be effective only for shock-refractory VF/pulseless ventricular tachycardia (pVT) in bystander-witnessed arrests (9).

The Amplitude Spectral Area (AMSA) of VF is a quantitative waveform measure that describes the amplitude-weighted mean frequency of VF. In animal studies AMSA correlates with intramyocardial adenosine triphosphate (ATP) concentration levels (10) and with coronary perfusion pressure (11). Therefore it has been proposed as a tool to monitor the effectiveness of chest compressions (12). The AMSA values can be influenced by the quality of CPR, different myocardial substrates (13, 14) and patient characteristics (15). Interestingly, it was highlighted that drugs, such as beta-blockers (16), may also alter AMSA. Amiodarone is largely used during resuscitation for unresponsive defibrillation of VF/pVT but no studies have determined if its administration is able to affect AMSA or the myocardium during CPR.

It has been demonstrated that higher AMSA values are associated with higher shock success and ROSC (15, 17). AMSA-driven shocks and epinephrine administration resulted in less post-resuscitation myocardial dysfunction and better survival (18). Because AMSA may predict if defibrillation could terminate VF with concurrent ROSC, AMSA was proposed as a tool to guide defibrillation in adults (17). However, it's unknown whether amiodarone may alter the predictive power of AMSA and consequently AMSA's clinical use.

We sought to determine if OHCA patients who received amiodarone during advanced cardiac life support (ACLS) had lower values of AMSA compared to those who did not receive amiodarone. Secondly, we wanted to examine whether the rates of successful defibrillation, ROSC and survived event would differ between the amiodarone and non-amiodarone groups. Finally, we wanted to assess if the role of AMSA as a predictor of shock success is maintained both in the amiodarone group and in the non-amiodarone group.

2. Material and methods

2.1. Type of study and population

This is a multicentre observational study based on retrospective analysis of prospectively collected data (ClinicalTrials.gov Identifier: NCT04997980). All OHCAs occurring between January 1, 2015, and December 31, 2020, in the province of Pavia (Italy) and between January 1, 2007, and December 31, 2018 in Vestfold county (Norway) were considered. If at least one shock for VF during ACLS was delivered, regardless of whether the first rhythm was shockable or not, the patient was eligible for inclusion. Data were retrieved from the Lombardia CARe Registry for the province of Pavia, and from the Vestfold Cardiac Arrest Registry for the region of Vestfold which are described in the **Supplementary materials**.

2.2. Data collection and analysis

Anonymized data from the two different databases were integrated and combined in a single *ad hoc* database for statistical analysis (see **Supplementary materials**). After the electronic data of all cases had been extracted from the monitor/defibrillators' memories (Corpuls 3 for the province of Pavia and LIFEPAK 12/15 monitors Vestfold), ECG signals were processed by Matlab software (The MathWorks, Inc., Natick, USA). Only OHCA patients who had at least one manual defibrillation attempt were considered. All shocks were independently reviewed by three cardiologists from our team and annotated as successful/unsuccessful shocks. Based on the lack of a uniform definition of shock success in literature (19) and consistent with our previous work (20) we have defined successful defibrillation as the cessation of VF or pVT with the subsequent emergence of an organized rhythm within 60 s. An organized rhythm required at least two QRS complexes separated by no more than 5 s each.

For every shock, AMSA was computed using a 2 s pre-shock ECG interval, free of chest compression artifacts, leaving a 1s guard before the shock. The ECG was bandpass filtered (0.5–30 Hz) using a forward-backward order 8 elliptic filter to remove baseline oscillations and high frequency noise. Fast Fourier Transform was used to compute the spectral amplitudes of the ECG, and AMSA was calculated in the 2–48 Hz frequency range (15).

For each patient, all pre-hospital variables were included according to the 2014 Utstein recommendations (21). ROSC was annotated by clinicians on scene after every shock. ROSC was assumed, even if transient, in the presence of a palpable pulse checked according to guidelines (2, 3).

Following international recommendations (2, 3) amiodarone was administered either via an intravenous or an intraosseous line at the dosage of 300 mg for the first bolus followed by an additional dose of 150 mg.

2.3. Statistical analysis

Categorical variables were compared with the Chi-square test and presented as number and percentage. Continuous variables were compared with the *t*-test and presented as mean ± standard deviation or compared with the Mann–Whitney test and presented as median and interquartile range (IQR) for normal distributions (tested with the D'Agostino-Pearson test). Uni- or

multivariable logistic regression were applied to assess the association between one binomial dependent variable and one or more not correlated independent variables.

In a per-shock analysis, the values of AMSA preceding shocks delivered to patients treated with amiodarone were compared with the values of AMSA preceding shocks delivered to patients not treated with amiodarone.

The same analysis was performed by a propensity score matching analysis. The propensity score was created based on the coefficients resulting from a multivariable logistic regression model for the probability of receiving amiodarone considering age, sex, the presence of bystander CPR, the call to shock time for every single shock, the use of mechanical CPR, the administration of dispatcher assisted CPR, the year and study site (Pavia or Vestfold) as independent variables. Once created, the propensity score was tested for linear prediction. A pool of shocks with a similar propensity score was identified and then, for each case in the amiodarone group, a control in the non-amiodarone group was randomly assigned.

The shock success prediction accuracy of AMSA was tested using the receiver operating characteristic (ROC) curve analysis. After the creation of the curve, by plotting for each value of AMSA the true positive rate (shock success in case of expected shock success) in function of false positive rate (shock failure in case of expected shock success) the area under the curve (AUC) was calculated according to the Hanley and McNeil methodology. The comparison the ROC curve was run according to the DeLong method.

3. Results

3.1. Study population characteristics

A total of 629 EMS-assessed OHCAs were enrolled in the study: 250 from Pavia and 379 from Vestfold. **Table 1** shows the main characteristics of the population.

By comparing two random samples (120 patients form Pavia and 120 patients from Vestfold), homogeneous for sex, number of shocks received, age and call to shock time, the AMSA values were similar in the two study sites [Pavia: 8.3 (5.1–10.9) mV·Hz vs. Vestfold: 9.4 (4.9–14.5) mV·Hz, $p = 0.11$]. Moreover, AMSA values were found to predict shock success in both regions' study groups with no statistical difference at the Receiver operating characteristic (ROC) curve analysis (AUC Pavia 0.786, 95%CI: 0.756–0.813; AUC Vestfold 0.759, 95%CI: 0.735–0.782; $p = 0.206$) **Supplementary Figure S1**.

Out of the entire population, 253 patients received amiodarone and 347 did not (29 patients data unknown). The amiodarone group had a higher percentage of males, of medical aetiology and of witnessed events. The number of shocks delivered were higher in the amiodarone group, as well as the frequency of both telephone and mechanical CPR. However, the trends of ROSC and survived event percentages were lower in the amiodarone group compared to the non-amiodarone group. Other patients' characteristics are presented in **Table 2**.

TABLE 1 Patients' characteristics.

Variable	Overall ($N = 629$)
Study site (%)	
Pavia	250 (40)
Vestfold	379 (60)
Age (IQR) (years)	68 (57–77)
Male gender (%)	480 (78)
EMS arrival time (IQR) (min)	9.5 (6.9–13.4)
Medical aetiology (%)	564 (90)
OHCA location (%)	
Home	414 (66)
Nursing home	6 (1)
Street	112 (18)
Public building	21 (3)
Workplace	17 (2.5)
Sport	4 (1)
Other	37 (6)
Unknown	18 (2.5)
Telephone CPR (%)	316 (50)
Witnessed event (%)	
No	112 (18)
EMS	68 (11)
Bystanders	425 (68)
Unknown	24 (3)
Bystander CPR (%)[a]	409 (76)
Shockable presenting rhythm (%)	397 (67)
AED Use before EMS arrival (%)[a]	67 (12)
Number of shocks delivered (IQR)	3 (1–6)
Amiodarone (%)	
Yes	253 (40)
No	347 (55)
Unknown	29 (5)
Amiodarone administered with <3 shocks (%)[b]	23 (9)
Amiodarone administered with ≤3 shocks (%)[b]	56 (22)
Amiodarone not administered with more than 3 shocks (%)[c]	64 (18.4)
Mechanical CPR (%)	389 (64)
ROSC (%)	267 (42)
Survived event (%)	230 (37)

[a]EMS Witnessed excluded.
[b]Only patients treated with amiodarone considered.
[c]Patients treated with amiodarone excluded.

3.2. Shock characteristics based on amiodarone administration

The total number of shocks, 2,077 for the 600 OHCA patients, were divided into patients with and without amiodarone administered. In the amiodarone group shock success rate was lower than in the non-amiodarone group. The AMSA values were also lower in the amiodarone group (**Table 3**).

3.3. Primary outcome

3.3.1. AMSA values according to amiodarone administration

In a per-shock analysis, AMSA values were significantly lower in the group of shocks delivered to patients treated with

TABLE 2 Patients' characteristics in amiodarone and non-amiodarone groups.

Variable	Amiodarone (*N* = 253)	Non-Amiodarone (*N* = 347)	*p*-value
Age (IQR) (years)	67 (56–76)	69 (58–78)	0.12
Male gender (%)	212 (84)	250 (72)	<0.001
EMS arrival time (IQR) (min)	9.6 (7–14)	9.5 (7–13)	0.56
Medical aetiology (%)	238 (94)	302 (87)	0.005
OHCA location (%)			0.49
Home	165 (65)	233 (67)	
Nursing home	1 (0)	5 (1)	
Street	49 (19)	53 (15)	
Public building	6 (2)	15 (4)	
Workplace	6 (2)	11 (3)	
Sport	1 (0)	3 (1)	
Other	16 (6)	19 (5)	
Unknown	9 (4)	8 (2)	
Telephone CPR (%)	141 (56)	160 (46)	0.01
Witnessed event (%)			0.005
No	40 (16)	68 (20)	
EMS	17 (7)	48 (14)	
Bystanders	187 (74)	219 (63)	
Unknown	9 (3)	12 (3)	
Bystander CPR (%)[a]	178 (78)	211 (74)	0.19
Shockable presenting rhythm (%)	194 (73)	187 (54)	<0.001
AED Use before EMS arrival (%)[a]	22 (10)	39 (14)	0.13
Number of shocks delivered (IQR)	6 (4–8)	2 (1–3)	<0.001
Mechanical CPR (%)	182 (72)	191 (55)	<0.001
Epinephrine (mg) (IQR)	5 (4–7)	4 (2–5)	<0.01
ROSC (%)	98 (39)	152 (44)	0.15
Survived event	87 (34)	127 (37)	0.51
AMSA at first shock median (IQR) (Hz·mV)	9.8 (7–13)	9.7 (6–15)	0.9

EMS, emergency medical service; CPR, cardiopulmonary resuscitation; AED, Automated external defibrillator.
[a]EMS witnessed excluded.

TABLE 3 Shocks characteristics in amiodarone and non-amiodarone groups.

