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Effect of myocardial scar size on the risk of ventricular arrhythmias in patients with chronic total coronary occlusion

Amira Assaf, Marisa van der Graaf, Nick van Boven, Maarten J.B. van Ettinger, Roberto Diletti, Mark G. Hoogendijk, Tamas Szili-Torok, Dominic A.M.J. Theuns, Sing-Chien Yap *

Department of Cardiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

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ABSTRACT

Background: The presence of an untreated chronic total coronary occlusion (CTO) is associated with a higher risk of ventricular arrhythmias (VAs). This increased risk may be modulated by the presence of an existing scar.
Objectives: To evaluate whether scar size is associated with VA in patients with an implantable cardioverter-defibrillator (ICD) and a CTO.
Methods: In this retrospective study we included patients with a CTO that received an ICD between 2005 and 2015. Scar size was estimated using the Selvester QRS score on a baseline 12-lead ECG. The primary endpoint was any appropriate ICD therapy.
Results: Our study population comprised 148 CTO patients with a median scar size at baseline of 18% (IQR, 9–27%). Patients with a scar size ≥18% more often had a CTO located in the left anterior descending artery and a higher proportion of poor left ventricular function (<35%) and infarct-related CTO compared to patients with a smaller scar size (<18%). During a median follow-up of 35 months (interquartile range [IQR], 8–60 months), 42 patients (28%) received appropriate ICD therapy. The cumulative 5-year event rate was higher in the patients with a large scar in comparison to those with a smaller or no scar (36% versus 19%, $P = 0.04$). Multivariable Cox regression analysis demonstrated that large scar and diabetes mellitus were independent factors associated with appropriate ICD therapy.
Conclusion: In ICD recipients with an untreated CTO, a larger scar is an independent factor associated with an increased risk of VA.

1. Introduction

A chronic total coronary occlusion (CTO) has been associated with an increased risk of ventricular arrhythmias, especially when the CTO is located in an infarct-related artery (IRA-CTO) [1–8]. The vulnerability for ventricular arrhythmias may be explained by the combination of presence of myocardial scar, scar border zone, and presence of residual ischemia despite collaterals [9]. This gives a complex myocardial infarction architecture consisting of islets of viable myocytes within scar tissue which may contribute to reentrant ventricular arrhythmias [10,11]. In patients with a previous myocardial infarction, total scar size as determined by late gadolinium enhanced cardiac magnetic resonance imaging (LGE-CMR) has been shown to be an independent predictor of ventricular arrhythmias [11–13]. To refine risk stratification in patients with untreated CTO, establishing the total scar size may thus be of potential value. As an alternative to LGE-CMR, the total scar size can be estimated from the 12-lead ECG using the Selvester QRS score [14,15]. The Selvester QRS score has shown a strong correlation with scar size and is applicable for patients with and without conduction abnormalities [16]. In the Selvester QRS score, points are awarded to Q-, R-, and S-wave amplitudes, durations, amplitude ratios, and notches in 10 of the 12 standard ECG leads (excluding leads III and aVR) [17]. We applied a semi-automatic method to determine the Selvester QRS score. Our hypothesis was that a larger myocardial scar size as determined by the

Abbreviations: CTO, chronic total coronary occlusion; ICD, implantable cardioverter-defibrillator; IRA-CTO, chronic total coronary occlusion in infarct-related artery; LGE-CRM, late gadolinium enhancement cardiac magnetic resonance imaging; LVEF, left ventricular ejection fraction; MEANS, modular ECG analysis system; PCI, percutaneous coronary intervention; SCD, sudden cardiac death; TIMI, Thrombolysis in Myocardial Infarction.

* Correspondence to: Sing-Chien Yap, Department of Cardiology, Erasmus MC, University Medical Center Rotterdam, dr. Molewaterplein 40, 3015, GD, Rotterdam, the Netherlands.
E-mail address: s.c.yap@erasmusmc.nl (S.-C. Yap).

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Selvester QRS scoring system is associated with a higher risk of ventricular arrhythmias in patients with an implantable cardioverter-defibrillator (ICD) and an untreated CTO.

2. Methods

2.1. Study population

The study population was identified using the prospective ICD registry of the Department of Cardiology of the Erasmus MC (Rotterdam, the Netherlands). First, we selected all consecutive patients with coronary artery disease who received an ICD for primary or secondary prevention between 2005 and 2015. Primary prevention ICD is defined as an ICD given to prevent sudden death in patients who have not yet suffered a life-threatening sustained ventricular arrhythmia, but who are at high risk of such an arrhythmia. Secondary prevention ICD is an ICD for patients who have already suffered a cardiac arrest or hemodynamic unstable ventricular tachycardia.

Secondly, we identified from this group all patients with an untreated CTO based on catheterization reports and/or coronary angiograms before ICD implantation. *CTO* was defined as an occlusion with absence of antegrade flow (TIMI [Thrombolysis in Myocardial Infarction] 0 flow) through the lesion with a presumed or documented duration of ≥3 months [18]. Occluded vessels that were surgically or percutaneously revascularized and secondary occluded vessels (i.e., diagonal branch, posterior descending artery, and posterolateral branches) were not classified as CTO in this study. Patients with untreated CTO were further subclassified as IRA-CTO or non-IRA CTO. IRA-CTO was defined as a CTO with a myocardial infarction in the territory of the affected coronary artery. Previous myocardial infarction had to be documented by Q waves on ECG and/or evidence of scar on imaging, such as regional wall motion abnormalities on echocardiography or late gadolinium enhancement on cardiac magnetic resonance imaging. Patients with only paced ECG were excluded for this study. The administrative censor date for follow-up data was January 2020. The Medical Ethics Committee of the Erasmus MC reviewed the study (MEC-2020-0971), and this study was not subjected to the Dutch Medical Research Involving Human Subjects Act. The study was carried out according to the ethical principles for medical research involving human subjects established by the Declaration of Helsinki, protecting the privacy of all the participants and the confidentiality of their personal information. This research was done without patient or public involvement.

2.2. Selvester QRS score

We calculated the Selvester QRS score based on baseline 12-lead ECGs according to the detailed guide for quantification of myocardial scar [17]. The raw data of digital 12-lead ECGs was collected and automated measurements were performed of the Q-, R-, and S-wave amplitudes, P-wave duration, and QRS duration using the modular ECG analysis system (MEANS) [19]. ECGs were then evaluated by two medical doctors for conduction disorders and placed into one of the following six categories: “left bundle branch block”, “right bundle branch block”, “left anterior fascicular block”, right bundle branch block and left anterior fascicular block”, “left ventricular hypertrophy”, or “no confounders” (*Supplemental Fig. 1*). Also, the presence of right atrial overload was considered when scoring (*Supplemental Fig. 2*). Age and sex adjustments were made to the scoring criteria: before scoring, all absolute amplitude criteria were corrected to the age of 55 in the scoresheet by increasing them 1%/year for those aged 54 and below and decreasing them 1%/year for those aged 56 years and above. For females, both duration and absolute amplitude criteria were further decreased by 10%. Subsequently, points were awarded for Q-, R-, and S-wave amplitudes, durations, amplitude ratios and notches in all leads except leads III and aVR. (*Supplemental Fig. 3 and 4*). Each point corresponds to a 3% scar of the left ventricular myocardium. There were no patients with pre-excitation, which would hamper QRS scoring.

2.3. Study endpoints

The primary endpoint was any appropriate ICD therapy defined as the delivery of ATP or shock for ventricular arrhythmias. The secondary endpoint was all-cause mortality.

2.4. Statistical analysis

Continuous data are presented as mean ± SD if the data were normally distributed or as median with interquartile range if otherwise. Categorical variables are presented by frequencies and percentages. Differences in continuous variables between groups were analyzed with an unpaired Student’s *t*-test or the Mann-Whitney *U* test, as appropriate. Differences in categorical variables were analyzed with the chi-square-test or Fisher’s exact test in the case of small expected cell frequencies.

The study population was divided into 2 groups based on the median scar size based on the Selvester QRS score. The cumulative event rates of appropriate ICD therapy of both groups were estimated with the Kaplan-Meier method and compared with the logrank test. Multivariable Cox regression analysis was used to identify independent factors associated with appropriate ICD therapy and all-cause mortality. The following candidate variables, besides scar size based on Selvester score, were considered: age at ICD implantation; sex; diabetes mellitus, left ventricular ejection fraction (LVEF) ≤35%; ICD indication (secondary versus primary prevention); and era of ICD implantation (before or after 2010). Factors with a P value <0.10 in the univariable Cox regression model were considered for the multivariable model. Data of the regression analysis are presented as hazard ratios (HR) and 95% confidence intervals (CI). P values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 28 (IBM Corporation, Armonk, NY).