Shocks characteristics (*N* = 2,077)	Amiodarone (*N* = 1,407)	Non-Amiodarone (*N* = 670)	*p*-value
Energy delivered (IQR) (J)	300 (200–360)	200 (150–200)	<0.001
Pavia (Corpuls)	200 (150–200)	150 (150–200)	<0.001
Vestfold (Lifepak)	360 (300–360)	200 (200–300)	<0.001
Successful (%)	463 (33)	278 (41)	<0.001
AMSA (IQR) (Hz·mV)	8.8 (6–13)	9.8 (6–14)	0.035

amiodarone [8.8 (6–12.7) mV·Hz vs. 9.8 (6–14) mV·Hz, $p = 0.035$] (Figure 1). In the non-amiodarone group, the reduction of AMSA values from the first two shocks to the successive ones was not statistically significant [10 mV·Hz (5.9–17.4) vs. 9.1 mV·Hz (5.8–12.8), $p = 0.123$]. On the contrary, in the amiodarone group AMSA decreased significantly after the second shock [10.2 mV·Hz (6.6–14.2) vs. 8.3 mV·Hz (5.8–12.2), $p < 0.01$]. Therefore, the extent of the reduction of AMSA after the second shock was greater in the amiodarone group [−1.3 (−1.9; −0.7) vs. −0.6 (−1.5; 0.2), $p < 0.001$] (Figure 2).

By plotting the median AMSA values of the amiodarone and non-amiodarone groups in each of the three tertiles based on the call to shock time, the amiodarone group showed a statistically significant reduction in AMSA between T1 and T2 and between T2 and T3. Conversely, in the non-amiodarone group there was a significant reduction only between T1 and T2 (Figure 3).

In the multivariable logistic regression analysis corrected for age, bystander CPR, witnessed event, year 2020, call to shock time, shockable presenting rhythm, shock energy, multiple shocks, sex and study site (Pavia and Vestfold), the treatment with amiodarone was independently associated with AMSA values lower than the median (9.4 mV·Hz) [OR 1.33, (95%CI: 1.1–1.6), $p = 0.009$].

AMSA values were then compared in two randomly matched propensity score-based groups of 261 shocks each. The covariates inserted in the model and the resulting coefficients are shown in Supplementary Table S1. AMSA was again demonstrated to be lower in the amiodarone group [8.2 (5.8–13.5) mV·Hz vs. 9.6 (5.6–11.6), $p = 0.042$] as shown in Figure 4.

3.4. Secondary outcomes

3.4.1. Shock success, ROSC and survived event rates

By comparing the amiodarone and the non-amiodarone randomly matched groups based on the propensity score analysis, the shock success rate did not statistically differ (non-amiodarone 38% vs. amiodarone 36%, $p = 0.6$). After correction for age, sex, EMS arrival time, the presence of bystander CPR, the presence of a shockable presenting rhythm, the number of shocks received, the study site and the first available AMSA value, the treatment with amiodarone did not influence the probability of both ROSC [OR 0.8 (95%CI: 0.4–1.4), $p = 0.38$] and survival [OR 0.8 (95%CI: 0.4–1.5), $p = 0.46$].

3.4.2. AMSA as a shock success predictor

In the ROC curve analysis (Figure 5), AMSA values were found to be able to predict shock success in both the amiodarone and the non-amiodarone groups, however the predictive power was significantly lower in the amiodarone group (AUC 0.812, 95%CI: 0.78–0.841 vs. 0.706, 95%CI: 0.68–0.73; $p < 0.0001$).

4. Discussion

Amiodarone is extensively used during resuscitation for unresponsive defibrillation of VF/pVT but very little is known about how and to what extent administration of intravenous amiodarone may affect VF. The main finding of this study was that the values of AMSA which quantitatively measure the VF waveform, in the amiodarone group were lower than in the non-amiodarone group. In fact, the values of the first shocks, prior to

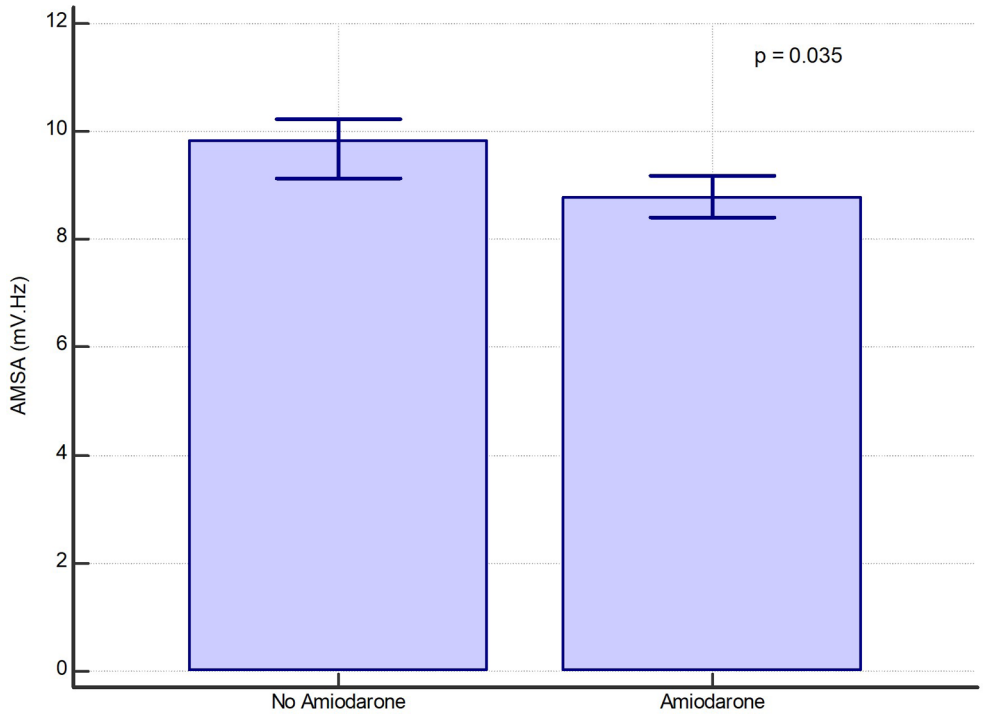

FIGURE 1
Bar graph of median values of AMSA with their 95% confidence interval in the amiodarone and in the non-amiodarone groups in the whole population of shocks.

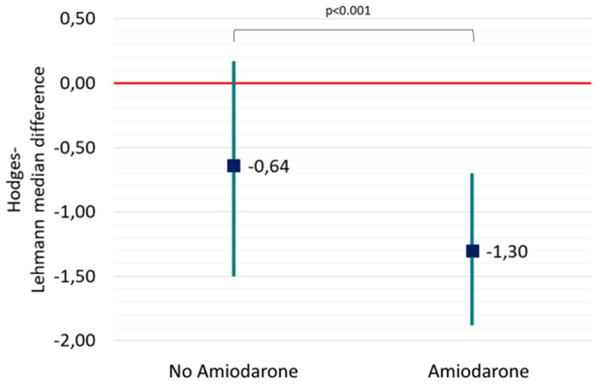

FIGURE 2
Hodges-Lehmann median difference and 95% confidence showing the reduction of AMSA values from the first two shock to the successive ones both in the non-amiodarone and in the amiodarone group.

the administration of amiodarone, were similar in the two groups while the reduction of AMSA at the successive shocks was more pronounced in the amiodarone group. In the amiodarone group there was an almost linear reduction of AMSA over time. This is in contrast to the non amiodarone group, in which the decline of AMSA values was not evident, as if amiodarone had hastened the decrease of amplitude of VF.

We might argue that the decreased values of AMSA in the amiodarone group could be explained by a longer resuscitation and a higher number of shocks. However, we found that amiodarone was independently associated with the probability of recording lower values of AMSA even after correction for all the OHCA characteristics known (or potentially able) to affect the patient's outcome, such as time to each shock, sex, age, witnessed event, bystander CPR, study site (Pavia and Vestfold) and year 2020. We adjusted our analysis for sex because it was suggested that males had lower AMSA than females (15). Time to shock and bystander CPR play a confounding role because longer resuscitation time leads to a greater loss of ATP in myocardiocytes which would be reflected by lower AMSA values (10). Finally, we corrected for the year 2020, which led to prolonged EMS response time due to the COVID-19 pandemic (22).

The hypothesis that antiarrhythmic effect of drugs on the myocardium would be quantifiable through the analysis of electrocardiograms was proposed ten years ago by Sherman et al. (16). This topic was also indirectly approached regarding the effect of lidocaine and amiodarone on quantitative ECG waveform measures in a recent sub-analysis from the clinical ROC-ALPS study by Salcido et al. (23). However, none of these types of quantification have had practical repercussions on resuscitation.

Amiodarone has predominantly a Vaughan-Williams class-III effect of potassium channel blockade resulting in lengthening of the cardiac action potential, together with a class I use-dependent sodium channel blockade of inward sodium currents, a class II beta receptor blockade and class IV calcium channel blockade (24). The consequent increased refractoriness of cardiac tissue and the slowed ventricular conduction are thought to facilitate successful defibrillation and to reduce the risk of

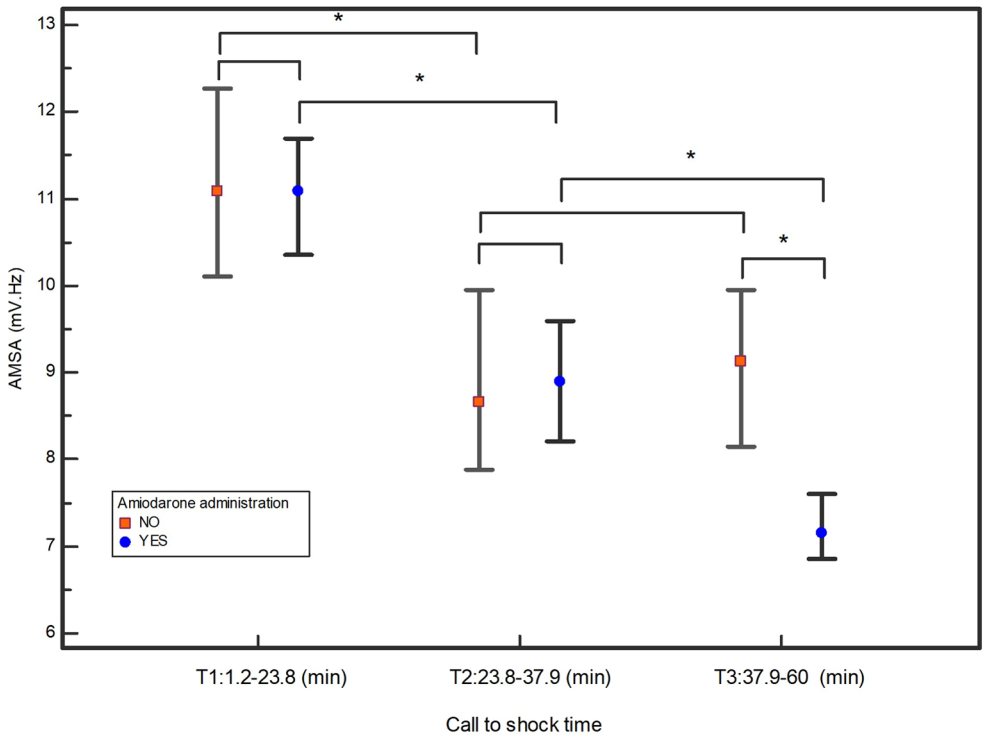

FIGURE 3
Median values of AMSA and their 95% confidential interval in the three tertiles of call to shock time. *indicates statistically significant differences.