3. Results

3.1. Study population

A total of 148 patients with an untreated CTO received an ICD during the study period. The baseline characteristics are presented in Table 1. The mean age at ICD implantation was 64 ± 10 years and 87% were men. An IRA-CTO was present in 55% of the study population. In patients with an available coronary angiogram (N = 83), angiographic CTO complexity was considered difficult (J-CTO score ≥ 2) in 78% of these patients and poor distal collateral flow (Rentrop grade ≤ 1) was observed in 29% of patients. Furthermore, complete (Rentrop grade 3) or partial (Rentrop grade 2) distal collateral filling was observed in 36% and 35%, respectively. As expected, patients who received an ICD for secondary prevention had a lower proportion of patients with a LVEF <35% in comparison to those who received an ICD for primary prevention (46% vs. 94%, P < 0.001). The baseline characteristics of patients with primary and secondary prevention ICD implantation is presented in *Supplemental Table 1*.

The calculated median scar size based on the Selvester QRS score was 18% (IQR 9%–27%). Eleven patients (7%) had a Selvester QRS score of zero. Using the median scar size as a cutoff-value, patients with a large scar (≥18%) more often had a CTO location in the left anterior descending artery, a higher proportion of LVEF <35% and IRA-CTO, and less hypertension and hypercholesterolemia compared to patients with a smaller or no scar (<18%) (Table 1).

3.2. Primary endpoint

During a median follow-up of 35 months (IQR 8–60), 42 patients (28%) experienced appropriate ICD therapy. The cumulative 5-year

Table 1
Baseline characteristics.

Variable	All patients $N = 148$	Scar size < 18% group $N = 68$	Scar size ≥ 18% group $N = 80$	P
Age at ICD implantation, years	64 ± 10	65 ± 9	63 ± 10	0.21
Male sex	129 (87)	63 (93)	66 (83)	0.07
Diabetes Mellitus	26 (18)	15 (22)	11 (14)	0.19
Hypertension	58 (39)	33 (49)	25 (31)	0.03
Hypercholesterolemia	59 (40)	36 (53)	23 (29)	0.01
eGFR, ml/min/1.73 m^2	69 ± 23	67 ± 24	71 ± 22	0.29
History of AF	23 (16)	11 (16)	12 (15)	0.84
LVEF ≤35%	105 (71)	42 (62)	63 (79)	0.02
Previous MI	129 (87)	58 (85)	71 (89)	0.53
History of PCI	71 (48)	34 (50)	37 (46)	0.65
History of CABG	14 (9)	6 (9)	8 (10)	0.81
Indication				
Primary prevention	77 (52)	31 (4)	46 (58)	0.15
Secondary prevention	71 (48)	37 (54)	34 (43)	0.15
Type of device				
Single chamber	87 (59)	18 (26)	17 (21)	0.46
Dual chamber	35 (23)	18 (26)	17 (21)	0.46
CRT-D	22 (15)	14 (21)	8 (10)	0.07
S-ICD	4 (3)	0 (0)	4 (5)	0.06
NYHA functional class				
Class I	24 (16)	9 (13)	15 (19)	0.36
Class II	106 (72)	48 (71)	58 (73)	0.80
Class III	18 (12)	11 (16)	7 (9)	0.17
ECG confounders				
ECG without confounders	77 (52)	41 (60)	36 (45)	0.06
LBBB	27 (18)	12 (18)	15 (19)	0.86
LAFB	26 (17)	8 (12)	18 (23)	0.08
RBBB	5 (3)	1 (1)	4 (5)	0.24
RBBB and LAFB	8 (5)	1 (1)	7 (9)	0.05
LVH	5 (3)	5 (7)	0 (0)	0.01
CTO characteristics				
CTO in multiple vessels	15 (10)	6 (9)	9 (11)	0.63
Patients with IRA-CTO	81 (55)	30 (44)	51 (64)	0.02
Localization of CTO				
- LAD	57 (39)	19 (28)	38 (48)	0.02
- RCA	88 (60)	48 (71)	40 (50)	0.01
- LCX	19 (13)	9 (13)	10 (13)	0.89
J-CTO registry score ≥ 2	65/83 (78)	33/40 (83)	32/43 (74)	0.37
Rentrop grade ≤ 1	24/83 (29)	9/40 (23)	15/43 (35)	0.21
Rentrop grade 2	29/83 (35)	13/40 (33)	16/43 (37)	0.65
Rentrop grade 3	30/83 (36)	18/40 (45)	12/43 (28)	0.11
Cardiac medication				
ACE inhibitor or ARB	125 (85)	57 (84)	68 (85)	0.84
Amiodaron	31 (21)	15 (22)	16 (20)	0.76
Betablocker	131 (89)	59 (87)	72 (90)	0.54
Antiplatelet therapy	125 (85)	56 (82)	69 (86)	0.51
Digoxin	15 (10)	4 (6)	11 (14)	0.11
Diuretics	84 (57)	37 (54)	47 (59)	0.60
Flecainide	1 (0.7)	1 (1)	0 (0)	0.28
Vitamin K antagonist	17 (11)	6 (9)	11 (14)	0.25
DOAC	1 (0.7)	1 (1)	0 (0)	0.28
Statin	126 (85)	60 (88)	66 (83)	0.33