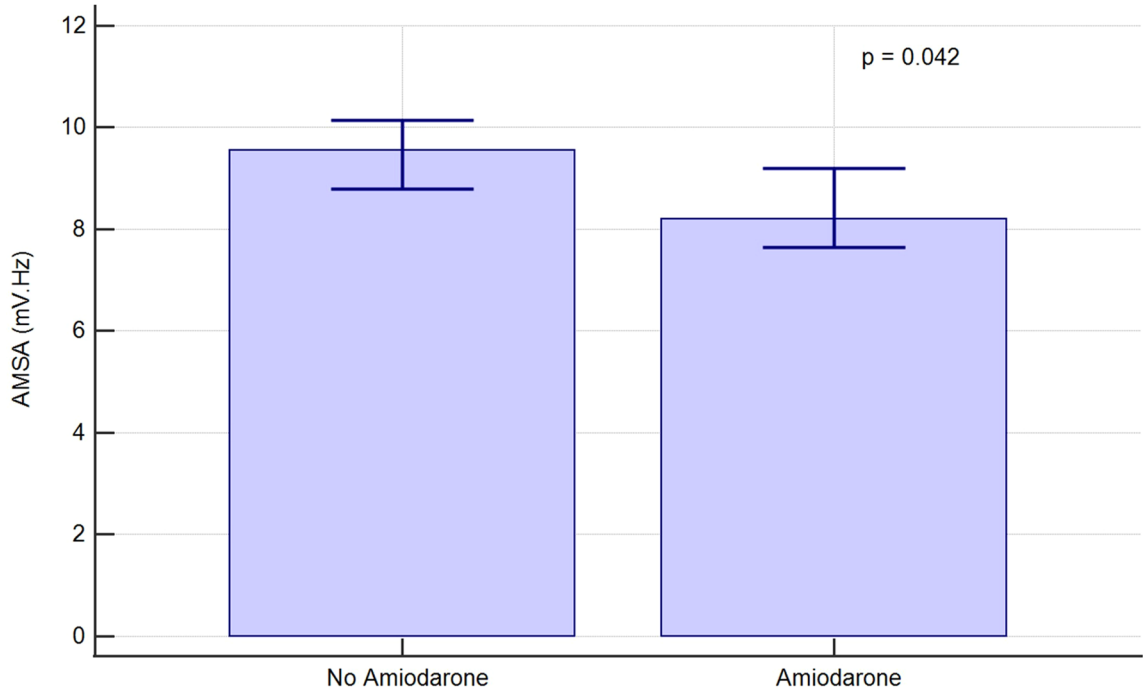

FIGURE 4
AMSA median values and 95% confidence interval in randomly matched, propensity score-based groups of shocks.

recurrent arrhythmias (25). The complex pharmacologic profile of amiodarone as well as the heterogeneity of underlying VF mechanisms make this query very challenging. Animal studies that have focused on the ionic and cellular mechanisms of amiodarone use or changes in the defibrillation threshold due to the acute administration of the drug (26–28) have been

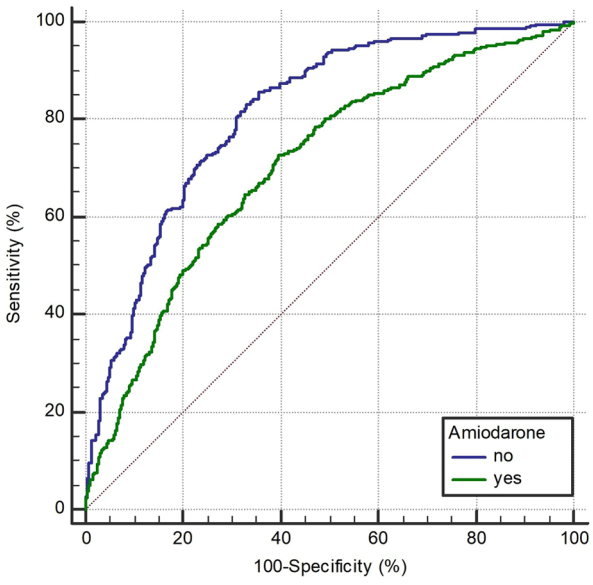

FIGURE 5
Receiver operating characteristic curve of AMSA for the prediction of shock success in amiodarone and non-amiodarone group.

somewhat contradictory. The rather modest evidence coming from human-based randomized trials and metanalyses (7–9) together with the limited existing therapeutic options in resuscitation have led to the adoption of amiodarone as the preferential treatment of life-threatening ventricular tachyarrhythmias.

Previous studies have suggested a marginal effect of cardiac medications on AMSA values (29, 30). However, that conclusion was drawn considering only oral chronic intake. In the paper by Hulleman and colleagues class III and I antiarrhythmic drugs were considered together and they found halved AMSA values even if with a non-statistically significant p value of 0.069 probably due to the small number of patients treated (only 1.8%). Conversely, the present study was focused on the acute effect of intravenous amiodarone. The administration route is accompanied by substantial differences; In fact, it has been shown how the oral and the intravenous administration were different due to the effects mediated by the active metabolite desethylamiodarone (DEA) resulting from the first-pass hepatic metabolism (28).

The underlying cause of cardiac arrest was also shown to affect AMSA values. Olasveengen and colleagues (31) found that patients with an acute myocardial infarction had lower AMSA values as compared to other cardiac arrest aetiology. Although we don't know the definite cause of cardiac arrest however an acute coronary syndrome is by far the most frequent cause of adult cardiac arrest (32) and it is included in the Utstein category named "medical aetiology" which accounted for about ninety percent and was higher in the amiodarone group.

Due to the observational nature of this study, the decision to administer amiodarone was not randomized. In Pavia the decision was done by the physician and in Vestfold by the paramedic crew. To reduce possible selection bias, we ran a propensity score analysis to compare two independent groups having *a priori* the same probability of receiving amiodarone. This additional analysis showed, once again, that patients treated with amiodarone had significantly lower values of AMSA.

Although this study was not designed for survival analysis, we found that amiodarone administration was not associated with a higher probability of shock success, ROSC or survived event. To our knowledge, no previous study has compared the efficacy of amiodarone in terms of shock success in OHCA patients. Our results regarding ROSC are aligned with the results from the ROC-ALPS trial (9), which randomized more than three thousand patients in three arms of treatment (amiodarone, lidocaine and placebo), finding no difference in terms of ROSC or survival at hospital discharge between amiodarone and placebo. However, the trial found a statistically significant difference in terms of the number of patients admitted to hospital (amiodarone 45.7% vs. placebo 39.7%, $p = 0.01$). In this regard, our results about survived event could seem in contrast with the ROC-ALPS trial at first glance. However, our endpoints are slightly different from that study. We have considered "survived event" according to the most recent Utstein definition that describes it as a ROSC sustained until arrival at the emergency department (ED) and transfer of care to medical staff at the receiving hospital. Instead, the ROC-ALPS used survival at hospital admission as a secondary endpoint. Our endpoint "survived event" does not exactly mirror "survived at hospital admission" because OHCA patients admitted to the hospital with ongoing CPR may still expire prior to achieving ROSC.

The effect of amiodarone could limit the ability of AMSA to predict defibrillation outcomes. This topic is of great clinical importance because AMSA is an emerging indicator that might guide defibrillation and resuscitation efforts. One randomized clinical study, even if terminated early due to low inclusion rates because it was started when the Covid 19 pandemic evolved, showed that the real-time AMSA measuring during resuscitation of OHCA patients is feasible (33). It is of pivotal importance to know if the administration of amiodarone can affect both the values and predictivity of AMSA. Our study found that, even though AMSA remains a shock success predictor in both groups, the area under the curve of the ROC-curve is significantly lower in the amiodarone group. After the administration of amiodarone, the cut-off of AMSA could be different from that at the beginning of ACLS. In a clinical scenario, we speculate that the chances of an error could be greater if defibrillation was guided by AMSA values after the administration of amiodarone. There is therefore a need for a prospective randomized clinical study where amiodarone effect on AMSA value is taken into consideration.

4.1. Limitations

This study has some potential limitations. First, it is an observational study with the related intrinsic limitations. Second, we were unable to provide a direct comparison between AMSA values before and after the administration of amiodarone. The main reason for this is that in our two registries, the use of

amiodarone is annotated but the exact time of administration is absent as this is not requested by the Utstein template. Because 22% of the patients treated with amiodarone received the drug within the third shock, we considered the first two shock as those most likely to be pre-amiodarone. One possibility for those who received amiodarone earlier than the third shock is that shocks given prior to ACLS (for example during BLS-D or by bystanders with AED) were considered for the purposes of the advanced resuscitation algorithm. We decided to run multivariable model of logistic regression, and a comparison of propensity score-matched group to mitigate this limitation. Third, consistently to the Utstein recommendations, we did not annotate the use of lidocaine. Presumably, some of the patients who did not receive amiodarone were treated with lidocaine; however, the reduction of AMSA from the first two shocks towards the successive shocks was not significant in this group. Fourth, we had no information of patient's home therapies or chronic comorbidities that could affect AMSA, but this is a common limitation for studies based on retrospectively collected Utstein data. Additionally, it was demonstrated by Hulleman et al. that these factors have little impact on AMSA values (29). Fifth, the definite cause of cardiac arrest was not available so we don't know the precise prevalence of acute myocardial infarction in the amiodarone and non-amiodarone group. According to the Utstein style acute myocardial infarction is included in the definition of "medical etiology" which was about ninety percent in both groups.

5. Conclusion

The use of amiodarone in advanced resuscitation is associated with lower values of AMSA of VF in patients with out-of-hospital arrest after correcting for patient and OHCA characteristics. Moreover, AMSA maintains its predictive role in shock success in patients who have received amiodarone, although with a significantly lower predictive power compared to patients who did not. We believe that these results will not only help to define AMSA's role and use in resuscitation but also could launch AMSA as an additional data point to better understand the controversial role of amiodarone in cardiac arrest.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

FG Conceptualization, Data curation, Methodology, Investigation, Writing—original draft, Writing—review & editing. LW Data curation, Methodology, Investigation, Writing—original draft, Writing—review & editing. EA Data curation, Methodology, Investigation, Writing—original draft, Writing—review & editing. EB Data curation, Investigation. II Data curation, Investigation. JS Data curation, Investigation. SC Data curation, Investigation. AF Data curation, Investigation. EC Data curation, Investigation. AP Data curation, Investigation. RP Data curation, Investigation. AC Data curation, Investigation. SB Data curation, Investigation. SS Conceptualization, Formal analysis, Writing—original draft, Writing—review & editing, Methodology, Data curation, Supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1179815/full#supplementary-material.

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Public attitudes towards automated external defibrillators: results of a survey in the Australian general population

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Background: Swift defibrillation by lay responders using automated external defibrillators (AEDs) increases survival in out-of-hospital cardiac arrest (OHCA). This study evaluated newly designed yellow–red vs. commonly used green–white signage for AEDs and cabinets and assessed public attitudes to using AEDs during OHCA.
Methods: New yellow–red signage was designed to enable easy identification of AEDs and cabinets. A prospective, cross-sectional study of the Australian public was conducted using an electronic, anonymised questionnaire between November 2021 and June 2022. The validated net promoter score investigated public engagement with the signage. Likert scales and binary comparisons evaluated preference, comfort and likelihood of using AEDs for OHCA.
Results: The yellow–red signage for AED and cabinet was preferred by 73.0% and 88%, respectively, over the green–white counterparts. Only 32% were uncomfortable with using AEDs, and only 19% indicated a low likelihood of using AEDs in OHCA.
Conclusion: The majority of the Australian public surveyed preferred yellow–red over green–white signage for AED and cabinet and indicated comfort and likelihood of using AEDs in OHCA. Steps are necessary to standardise yellow–red signage of AED and cabinet and enable widespread availability of AEDs for public access defibrillation.