Data are presented as n (%) or mean ± standard deviation. Abbreviations: AAD, antiarrhythmic drugs; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CRT—D, cardiac resynchronization therapy defibrillator; CTO, chronic total occlusion; DOAC, direct acting oral anticoagulant; IRA-CTO, infarct-related artery chronic total occlusion; J-CTO, Japanese Multicenter CTO Registry score; LAD, left anterior descending coronary artery; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LCX, left circumflex coronary artery; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RCA, right coronary artery; RBBB, right bundle branch block; S-ICD, subcutaneous implantable cardioverter defibrillator.

event rate was higher in CTO patients with a large scar (≥18%) in comparison to those with a smaller or no scar (<18%) (36% versus 19%, $P = 0.04$) (Fig. 1). Univariable Cox regression analysis showed that a large scar (≥18%) was associated with an almost two-fold increased risk of appropriate ICD therapy (HR 1.97; 95% CI 1.02–3.79, $P = 0.04$) (Table 2). Multivariable Cox regression analysis demonstrated that a large scar (adjusted HR 2.29; 95% CI 1.16–4.51, $P = 0.02$) and diabetes mellitus (adjusted HR 0.23; 95% CI 0.06–0.94, $P = 0.04$) were independent predictors of appropriate ICD therapy (Table 2). In the multivariable analysis, a secondary prevention ICD demonstrated a trend towards a higher risk of appropriate ICD therapy (adjusted HR 2.02; 95% CI 0.99–4.10, $P = 0.051$), but this did not reach statistical significance.

As a sensitivity analysis, a subgroup analysis was performed for patients who received an ICD for primary prevention ($N = 77$) or secondary prevention ($N = 71$) (*Supplemental Fig. 5 and 6*). In the primary prevention ICD group, a large scar demonstrated a trend towards an increased risk of appropriate ICD therapy ($P = 0.06$). In the secondary prevention ICD group, a large scar was not associated with an increased risk of appropriate ICD therapy ($P = 0.21$). However, there was also no significant interaction between the primary and secondary prevention ICD groups (P for interaction = 0.49).

3.3. Secondary endpoint

A total of 31 patients (21%) died during follow-up. The all-cause mortality rate was similar between groups based on the scar size (log-rank $P = 0.18$) (Fig. 2). The 5-year cumulative rate of all-cause mortality was 23% and 19% for patients with a large (≥18%) and smaller scar (<18%), respectively. Univariable Cox regression analysis demonstrated that only older age was associated with a higher risk of all-cause mortality (Table 3). Furthermore, a LVEF <35% demonstrated a trend towards a higher risk of death, but this was not statistically significant.

4. Discussion

The present study demonstrates that scar size is an important risk marker for ventricular arrhythmias in ICD recipients with an untreated CTO. Patients with a large scar (≥18%) as determined by the Selvester QRS score had a two-fold increased risk of appropriate ICD therapy compared to patients with a smaller or no scar (<18%). Survival rates were similar between groups with large or small scar. This is the first study evaluating the use of the Selvester QRS score as a risk stratifying tool in ICD recipients with an untreated CTO.