KEYWORDS
automated external defibrillator (AED), public attitude, sudden cardiac arrest, cardiopulmonary resuscitation, society, Australia

Introduction

Out-of-hospital cardiac arrest (OHCA) is a prevalent global health concern where over nine in 10 patients do not survive, and most die before reaching a hospital (1–4). Rapid defibrillation is crucial to potential survival and long-term quality of life (5, 6). In cases of OHCA, chances of survival decrease by 3% every minute that defibrillation is delayed after cardiopulmonary resuscitation (CPR) is commenced (7). When OHCA occurs in the community, lay responders play a crucial role in giving patients a chance of survival, through alerting emergency medical services (EMS) and initiating CPR and early defibrillation (8). Initial defibrillation by lay first responders is associated with greater OHCA survival than initial defibrillation by dispatched EMS (9). The primary method by

which lay responders can deliver rapid defibrillation to OHCA patients is via the use of publicly accessible automated external defibrillators (AEDs), which is safe and effective for improving survival even with no training (10). However, within Australia, despite investments by many governments to increase the number of publicly accessible AEDs found within communities, many OHCA cases still occur over 100 m away from the locations where these are situated, indicating that current coverage is inadequate (11). This paucity of publicly accessible AEDs within communities (12) provides a potential explanation for bystander use of AEDs occurring in under 2% of non-EMS witnessed OHCA cases in Australia (4).

In situations of community OHCA, rapid defibrillation by lay responders relies on AEDs being swiftly identifiable and publicly accessible. The primary method of identification is via signage and the exterior of the cabinet in which the AED is placed. In 2008, the International Liaison Committee on Resuscitation (ILCOR) proposed a sign indicating the presence of AEDs worldwide, utilising a green–white colour combination (13, 14). Further investigations of variants of AED sign designs have also utilised this green–white colour scheme (15). However, it has been demonstrated that public recognition and understanding of current green–white AED signage is limited and no single sign is unanimously recommended by national resuscitation councils or implemented in a standardised fashion in communities worldwide (16).

Colour perception is an important factor influencing human interaction with different environments (17). Past literature has found the colour green to be associated with lower alertness and greater calmness, whereas more vivid colours such as red and yellow have been associated with increased alertness and memory retention (18). Accordingly, the combination of vivid colours such as yellow and red is integral to the marketing strategy of some of the world's top corporations (19). In the emergency of OHCA, signage incorporating primarily vivid colours may be effective in facilitating a lay responder's rapid identification of a publicly accessible AED's location and potentially heightened awareness of their locations generally. Accordingly, we conducted a national survey of the Australian general public to evaluate a proposed new yellow–red sign and cabinet vs. the most commonly used green–white version for identifying AEDs.

Methods

Study design and oversight

This prospective, cross-sectional study was undertaken in collaboration with Heart of the Nation (an initiative of the registered Australian Charity, Our National Heart Pty Limited) and the Westmead Applied Research Centre. It followed the STROBE guidelines for reporting observational studies (20) and was conducted between November 2021 and June 2022 across Australia. The AED signs and cabinets investigated in this study are presented in **Figure 1**. The evaluated yellow–red sign and cabinet were designed by Heart of the Nation, in accordance with the International Organization for Standardization for Graphical Symbols and Test Methods (ISO 9186-1) (21). As co-authors and collaborators, members of Heart of the Nation and Westmead Applied Research Centre were responsible for the study's design and execution, including data acquisition, analysis and interpretation. They also critically revised the article for crucial intellectual content and made the final decision to submit the manuscript for publication. Ethical approval was obtained from the Western Sydney Local Health District Human Research Ethics Committee (reference number: 2021/ETH12008).

Participants and data collection

The study population comprised members of the Australian general population. To ensure that the sample was representative, we included all demographic subgroups, and no restrictions or exclusion criteria were applied. An electronic, anonymised questionnaire was developed using a web application (REDCap, Vanderbilt University, TN, United States) (22) and distributed using emails and social media posts containing the survey link, inviting members of the general public to participate. No random assignment or balancing was conducted.

Outcome measures

The primary outcome was the validated net promoter score (NPS), which was used to investigate public engagement with the signs and cabinets presented in the survey and provide respective ratios of promoters to detractors (23). Other measures included Likert scales and binary comparisons evaluating the yellow–red vs. green–white signs and cabinets for preference, ease of identification in an emergency such as cardiac arrest and comfort and likelihood of using AEDs in situations of OHCA.

Statistical analysis

Quantitative data were analysed using descriptive statistics. The proportion of the community that would find the new sign easier to identify in an emergency such as a cardiac arrest, and similarly for the cabinet, was estimated with a 95% confidence interval. Logistic regression models were used to assess the effect of age, ethnicity and region on this proportion. NPS estimates were calculated, and 95% confidence intervals were presented for the new and original sign and cabinet. Ordinal regression models were used to assess the effect of age, ethnicity and region on the NPS for each cabinet and sign. The McNemar–Bowker Test was used to compare the distribution of promoters, passives and detractors between the new and original signs and similarly for the cabinets. Analyses were performed using R (version 4.0.2) (24) packages Gmisc (25) for plot and table output and knitr (26) for reproducible research. p-values of less than 0.05 were considered statistically significant unless stated otherwise. The full survey and

FIGURE 1
AED signs and cabinets investigated in this study. AED, automated external defibrillator.

statistical report can be found in the **Supplementary Appendix**. Details on the measurement of outcomes, including survey scores and raw data, are available on reasonable request to the corresponding author.

Results

Study sample

A total of 2,538 members of the Australian general population participated in the study by clicking on the survey link distributed by email and social media. The data regarding the number of people who had access to the survey link, but did not participate, were not available. The mean age was 30.9 (SD: 14.9) years. Regarding gender, 1,454 (59.4%) were female, 897 (36.6%) male and 70 (2.9%) non-binary, and the remainder preferred not to say. Regarding race and ethnicity, 2,055 (81.0%) were white, 293 (11.5%) Asian, 86 (3.4%) Aboriginal or Torres Strait Islander (ATSI), 36 (1.4%) Pacific Islander, 34 (1.3%) Hispanic, 24 (0.9%) African-American and 7 (0.3%) American Indian. Of the study population, 510 (21.0%) were healthcare workers.

Preference and ease of identification

The yellow–red sign was preferred by 1,778 (73.0%) as easier to identify in emergencies such as cardiac arrest vs. 658 (27.0%) for green–white. The yellow–red cabinet was reported as easier to identify by 2,139 (87.6%) vs. 302 (12.4%) green–white. With similar rates of preference by gender and ethnicity, older people had the greatest preference for yellow–red signs and cabinets (**Figure 2**). Age and ethnicity were significantly associated with the ease of identifying yellow–red signs or cabinets (**Table 1**). The likelihood of preferring the yellow–red over the green–white sign grew by 2% for every additional year of age.

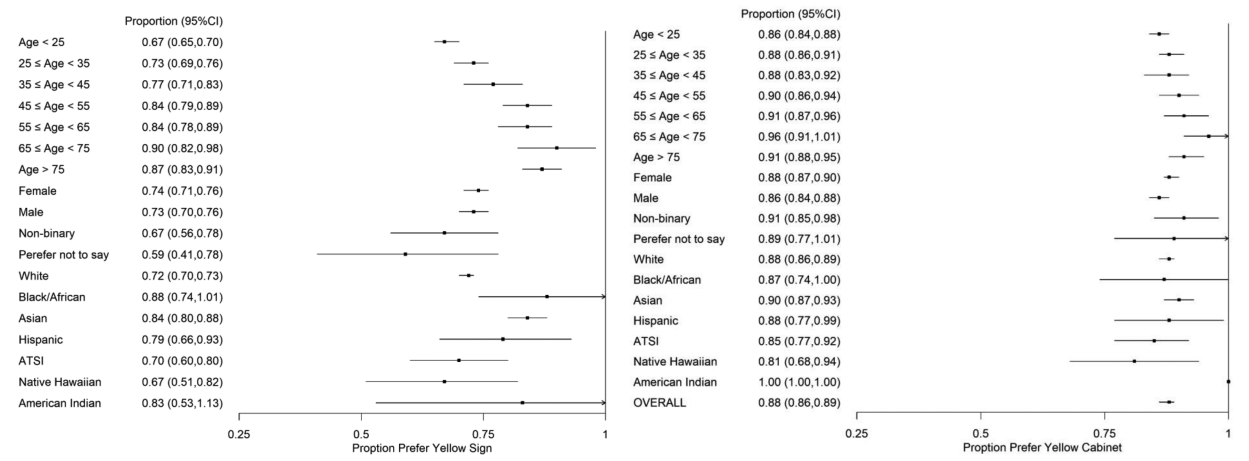

FIGURE 2
Demographics of yellow–red AED sign and cabinet preference.

TABLE 1 Variables significantly associated with stronger ease for identifying yellow signs and cabinets[a].

	Odds ratio and 95% confidence interval	*p*-value
Variables found associated with easily identifying the **yellow–red sign compared to the green–white sign**		
Age	1.024 (1.016–1.031)	<0.0001
Ethnicity: Asian	1.86 (1.33–2.60)	0.0003
Variables found associated with easily identifying the **yellow–red cabinet compared to the green–white cabinet**		
Age	1.014 (1.004–1.023)	0.0038
Ethnicity: Asian	1.70 (1.08–2.77)	0.0213
Ethnicity: White	1.89 (1.08–3.33)	0.0269

[a]Raw data in Supplementary Appendix.

TABLE 2 Net promoter score results[a].

	Promoters	Detractors	Passive	NPS and 95% CI
Green–white sign	19.4%	60.1%	20.5%	−0.41 (−0.44 to −0.38)
Yellow–red sign	53.5%	20.6%	26.0%	0.33 (0.30 to 0.36)
Green–white cabinet	11.6%	72.5%	15.8%	−0.61 (−0.64 to −0.58)
Yellow–red cabinet	62.3%	14.3%	23.4%	0.48 (0.45 to 0.51)

[a]Raw data in Supplementary Appendix.

Comfort and likelihood of using AEDs

Regarding comfort using AEDs in OHCA, 631 (26.0%) were very comfortable, 684 (28.2%) slightly comfortable, 344 (14.2%) neutral, 499 (20.5%) slightly uncomfortable and 271 (11.2%) very uncomfortable. Regarding the likelihood of using AEDs in OHCA, 1,013 (42.0%) were very likely, 536 (22.2%) slightly likely, 415 (17.2%) neutral, 233 (9.7%) slightly unlikely and 217 (9.0%) very unlikely.

Public engagement

Within NPS results, the yellow–red AED sign and cabinet demonstrated significantly higher proportions of promoters and lower proportions of detractors, vs. green–white (Table 2). The yellow–red sign achieved an NPS of 0.33 (95% CI 0.30–0.36) vs. −0.41 (95% CI −0.44 to −0.38) for green–white. The yellow–red cabinet achieved an NPS of 0.48 (95% CI 0.45–0.51) vs. −0.61 (95% CI −0.64 to −0.58) for green–white.

Discussion

This prospective, small, non-representative pilot study of the Australian general population found that yellow–red signs and cabinets may be significantly preferred and reported as easier to identify over green–white counterparts for the public identification of AEDs. Age and ethnicity may be associated with the ease of identifying the yellow–red signs and cabinets. Of note, increased age may be associated with an increased preference for the yellow–red sign over the green–white alternative. It was very encouraging that the majority of the general population may be comfortable in using AEDs in a situation of OHCA and the majority may be likely to use an AED if this situation did arise. In comparison with those of green–white alternatives, yellow–red AED signs and cabinets may have higher proportions of promoters and lower proportions of detractors regarding public engagement.

The societal toll of sudden cardiac arrest is large. Australia experiences over 20,000 sudden cardiac arrests each year, which is associated with annual economic losses of AUD 2 billion

(USD 1.42 billion) and productivity losses comparable to those from all cancers combined (27). To reduce sudden cardiac death, specifically that associated with OHCA, societal change is necessary (12). It is known that rapid defibrillation is a necessary complement to CPR for preventing mortality in cases of OHCA (5–7), and it is intuitive that the swift use of an AED by a lay responder in this situation (8–10) relies on them being able to quickly identify the AED's location within a community environment. In this emergency scenario, it is also intuitive that the use of signs utilising vivid colour combinations, such as yellow–red, would likely catch the attention of lay responders quicker and more effectively than the use of placid colour combinations, such as green–white (18). Further, the green–white colour combination is commonly used in society to indicate a range of signs, including those demarcating first aid kits and building exits, and, accordingly, it is likely to be less clear in the public's psyche as a sign specifically indicating the presence of an AED in life-threatening emergencies. However, given that only yellow–red and green–white colour combinations were evaluated in the present study, future research should consider investigating other vivid colour combinations that are different to these green–white colour combinations, such as blue–red.

There would likely be significant societal benefit from a unique, clearly recognisable sign, utilising a vivid yellow–red colour combination, for the broadly standardised identification of publicly accessible AEDs. The present study provides evidence that members of the Australian general population may engage more with, prefer and more easily identify yellow–red AED signs and cabinets compared with current green–white alternatives. As the public recognition of current green–white AED signage is limited and no single sign is implemented broadly (16), we propose that yellow–red signs and cabinets be considered by public health authorities for the standardised identification of publicly accessible AEDs. We also urge public health authorities to acknowledge the public's willingness to use AED and to take urgent steps to enable widespread availability of AEDs for prompt public access defibrillation in cases of OHCA. However, the issue of signage colour applies to all emergencies within society, especially those that involve EMS vehicles. Signage for emergencies should be vibrant wherever possible, to increase alertness and engagement for the situation in the members of the public that view them (17, 18).

However, colour combinations must be distinct for each respective emergency, to not confuse the lay responders.

This study has multiple limitations. Although the survey was open to all members of the Australian general population and no restrictions or exclusion criteria were applied so that the sample would be representative, potential bias may have been incurred as those that responded to the email and social media invitation to participate may have been those with greater engagement with the content evaluated in the present study. Further, data were not available regarding the number of people who had access to the survey link but did not participate. As the outcomes of the study were self-reported, there is the potential for either under or overreporting based on participant characteristics. Although no socioeconomic restrictions were employed within the study's inclusion criteria, only people within Australia were evaluated, and accordingly the translatability of the present findings to other countries is unknown and requires future investigation. The characteristics of the study population may provide a source of bias and may not be completely representative of the general population, particularly given that the mean age was just over 30 years old, about 60% were of female gender, over 80% were of white race and ethnicity and over 20% were healthcare workers. As no questions were proposed regarding participants' prior experience with OHCAs, it is challenging to infer from the present survey how and whether the colour of publicly accessible AED signs and cabinets may effectively affect the public attitudes to use a publicly accessible AED in the event of OHCA. In addition to this question, future research should also seek to investigate if participants have ever been involved in an OHCA resuscitation, if they found it difficult to locate an AED and, if so, was it due to AED location, sign or cabinet colour or another reason. These data are crucial to completely describing the role of sign and cabinet colours in influencing public attitudes to AED use in OHCA.

Conclusions

This prospective, small, non-representative pilot study of the Australian general population found that yellow–red signs and cabinets may be significantly preferred and easier to identify over green–white counterparts for the public identification of AEDs. There may also be a reasonable public willingness to use AEDs in OHCAs. As the public recognition of current green–white AED signage is limited and no single sign is implemented broadly, we propose that yellow–red signs and cabinets be considered for the standardised identification of publicly accessible AEDs. Public health authorities should be encouraged by the public's willingness to use AEDs and initiate steps to have widespread availability of AEDs in out-of-hospital cardiac arrest. However, further major and more representative, public consideration and investigation must be conducted.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Western Sydney Local Health District Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JGK: conception, acquisition of data, analysis and interpretation of data, drafting article, revising the article critically for intellectual content, final approval of the version to be published. SM, AA, MN, GJP, CKC, AT, and PK: conception, analysis and interpretation of data, revising the article critically for intellectual content, final approval of the version to be published. All authors contributed to the article and approved the submitted version.

Conflict of interest

PK is currently the principal investigator of the PROTECT-ICD trial, which is supported by funding from Biotronik Australia via a research grant to Western Sydney Local Health District, Sydney, Australia.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1178148/full#supplementary-material

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Non-revascularized chronic total occlusions impact on substrate and post-ablation results in drug-refractory electrical storm

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Background and aims: There is limited data concerning the effect of non-revascularized chronic total occlusions (NR-CTOs) after VT ablation. This study sought to evaluate the impact of NR-CTOs after ablation for electrical storm (ES).
Methods: Post-hoc retrospective analysis of data regarding 64 consecutive post-myocardial infarction patients (out of which 12 patients with NR-CTOs and 52 without NR-CTOs) undergoing substrate ablation for ES with an available median follow-up of 37.53 (7.25–64.65) months. Ablation result was assessed by inducibility of sustained monomorphic VT (SMVT) during final programmed ventricular stimulation (PVS). The primary endpoints were all-cause mortality and VT/VF recurrences after ablation, respectively, stratified by the presence of NR-CTOs. The secondary endpoint was to assess the predictive effect of NR-CTOs on all-cause mortality and VT/VF recurrences in relation to other relevant prognostic factors.
Results: At baseline, the presence of NR-CTOs was associated with higher bipolar BZ-to-total scar ratio (72.4% ± 17.9% vs. 52% ± 37.7%, $p = 0.022$) and more failure to eliminate the clinical VT (25% (3) vs. 0% (0), $p < 0.001$). During follow-up, overall all-cause mortality and recurrences were more frequent in the NR-CTO subgroup (75% (9) vs. 19.2% (10), log rank $p = 0.003$ and 58.3% vs. 23.1% (12), log rank $p = 0.042$ respectively). After adjusting for end-procedural residual SMVT inducibility, NR-CTOs predicted death during follow-up (HR 3.380, $p = 0.009$) however not recurrence (HR 1.986, $p = 0.154$).
Conclusions: NR-CTO patients treated by RFCA for drug-refractory ES demonstrated a higher ratio of BZ-to-total-scar area. In this analysis, NR-CTO was associated with worse acute procedural results and may as well impact long-term outcomes which should be further assessed in larger patient populations.

KEYWORDS
chronic total occlusion, electrical storm, catheter ablation, risk stratification, ventricular tachycardia, ischemic cardiomyopathy

1. Introduction

Non-revascularized chronic total occlusions (NR-CTOs) increase long-term mortality and appropriate implantable cardioverter defibrillator (ICD) therapies in patients with ischemic cardiomyopathy (ICM) (1–4). This has been demonstrated in both primary and secondary sudden cardiac death prevention ICD recipients. Limited data has assessed the

prognostic effect of NR-CTOs after ventricular tachycardia (VT) ablation (5–7). However, the impact of NR-CTOs after electrical storm (ES) ablation is unknown.

2. Methods

2.1. Study population

We performed a single-centre longitudinal retrospective analysis on available data regarding the baseline characteristics and post-procedural course of consecutive patients that fulfilled the following set of inclusion criteria.

- Post-myocardial infarction (post-MI) patients.
- At least three distinct episodes of sustained ventricular monomorphic tachycardia (SMVT) treated by adequate ICD therapies in a 24-h interval refractory to medical treatment and without reversible triggers (8–10).
- Treated by radiofrequency catheter ablation (RFCA) targeting ventricular arrhythmic substrate from January 2014 to June 2021.

Patients with ES induced by acute coronary syndromes, patients with no coronary angiography prior to ablation (two patients) and patients receiving surgical or percutaneous revascularization (one patient during index hospitalization) during the follow-up interval were excluded.

2.2. Imaging, electrophysiology study and ablation strategy

All patients underwent coronary angiography during the same hospitalization, prior to the moment of ablation or at the referring hospital, prior to transfer. With the exception of NR-CTOs, potentially significant lesions were defined by ≥70% luminal stenosis (50% for left main lesions), as assessed by two senior interventional cardiologists. Multivessel disease (MVD) was defined by at least one lesion ≥70% simultaneously present or previously treated in at least two epicardial coronary arteries. NR-CTOs were defined angiographically in an untreated [neither surgically nor percutaneously (PCI)] vessel based on the lesion morphology characteristics (as evaluated by two senior interventional cardiologists), irrespective of the degree of anterograde or retrograde collateral flow. NR-CTOs were considered to be incidentally diagnosed by pre-ablation angiography if the patient had no previously documented MI compatible with the NR-CTO localization; NR-CTOs were considered to be clinical if the patient had a previously documented MI compatible to the NR-CTO localization. Mitral regurgitation severity and biplane Simpson-based left ventricular ejection fraction (LVEF) were defined by transthoracic echocardiography formally-recommended criteria prior to ablation (11, 12).

All patients underwent electrophysiological study (EPS) and RFCA in a fasting state under conscious sedation and analgesia. EPS was performed using dedicated recording and analysis system (Boston Scientific Labsystem PRO EP Recording System v.2.7.0.16). High density electroanatomical mapping [>1,800 points, 70% of points focusing on scar and its border-zone (BZ)] was performed in sinus rhythm (SR) with 16–500 Hz signal filtering (CARTO-3^{TM}, Biosense Webster, Diamond Bar, California). Mapping/ablation catheter was placed into the RV via transfemoral approach or into the LV via transseptal or retrograde aortic approach. When required, epicardial access was obtained by fluoroscopy-guided anterior percutaneous subxiphoid puncture. Remote magnetic navigation (RMN) (Niobe II, Stereotaxis Inc., St. Louis, MO) and/or multielectrode catheter mapping (decapolar or duodecapolar) was used at the discretion of the electrophysiologist.