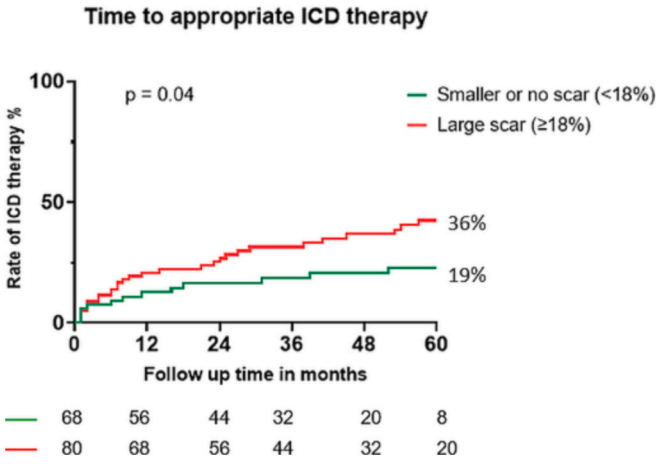

Fig. 1. Comparison of the cumulative rate of appropriate ICD therapy between patients with a large (≥18%) and small (<18%) scar.

Table 2
Predictors of appropriate ICD therapy.

	Univariable		Multivariable	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Large scar (≥18%)	1.97 (1.02–3.79)	0.04	2.29 (1.16–4.51)	0.02
Diabetes mellitus	0.19 (0.05–0.79)	0.02	0.23 (0.06–0.94)	0.04
Secondary prevention ICD	2.24 (1.20–4.19)	0.01	2.02 (0.99–4.10)	0.05
LVEF ≤35%	0.57 (0.31–1.07)	0.08	0.71 (0.35–1.44)	0.34
IRA-CTO	1.50 (0.805–2.80)	0.20		
Age at implantation	1.02 (0.99–1.06)	0.20		
Male sex	1.32 (0.59–2.98)	0.50		
ICD implantation before 2010	0.71 (0.35–1.41)	0.32		

Abbreviations: ICD, implantable cardioverter defibrillator; IRA-CTO, infarct-related chronic occlusion; LVEF, left ventricular ejection fraction.

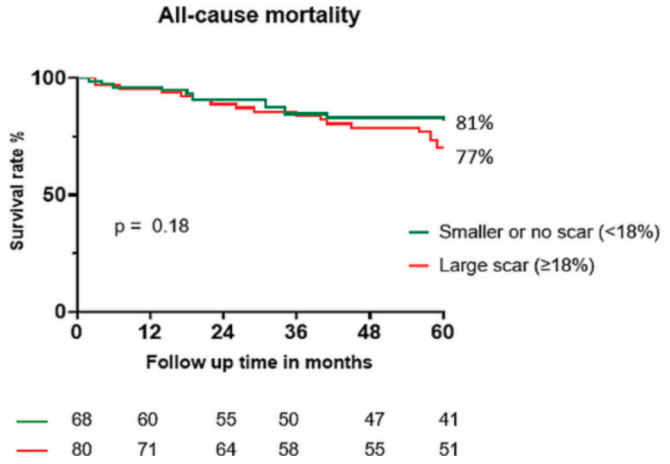

Fig. 2. Comparison of the cumulative survival rate between patients with a large (≥18%) and small (<18%) scar.

Table 3
Predictors of all-cause mortality.

	Univariable	
	HR (95%CI)	*P*
Large scar (≥18%)	0.62 (0.30–1.26)	0.19
Secondary prevention ICD	1.23 (0.61–2.48)	0.57
LVEF ≤35%	2.08 (0.80–5.43)	0.13
IRA-CTO	0.84 (0.42–1.71)	0.64
Age at implantation	1.05 (1.01–1.10)	0.02
Male sex	0.99 (0.35–2.82)	0.98
ICD implantation before 2010	0.96 (0.44–2.09)	0.28
Diabetes Mellitus	1.49 (0.67–3.35)	0.32

Abbreviations: ICD, implantable cardioverter defibrillator; IRA-CTO, infarct-related chronic occlusion; LVEF, left ventricular ejection fraction.

4.1. CTO and ventricular arrhythmias

Several observational studies have shown that an untreated CTO is an independent predictor of ventricular arrhythmias in patients who have an ICD for primary or secondary prevention [1–6]. Furthermore, some authors have argued that specifically an IRA-CTO renders a patient more vulnerable to ventricular arrhythmias [2,7,8]. An IRA-CTO has been associated with a larger myocardial scar and also an increased area of scar border zone in patients with a prior history of myocardial infarction undergoing VT ablation [20]. The scar and scar border zone comprise the critical substrate for the development of reentrant arrhythmias [21,22]. Several studies using LGE-CMR have demonstrated that a larger scar border zone was associated with an increased risk of ventricular arrhythmias in ICD recipients [11–13]. Of note, patients with IRA-CTO did not demonstrate an increased vulnerability for ventricular arrhythmias in comparison to patients without IRA-CTO in our study population.