Normal myocardium was electrically defined by endocardial bipolar signals amplitude >1.5 mV, LV unipolar signals amplitude >8.3 mV, RV unipolar signals amplitude >5.5 mV and epicardial bipolar signals amplitude >1 mV, while dense scar and borderzone (BZ) myocardium were defined by endocardial bipolar signals <0.5 mv and 0.5–1.5 mV, respectively. Area measurements (total scar area, dense scar area) were manually performed using the integrated CARTO-3 measuring software tool based on the end-procedural voltage electroanatomical map as defined above (BZ scar area and BZ to total scar ratio were derived from the directly measured values). The ablation strategy was based on a previously published scar-dechannelling protocol targeting conduction channel entrances (CCEs) (13) within the scar BZ using open-irrigated ablation catheters (35–50 W, 45°C). Activation/entrainment mapping were performed if VTs were spontaneously or mechanically induced during mapping and were hemodynamically tolerated by the patient.

After elimination of CCEs, a programmed ventricular stimulation (PVS) was routinely performed with at least 2 drive cycle lengths (CLs) and 4 extra stimuli (ESx) [3 ESx in patients with heart failure (HF) symptoms at rest or extreme frailty] (at a minimum of 200 ms or until ventricular refractoriness was reached) from 2 sites of the BZ area (usually medially and laterally to the scar) to assess for VT inducibility [as previously described (14)]. PVS could not be performed in three patients (4.68% of the entire population, all of them without NR-CTOs). If SMVTs [which were considered relevant if their cycle lengths (CLs) ≥250 ms] (15) were induced during PVS, scar reconnection was reassessed and the scar-dechannelling protocol was repeated. If the end-procedural post-ablation PVS induced any SMVT (CL ≥250 ms), the patient was considered to have residual SMVT PVS-inducibility. A SMVT was considered to be the clinical SMVT based on the 12-lead electrocardiogram QRS morphology or based on ICD-derived intracardiac electrograms with similar (±20 ms) CLs. Data regarding procedural characteristics was reported from each patient's last performed ablation procedure.

2.3. Follow-up protocol

All patients were monitored from the most recent ES ablation procedure and all the observed events were assessed in relation to the last procedure. Data was obtained from medical records and routine periodical 6 month-interval post-RFCA ICD

interrogation. For patients not evaluated in our center, data was obtained from telephone interviews addressed to the referring physicians and patients and from ICD interrogations performed by the referring physicians. ICD interrogation was performed in all patients that were alive in January 2022.

Post-ablation recurrence was defined by SMVT or VF episodes which were adequately treated by either antitachycardia pacing and/or internal electrical shock. Post-ablation detection zones were programmed accordingly to allow detection of any ventricular arrhythmia which was previously spontaneously or PVS-induced (−20 bpm relative the slowest recorded VT). There were no monitoring zones below this VT rate threshold. All-cause mortality rates were retrospectively analyzed during the post-RFCA monitoring interval, irrespective of cardiovascular and non-cardiovascular causes of death.

The study protocol complied with the Declaration of Helsinki and it was approved by the human research committee of the Emergency Clinical Hospital of Bucharest Ethics Committee (12521-01/04/2022).

2.4. Endpoints

The primary endpoints were all-cause mortality and VT/VF recurrences, respectively, in the two subgroups (with NR-CTOs and without NR-CTOs, respectively). The secondary endpoint was to evaluate the predictive effect of NR-CTOs on primary endpoints in relation to other relevant prognostic factors.

2.5. Statistical analysis

Continuous data was expressed as mean ± standard deviation (SD) for normally distributed data and median (IQR) for non-normally distributed data. Categorical data was expressed as percentage (count). The normality of data was evaluated by Kolmogorov-Smirnov test. Categorical variables were compared using the Fisher's exact test/chi-square analysis and continuous variables were compared using Student t-test if normally distributed and non-parametric tests (Mann-Whitney *U*-Test).

Survival curves were plotted via Kaplan–Meier method and the statistical pairwise over strata comparison between curves was determined using the log-rank test. Univariate and multivariate Cox regression analyses were performed in order to determine the predictive factors. Variables with $P < 0.2$ in the univariate analysis or were then included in the multivariable Cox regression analysis for the determination of hazard ratio (HR) and its 95% confidence interval (CI). The number of predictors assessed in each multivariable model was adapted to the number of events observed during follow-up.

A 2-sided p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 23 (IBM Corp., Armonk, NY) software and Prism 9 Version 9.5.0 (GraphPad Software, LLC).

3. Results

3.1. Baseline characteristics

Sixty-four consecutive patients were included and monitored for a median interval of 34.36 (7.25–63.65) months. The baseline characteristics are summarized in **Table 1**. The median interval between ES diagnosis and the ablation procedure was 0.8 (0.05–2) weeks.

In the NR-CTO group, there were seven ($n = 7$) patients with one NR-CTO and five ($n = 5$) patients with two NR-CTOs. The localization of the NR-CTOs was as following: LAD (41.7%, $n = 5$), LCX (25%, $n = 3$) and RCA (75%, $n = 9$). There were only two patients (16.7%) within the NR-CTO subgroup with incidentally diagnosed NR-CTOs and ten patients (83.3%) with NR-CTOs compatible to the localization of previously documented MIs. Additionally, at the moment of ablation there were five patients with residual potentially significant coronary stenoses [LCX (3.1%, $n = 2$) and RCA (4.7%, $n = 3$)], all of which only received medical treatment during the follow-up interval.

Hospitalization duration was almost two-fold higher in the NR-CTO subgroup (10 (23) vs. 5 (3) days), however without statistical significance ($p = 0.06$).

TABLE 1 Baseline characteristics of the electrical storm cohort stratified by the presence of NR-CTO.

	All ($n = 64$)	NR-CTO ($n = 12$)	Without NR-CTO ($n = 52$)	p
Males	85.9% (55)	83.3% (10)	86.5% (45)	0.67
Age	62.6 ± 11.1	66.9 ± 7.76	61.6 ± 11.6	0.14
Hypertension	73.4% (47)	75% (9)	73.1% (38)	0.99
T2DM	29.7% (19)	33.3% (4)	28.8% (15)	0.73
CKD	25% (16)	25% (3)	25% (13)	0.99
Active smoker	26.6% (17)	25% (3)	26.9% (14)	0.99
Multivessel CAD	64.1% (41)	83.3% (10)	59.6% (31)	0.18
Single vessel CAD	35.9% (23)	16.7% (2)	40.4% (21)	0.02
Two vessel CAD	31.3% (20	16.7% (2)	34.6% (18)	
Three vessel CAD	32.8% (21)	66.7% (8)	25% (13)	
Prior PCI	59.4% (38)	41.7% (5)	63.5% (33)	0.20
Prior CABG	15.6% (10)	41.7% (5)	9.6% (5)	0.01
Beta-blocker prior to current ES	79.7% (51)	83.3% (10)	78.8% (41)	0.99
Amiodarone prior to current ES	60.9% (39)	66.7% (8)	59.6% (31)	0.75
AF at admission	14.1% (9)	16.7% (2)	13.5% (7)	0.67
NYHA III/IV at admission	29.7% (19)	41.7% (5)	26.9% (14)	0.31
Number of internal shocks	5 (3.5–12)	4.5 (4–6.5)	5 (3–17)	0.35
Clinical VT rate (bpm)	161.36 ± 43.43	156 ± 56.22	162.25 ± 42.38	0.79
Prior CRT	10.9% (7)	0 (0)	13.5% (7)	0.33
LVEF	31.41 ± 10.9	27.7 ± 8.69	32.2 ± 11.3	0.14
Moderate-or-severe FMR	35.9% (23)	66.7% (8)	28.8% (15)	0.02

NR-CTO, non-revascularized chronic total occlusion; T2DM, type 2 diabetes mellitus; AF, atrial fibrillation; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; FMR, functional mitral regurgitation; VT, ventricular tachycardia; CRT, cardiac resynchronization therapy; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; CAD, coronary artery disease; CKD, chronic kidney disease; ES, electrical storm.

Overall, 35.9% ($n = 23$) patients had moderate-or-severe functional mitral regurgitation (FMR) (66.7% ($n = 8$) in the NR-CTO subgroup compared with 28.8% ($n = 15$) in the subgroup without NR-CTOs, $p = 0.02$).

3.2. Procedural characteristics

Procedural characteristics are summarized in Table 2. The number of procedures per patient were: one procedure (71.9%, $n = 46$), two (20.3%, $n = 13$), three (6.3%, $n = 4$) and one patient (1.6%) underwent four procedures. There were no significant differences between NR-CTO and without NR-CTO subgroups with the exception of failure of clinical VT elimination ablation result which was more frequent in the NR-CTO subgroup compared to those without (25% vs. 0%, $p < 0.001$). Out of the five ($n = 5$) NR-CTO patients with residual SMVT inducibility, three ($n = 3$) developed periprocedural progressive HF symptoms and were deferred from epicardial mapping. The other two patients ($n = 2$) underwent epicardial mapping with no targetable subepicardial substrate.

There were no significant differences in the number of ESx used during PVS in the cases with NR-CTOs vs. those without NR-CTOs ($p = 0.489$). There were three patients from the subgroup with no NR-CTOs which were deferred from post-ablation PVS testing.

The NR-CTO subgroup had a higher bipolar BZ-to-scar ratio (%) compared to the subgroup without NR-CTO (72.4 (17.9) vs. 52.0 (37.7), $p = 0.022$). There were no differences in bipolar BZ-to-scar ratio in the NR-CTO subgroup in the presence of incidental NR-CTOs (71.7% vs. 72.4% in those with localization-compatible MI history, $p = 0.936$). Moderate-or-severe FMR did not influence residual SMVT inducibility at PVS (OR 2.286, CI 95% 0.748–6.986, $p = 0.147$). However, BZ-to-scar ratio did not predict SMVT inducibility (OR 0.985, CI 95% 0.985–1.045, $p = 0.329$).

At final PVS, the NR-CTO subgroup had a significantly higher rate of residual clinical VT inducibility (25% (3) vs. 0% (0), $p < 0.001$) and a higher (yet non-significant) rate of residually inducible SMVTs compared to the subgroup without (41.6% (5) vs. 23.1% (12), $p = 0.27$).

TABLE 2 Procedural characteristics stratified by the presence of NR-CTO.

	All ($n = 64$)	NR-CTO ($n = 12$)	Without NR-CTO ($n = 52$)	p
Multiple procedures	28.1% (18)	50% (6)	23.1% (12)	0.08
Procedure duration (mins)	190.78 ± 69.73	201 ± 60.62	188.23 ± 72.23	0.59
Fluoroscopy duration (mins)	9.36 ± 6.59	7.97 ± 5.63	10.29 ± 7.25	0.43
Duration of hospitalization (days) [median (IQR)]	6 (6)	10 (23)	5 (3)	0.06
Epicardial ablation	10.9% (7)	0 (0)	13.5% (7)	0.33
RMN-guided ablation	76.6% (49)	75% (9)	76.9% (40)	0.99
Multielectrode catheter-mapping during EP study	25% (16)	16.7% (2)	26.9% (14)	0.71
Ablation points	46.41 ± 20.4	46.88 ± 26.04	46.29 ± 19.22	0.91
Total scar area [bipolar, sqcm (SD)]	54.5 (50.3)	74.7 (46)	53.7 (54.8)	0.743
Dense scar area [bipolar. sqcm (SD)]	19.4 (19.7)	20.8 (19.8)	18.4 (24.2)	0.743
Border-zone area [bipolar. sqcm (SD)]	31.2 (32.6)	46 (31.6)	27.7 (32.4)	0.326
BZ to total scar ratio [bipolar. % (SD)]	60.7 (35.8)	72.4 (17.9)	52.0 (37.7)	0.022
BZ to total scar ratio [unipolar, % (SD)]	45.4 (17.7)	54 (17.5)	41.7 (16.7)	0.043
PVS with 4 ESx	68.9 (42)	58.3 (7)	71.4 (35)	0.489
PVS with 3-ESx	31.1 (19)	41.7 (5)	28.6 (14)	
Number of induced VTs	2.14 ± 2.25	1.60 ± 0.84	2.26 ± 2.44	0.40
SMVT at PVS	26.5% (17)	41.6% (5)	23.1% (12)	0.27
Failure of clinical VT elimination	4.6% (3)	25% (3)	0% (0)	<0.001

NR-CTO, non-revascularized chronic total occlusion; VT, ventricular tachycardia; SMVT, sustained monomorphic ventricular tachycardia; PVS, programmed ventricular stimulation; EP, electrophysiological study; RMN, remote magnetic navigation; BZ, border zone.

3.3. Post-ablation outcomes

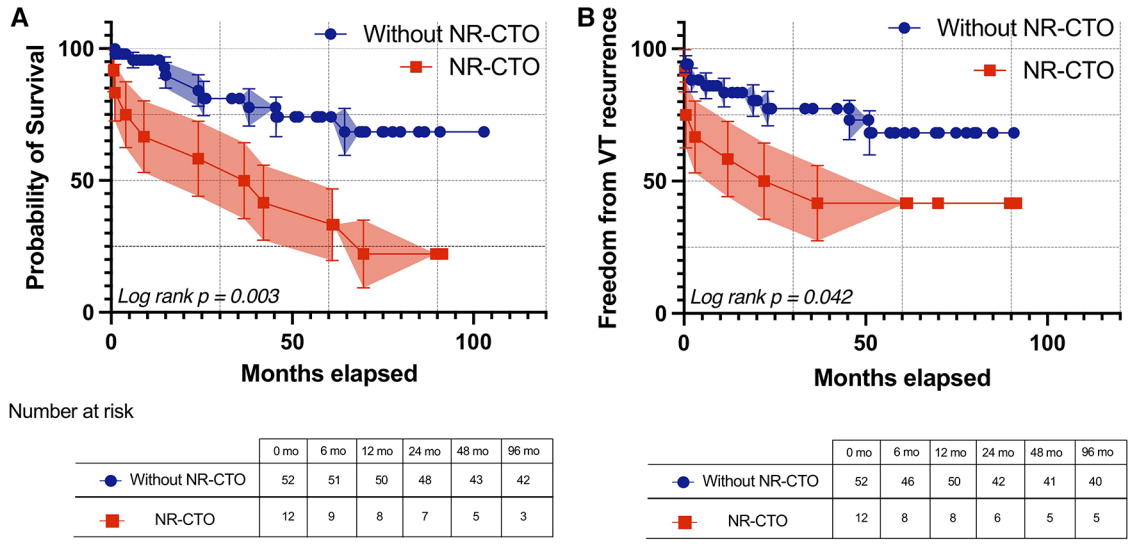
During the follow-up interval, Kaplan-Meier survival curves (Figure 1A) demonstrated that the NR-CTO subgroup had significantly lower survival compared to patients without NR-CTO (log-rank $p = 0.003$) and more frequent recurrences (log rank $p = 0.042$) (Figure 1B).

The overall rate of all-cause mortality during follow-up was 29.7% ($n = 19$). All-cause mortality was higher in patients with inducible SMVT at PVS (55.6%, $n = 10$) vs. those without inducible SMVT at PVS (19.6%, $n = 9$), $p = 0.007$. The overall rate of recurrence during follow-up was 29.7% ($n = 19$). Recurrences were higher in patients with inducible SMVT at PVS (66.7%, $n = 12$) vs. those without inducible SMVT at PVS (15.2%, $n = 7$), $p < 0.001$.

Overall post-ablation, 84.4% (n = 54) patients received beta-blockers (NR-CTO 91.7% ($n = 11$) vs. without NR-CTO 82.7% ($n = 43$), $p = 0.672$) and amiodarone in 65.5% ($n = 42$) (NR-CTO 83.3% ($n = 10$) vs. without NR-CTO 61.5% ($n = 32$), $p = 0.193$). Neither post-ablation beta-blockers ($p = 0.99$ for mortality, $p = 0.99$ for recurrences) nor post-ablation amiodarone ($p = 0.16$ for mortality, $p = 0.56$ for recurrences) influenced mortality or recurrences.

3.4. Predictive risk factors for clinical endpoints

Cox regression analysis results are summarized in Table 3 and are further detailed in Supplementary Table S1. Residual SMVT at PVS predicted all-cause mortality (HR 5.384, CI 95% 2.155–13.446, $p < 0.001$) and recurrences (HR 7.185, CI 95% 2.666–19.365, $p < 0.001$). In multivariable analysis, residual SMVT at PVS independently predicted all-cause mortality when adjusted by age aHR 4.965, CI 95% 1.847–11.933, $p < 0.001$) and recurrences



Number at risk

	0 mo	6 mo	12 mo	24 mo	48 mo	96 mo
Without NR-CTO	52	51	50	48	43	42
NR-CTO	12	9	8	7	5	3

	0 mo	6 mo	12 mo	24 mo	48 mo	96 mo
Without NR-CTO	52	46	50	42	41	40
NR-CTO	12	8	8	6	5	5

FIGURE 1
Kaplan-Meier survival curves with 95% confidence intervals of all-cause mortality (A) and freedom from ventricular arrhythmia recurrence (B) during follow-up in patients with at least one NR-CTO (red line) and without NR-CTOs (blue line). NR-CTO, non-revascularized chronic total occlusion; VT, ventricular tachycardia.

when adjusted by NYHA III or IV symptoms at admission (aHR 5.214, CI 95% 2.056–13.219, $p = 0.001$).

Particularly, univariable Cox regression showed that NR-CTO predicted all-cause mortality (HR 3.601, CI 95% 1.459–8.886, $p = 0.005$). In multivariable Cox regression, although NR-CTO remained an independent predictor for all-cause mortality during follow-up when adjusting for residual SMVT at PVS [adjusted HR (aHR) for NR-CTO 5.605, $p = 0.001$], age (aHR for NR-CTO 2.76, $p = 0.03$) and NYHA III or IV symptoms at admission (aHR for NR-CTO 2.09, $p = 0.003$), respectively, it was not significant when adjusting for the presence of moderate-or-severe FMR ($p = 0.15$) (**Table 3** and **Supplementary Table S1**). NR-CTO did not predict recurrence (HR 2.252, CI 95% 0.992–6.435, $p = 0.052$) in univariable Cox regression.

4. Discussions

4.1. Acute ablation results

In our study, five of twelve NR-CTO patients had residual post-ablation SMVT inducibility compared to the lower rates of positive PVS observed in those without NR-CTOs (23.1%). Moreover, ablation was not able to eliminate the clinical VT in three out of twelve NR-CTO patients (which was however successfully abolished in all those without NR-CTO). This is highly significant as failure to eliminate the clinical VT during ES ablation is strongly associated with short-term very high mortality (16). Furthermore, we emphasize that the PVS protocol was similarly aggressive and there were no significant differences of medical treatment in NR-CTO subjects compared to those without NR-CTOs.

Our results contrast with those of the only three analysed post-VT ablation NR-CTO cohorts in which ablation results were not affected by NR-CTOs (5–7). However, this difference may be influenced firstly by the lower ratio of ES patients included in their analysis (less than one third in the former and ≈60% in the latter) and the relatively lower LVEF observed in our NR-CTO subgroup. Moreover, only three-ESx based PVS was used in Lurz et al.'s protocol which may impact its sensitivity (5).

We hypothesize that our observations can be explained by more complex substrate which limits RFCA efficiency, especially in ES acute settings. In the presence of CTOs, scar border-zone (BZ) area is usually expected to be larger and more heterogenous (6) which strongly correlates with both spontaneous incident VTs (17) and VT inducibility at PVS (18). Most myocardial segments which are supplied by NR-CTOs have less than 50% scar transmurality (19). Even more, recanalization of CTOs may promote reverse remodelling particularly within the BZ (20). Hence, the presence of infarct-related CTOs is known to double the risk of ES development (21). Our dataset showed that although the total scar area was not significantly higher in the NR-CTO subgroup (74.7 sqcm vs. 53.7 sqcm), there was however a significantly higher proportion of BZ myocardium within the total scar identified at electroanatomical mapping (72.4% compared to 52% in those without NR-CTOs) (**Figure 2**). Additionally, we considered the lack of epicardial ablation in the NR-CTO subgroup is most likely a result of the reduced analyzed sample. Out of the five NR-CTO patients with residual SMVT inducibility, three developed periprocedural progressive HF symptoms and were deferred from epicardial mapping. The other two patients underwent epicardial mapping with no targetable subepicardial substrate.

TABLE 3 Cox regression univariable and multivariable proportional hazards model for prediction of death during follow-up and recurrence during follow-up.

Outcome: Death during follow-up			
Univariable analysis			
Variable	HR	95% CI	*p*
NR-CTO	3.601	1.459–8.886	0.005
NYHA III or IV	2.846	1.148–7.052	0.02
Age	1.093	1.036–1.154	0.001
Residual SMVT	5.384	2.155–13.446	<0.001
LVEF	0.971	0.929–1.013	0.17
Male sex	1.131	0.646–1.980	0.66
Moderate-or-severe FMR	4.299	1.684–10.979	0.002
Multivessel disease	2.242	0.651–7.718	0.201
Multivariable analysis			
Residual SMVT	4.965	1.847–11.933	<0.001
Age	1.102	1.034–1.174	0.003
Outcome: recurrence during follow-up			
Univariable analysis			
Variable	HR	95% CI	*p*
NR-CTO	2.527	0.992–6.435	0.052
NYHA III or IV	2.962	1.198–7.325	0.01
Age	1.042	0.993–1.092	0.09
Residual SMVT	7.185	2.666–19.365	<0.001
LVEF	0.956	0.912–1.003	0.06
Male sex	1.076	0.580–1.995	0.81
Moderate-or-severe FMR	2.122	0.858–5.252	0.10
Multivessel disease	1.139	0.433–2.999	0.792
Multivariable analysis			
Residual SMVT	5.214	2.056–13.219	0.001
NYHA III or IV	2.675	1.059–6.760	0.037

The multivariable models included in this table consist of two of the most significant predictors in univariable Cox regression for death during follow-up and recurrences, respectively (see Supplementary Table S1 for other two-by-two prediction models related to NR-CTO effect and residual SMVT effect on long-term all-cause mortality and recurrences); SMVT, sustained monomorphic ventricular tachycardia; NR-CTO, non-revascularized chronic total occlusion; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; FMR, functional mitral regurgitation.

Considering that almost all CTOs generate myocardial ischemia even at rest, as proven by abnormal fractional flow-reserve (FFR), irrespective of collateral flow (22), it may be speculated that variable coronary flow can lead to changes in relevant electrical substrate which hinders its complete characterization during EPS (which can alter ablation results and, importantly, subsequent recurrences).

In addition, NR-CTO patients exhibited significantly more extensive CAD and significantly more frequent moderate or severe FMR. All of these may contribute to the trend of more severe HF symptoms (five out of twelve NYHA III/IV) in the NR-CTOs subgroup. Furthermore, more extensive CAD, systolic dysfunction and, interestingly enough, better developed collateralization have all predicted development of ischemic FMR after primary PCI in ST-elevation MIs (23).