4.2. Role of myocardial scar in CTO patients

Quantification of myocardial scar using LGE-CMR can be challenging in patients with an ICD due to artifacts created by the ICD generator, especially in the anterior wall. To evaluate the effect of myocardial scar size in ICD recipients, several researchers have used the Selvester QRS score to estimate the scar size as this it only requires a 12-lead ECG. The Selvester QRS score has shown a good correlation with scar size as determined by LGE-CMR and has also been validated in patients with a CTO [16,23,24]. A recent multicenter study of primary prevention ICD recipients with ischemic and non-ischemic cardiomyopathy demonstrated that a large scar (≥15%), as determined by the Selvester QRS score, was associated with an almost two-fold (HR 1.83, 95% CI 1.07–3.14) higher risk of appropriate ICD therapy in the subgroup of patients (N = 434) with a baseline QRS duration ≥130 ms [25]. Furthermore, a substudy of the *Sudden Cardiac Death in Heart Failure* (SCD-HeFT) trial demonstrated that an increasing Selvester QRS score scar size predicted higher rates of ventricular arrhythmias in the ICD arm (N = 797) [16]. Patients with no scar by QRS scoring had 48% fewer arrhythmic events than those patients with scar. Importantly, in our study population only a minority (7%) did not have scar by QRS scoring. Both abovementioned studies were conducted in patients who received an ICD for primary prevention and, thus, had severe LV dysfunction at baseline. Furthermore, both studies were not focused on a CTO population. We expand the prognostic value of the Selvester QRS score to primary and secondary prevention ICD recipients with an untreated CTO. In agreement with the study of Reichlin et al., we also demonstrate that a large scar (≥18%) was associated with a two-fold higher risk of appropriate ICD therapy. Scar size was a stronger factor associated with ventricular arrhythmias than LV function in our specific cohort of ICD recipients with untreated CTO.

4.3. Clinical implications and future directions

Currently, only LVEF <35% is used as a determinant of the need of an ICD in patients with ischemic cardiomyopathy [26]. However, many cases of sudden cardiac death occur in patients with moderately reduced or preserved ejection fraction. There is accumulating evidence that a CTO is associated with an increased risk of ventricular arrhythmias and sudden death [1–6]. Our study provides additional risk stratification and identifies a CTO population who is at high arrhythmic risk. Thus, the present study supports the increasing trend to use LGE-CMR for refinement of individual risk stratification. Merely the presence of LGE has shown to be a strong predictor of ventricular arrhythmias in patients with nonischemic and ischemic cardiomyopathy [27]. In addition, the extent of LGE (>5% of LV mass) has also shown to predict future arrhythmic events in patients with moderately reduced ejection fraction [28]. Large prospective studies evaluating the risk of ventricular arrhythmias in CTO patients with a large scar burden, determined by LGE-CMR and/or Selvester QRS score, and moderately reduced ejection fraction (>35%) are highly anticipated.

Another important question is whether CTO revascularization may mitigate this increased risk of ventricular arrhythmias. There is limited data that percutaneous CTO revascularization results in electrical homogenization (e.g., reduction in QT dispersion and T-wave peak-to-end interval), abolishment of late potentials, and reduction of the border zone area [9,29]. Currently, there are no randomized trials which have

focused on the effect of percutaneous CTO revascularization on the incidence of ventricular arrhythmias.

4.4. Study limitations

There are several limitations. Although calculation of the Selvester QRS score was semi-automated with dedicated software, qualitative assessment (e.g., assessment of notching) was still necessary which may introduce inter- and intra-observer variability. Furthermore, although the correlation of the Selvester QRS score with total scar size on LGE-MRI is good, the Selvester QRS scar does not provide information on scar border zone (infarct grey zone) which may be more relevant than the total scar size [11]. Finally, the single center design limits generalizability of the data. Considering abovementioned limitations, all conclusions of the present study should be seen as hypothesis-generating.

5. Conclusion

In ICD recipients with an untreated CTO, the presence of a large scar (>18%), as determined by the Selvester QRS score, is an independent predictor of ventricular arrhythmias. The size of the scar was not associated with mortality rates in this specific CTO population. Thus, the presence of a large scar in a patient with an untreated CTO identifies a patient who is vulnerable for ventricular arrhythmias, irrespective of LV function.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131205.

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