Therefore, the presence of NR-CTOs may impact ES ablation outcomes due to substrate complexity and disease severity.

4.2. Long-term clinical course after ES ablation

In our cohort, post-ablation ES patients demonstrated high all-cause mortality (29.7% overall & 9.4% in the first year) and recurrences (29.7% overall & 20.3% in the first year). We observed that the most prominent driver of mortality in univariable analysis (5-fold higher risk) and recurrences (7-fold more probable) is residual SMVT inducibility at post-ablation PVS which is in line with previous publications (5, 6). Furthermore, residual SMVT maintained predictive effects on death and recurrences when adjusted by the presence of NR-CTOs and all other included factors. There are, however, multivariable models which have shown that other predictors (such as disease severity, comorbidities and procedural complications) may outweigh the effect of persistent inducibility at PVS (24).

In the presence of NR-CTOs, overall all-cause mortality (75%) and recurrences (58.3%) were significantly higher. However, these observations stem from a limited number of included patients (particularly with NR-CTOs) and should be further evaluated in larger samples. The excess mortality and incident VT episodes associated with NR-CTOs has been demonstrated in ICM patients, particularly in primary and secondary prevention ICD recipients (1–4, 25, 26). In addition, previous studies suggest that outcomes may be improved after NR-CTO revascularization (27). There is however, very limited published experience with NR-CTO patients after VT ablation (5–7).

Our analysis suggests that NR-CTOs independently predicted death after ES ablation when adjusted by SMVT inducibility at PVS, severe HF symptoms at admission, age and LVEF, respectively. Existing data suggests this effect was attenuated by confounding factors during a shorter interval of monitoring (≤20 months) predominantly after VT ablation (not ES) (5). One possible explanation of this difference could be the significantly longer monitored interval in our study. As previously emphasized, ES development in ICD recipients can be both a cause and an effect of HF progression, especially in certain HFrEF subgroups of patients (28). We believe it is highly valuable to distinguish previously stable patients which are more likely to respond well to ablation as opposed to end-stage HF cases which should rather receive specific advanced HF treatment such as cardiac transplant or mechanical devices.

In our cohort, NR-CTOs did not predict recurrences, which contrasts Di Marco et al.'s observations (6). This was especially evident when adjusting for PVS inducibility, which was not previously included in any prediction models. PVS (especially aggressive protocol with 4-extrastimuli) unmasks residual arrhythmogenic substrate which may become relevant for subsequent VT episodes which may explain why it drives recurrence prediction during follow-up.

Although significant coronary stenoses should be revascularized prior to ES ablation, addressing NR-CTOs before ablation may not be a reasonable option (especially if J-CTO scores are high). However, the NR-CTO effect on long-term mortality suggest that this decision should be revisited after ES

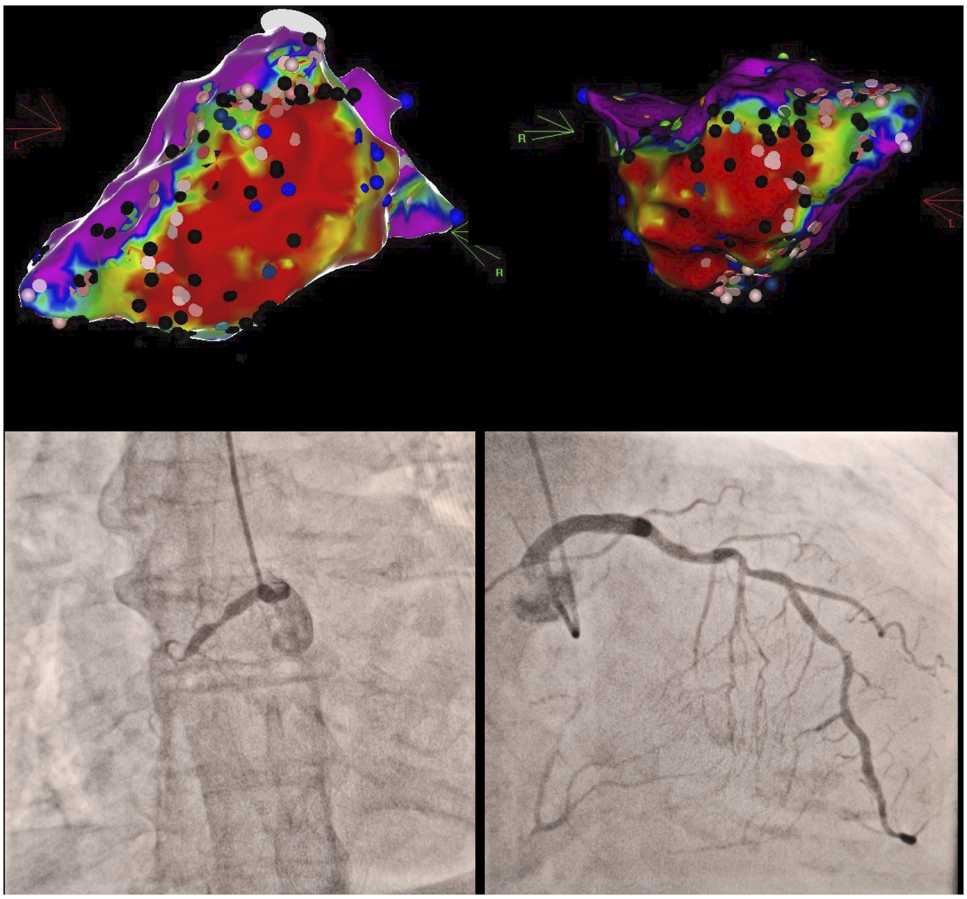


FIGURE 2
Clinical vignette in a case of proximal RCA chronic total occlusion with contralateral LAD septal collaterals (bottom) and extensive inferior wall to apical segment scar tissue in electroanatomical bipolar voltage mapping (top) with multiple conduction channel entries (black marks), intra-scar late potentials (blue marks).Red areas correspond to dense scar bipolar voltages (<0.5 mV), purple areas correspond to normal bipolar voltages (>1.5 mV), whereas intermediate colours (yellow-green-blue) correspond to border zone myocardial bipolar voltages (0.5–1.5 mV). RCA, right coronary artery; LAD, left anterior descending.

treatment, as selective revascularization may improve outcomes, particularly guided by viability (27). Considering the ongoing ischemia attributed to NR-CTO even at rest, tackling HF-inducing mechanisms by targeted therapies (as shown by the anti-arrhythmic effect of CRT vs. ICD in propensity-matched previous registries) may deny the manifestation (or recurrence) of ES or non-clustered VTs (29).

In summary, our data suggests there may be incremental mortality attributable to the presence of NR-CTOs in ablated ES patients. However, it seems not to be driven by recurrences, but by other mechanisms (most likely due to progressive HF deterioration). Consequently, identifying NR-CTOs in ES patients may warrant close monitoring after ablation due to the higher risk of unfavourable outcomes.

Last but not least, advanced age and severe HF symptoms at admission maintained independent prediction of death after ES ablation when adjusted by NR-CTO and positive PVS, respectively. This is in line with previous dedicated prognostic scores such as PAAINESD and I-VT (30–32). Furthermore, moderate-or-severe FMR is known to independently aggravate outcomes in HF patients (25, 33) and attenuated the effect of NR-CTOs on all-cause mortality. In our dataset, moderate-or-severe FMR did not influence recurrences.

5. Limitations

1. Data regarding NR-CTOs and CAD complexity were retrospectively acquired on a limited number of patients which were included in a post-hoc analysis. However, our cohort solely consisted of ES patients as opposed to previous cohorts which also included isolated VT cases.
2. The small number of events during follow-up (19 deaths and 19 recurrences) limited the maximum number of variables to be included in multivariable Cox regression models. Two-by-two Cox regression models have been included in Supplementary data section (**Supplementary Tables S1** and **S2**). This may hinder the complete understanding of each factor's effect in ES long-term clinical course.
3. There was no data available regarding Rentrop collateral grading and/or myocardial viability or ischemia inducibility. The potentially significant coronary lesions were not

evaluated by FFR (as defined in the Methods section). There were five patients with potentially significant lesions during ablation (however none with previous documented ischemia).
4. Monitoring zones were not uniformly applied below the previously described ICD programmed zones which may influence recurrence rates. However, if patients became symptomatic or if VT was diagnosed during follow-up, ICD zones were reprogrammed accordingly.
5. Long-term mortality endpoints were only based on all-cause mortality (irrespective of cardiovascular vs. non-cardiovascular mortality).
6. There was limited data concerning beta-blocker or amiodarone doses (or HF-directed treatment) prescribed prior to or post-ablation. However, there was no effect caused by post-ablation beta-blocker or amiodarone presence on the evaluated end-points.

6. Conclusions

NR-CTO patients treated by RFCA for drug-refractory ES demonstrated a higher ratio of BZ-to-total-scar area. In this analysis, NR-CTO was associated with worse acute procedural results and may as well impact long-term outcomes which should be further assessed in larger patient populations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Emergency Clinical Hospital of Bucharest Ethics Committee (12521-01/04/2022). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CC: Investigation, Methodology, Conceptualization, Data curation, Formal Analysis, Software, Visualization, Writing – original draft, Writing – review & editing. AN: Writing – review & editing, Data curation, Investigation, Resources. SB: Writing – review & editing, Conceptualization, Methodology, Project administration. CI: Writing – review & editing, Investigation, Methodology, Supervision. AD: Writing – review & editing, Investigation, Supervision. SO: Writing – review & editing, Conceptualization, Methodology, Supervision. RV: Validation, Visualization, Writing – review & editing, Writing – original draft, Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1258373/full#supplementary-material

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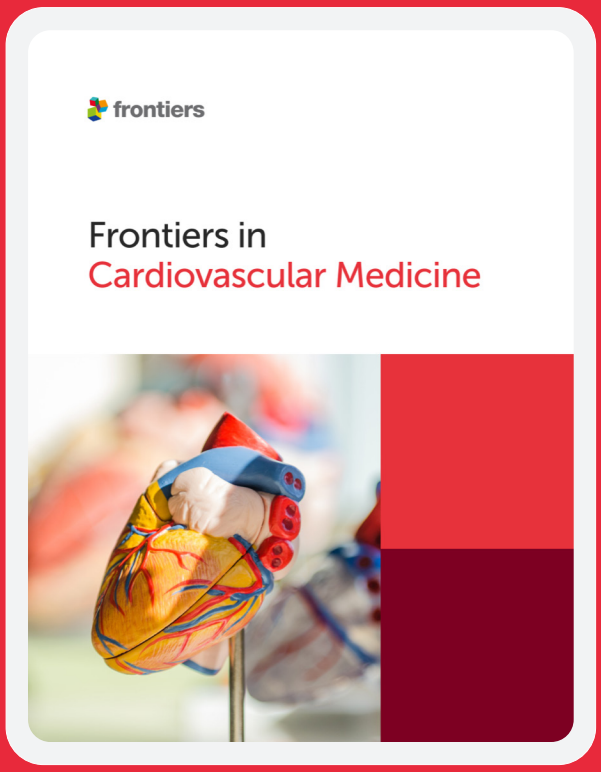

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