Increased risk of ventricular arrhythmias in survivors of out-of-hospital cardiac arrest with chronic total coronary occlusion

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BACKGROUND Chronic total occlusion (CTO) is common in out-of-hospital cardiac arrest (OHCA) survivors with coronary artery disease. It is unclear whether CTO contributes to ventricular arrhythmias in this population.

OBJECTIVE This study sought to evaluate the impact of unrevascularized CTOs on the occurrence of appropriate implantable cardioverter-defibrillator (ICD) therapy and all-cause mortality in OHCA survivors with coronary artery disease.

METHODS This was a retrospective study that included all consecutive OHCA survivors with coronary artery disease who received an ICD from December 1999 until June 2015. Study end points were appropriate ICD therapy and all-cause mortality.

RESULTS We identified 217 OHCA survivors (mean age 63 ± 10 years; 187 men (86%)) with coronary artery disease. Unrevascularized CTO was present in 71 of 217 patients (33%) at the time of ICD implantation. During a median follow-up of 61 months (interquartile range, 28–97 months), 57 of 217 patients (26%) experienced an appropriate ICD therapy. Patients with CTO had a higher incidence of appropriate ICD therapy in comparison to patients without CTO (log-rank, $P = .002$). Multivariate Cox regression analysis identified CTO (hazard ratio 2.07; 95% confidence interval 1.23–3.50; $P = .007$) as an independent predictor of appropriate ICD therapy. The presence of CTO was not associated with a higher mortality rate (log-rank, $P = .18$).

CONCLUSIONS In OHCA survivors with coronary artery disease receiving an ICD for secondary prevention, CTO was an independent predictor for the occurrence of ventricular arrhythmias but not for mortality.

KEYWORDS Chronic total occlusion; Ventricular tachycardia; Ventricular fibrillation; Implantable cardioverter-defibrillator; Out-of-hospital cardiac arrest

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Introduction

The exact role of chronic total occlusion (CTO) in causing life-threatening ventricular arrhythmias (VAs) is not clear. In clinical practice we encounter out-of-hospital cardiac arrest (OHCA) survivors with CTO who have a relatively preserved left ventricular (LV) function and no significant rise in cardiac enzymes. One may speculate that the presence of CTO may contribute to the VAs event by a complex interplay of scar and ischemia. A previous nonrandomized study showed that failed or unattempted CTO recanalization in patients with stable coronary artery disease was associated with an increased risk of sudden cardiac death in comparison to those with revascularized CTO.[1] Furthermore, several studies in patients with ischemic cardiomyopathy and severe LV dysfunction who receive an implantable cardioverter-defibrillator (ICD) for primary prevention have shown that CTO is an independent predictor of VAs.[2,3] Currently, there are limited data on the prognostic implications of CTO in patients with coronary artery disease who present with OHCA due to VAs. The aim of the present study was to evaluate the impact of CTO on the occurrence of VAs and all-cause mortality in survivors of OHCA with coronary artery disease.

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Methods

Study population

The study population was identified using the prospective ICD registry of the Department of Cardiology of the Erasmus Medical Center in Rotterdam, The Netherlands. Baseline clinical and echocardiography data, characteristics of the implant procedure, and data for all follow-up visits were prospectively recorded in a dedicated database. We identified all consecutive patients with coronary artery disease who received an ICD for secondary prevention after OHCA due to VAs between December 1999 and June 2015. *Coronary artery disease* was defined as the presence of significant

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Table 1 Baseline characteristics

Characteristic	All patients (n = 217)	Non-CTO group (n = 146)	CTO group (n = 71)	*P*
Age (y)	63 ± 10	62 ± 11	65 ± 9	.03
Sex: male	187 (86)	123 (84)	64 (90)	.24
Medical history				
Diabetes mellitus	39 (18)	26 (18)	13 (18)	.93
Renal dysfunction (GFR <60 mL/min)	50 (23)	31 (21)	19 (27)	.36
Previous CABG	66 (30)	55 (38)	11 (16)	.001
Previous PCI	121 (56)	81 (56)	40 (56)	.91
NYHA class ≥II	144 (66)	95 (65)	49 (69)	.56
Multivessel disease	40 (18)	7 (5)	33 (47)	<.001
LVEF <35%	112 (52)	71 (49)	41 (58)	.21
QRS duration ≥130 ms	55 (25)	33 (23)	22 (31)	.18
Medication at ICD implantation				
ACE inhibitor	177 (82)	120 (82)	57 (80)	.73
β-Blocker	177 (82)	121 (83)	56 (79)	.48
Statin	171 (79)	115 (79)	56 (79)	.99
Diuretic	106 (49)	71 (49)	35 (49)	.93
Amiodarone	39 (18)	29 (20)	10 (14)	.30
Digoxin	20 (9)	14 (10)	6 (9)	.79
ICD type				.81
Single-chamber	135 (62)	93 (64)	42 (59)	
Dual-chamber	59 (27)	38 (26)	21 (30)	
CRT-D	23 (11)	15 (10)	8 (11)	

Values are presented as mean ± SD or as n (%).

ACE = angiotensin-converting-enzyme; CABG = coronary artery bypass graft; CTO = chronic total occlusion; CRT-D = cardiac resynchronization therapy with defibrillator; GFR = glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

coronary artery stenosis (>50%) or a history of percutaneous or surgical revascularization.

For analysis of the association between CTO and VAs, 2 researchers (S.C.Y. and Y.E.Y.) analyzed every patient in our cohort for the presence of CTO at the time of ICD implantation by evaluating the coronary angiograms and catheterization reports before ICD implantation. This study was approved by the institutional review board of the Erasmus Medical Center.

Definition of study variables

CTO was defined as complete vessel occlusion with TIMI 0 flow within the occluded segment and an estimated occlusion duration of ≥3 months.[4,5] Occluded vessels that were surgically or percutaneously revascularized and secondary occluded vessels (ie, diagonal branch, posterior descending artery, and posterolateral branches) were not classified as CTO in this study. *Multivessel disease* was defined as the presence of ≥2 coronary arteries with significant nonrevascularized lesions at the time of ICD implantation.

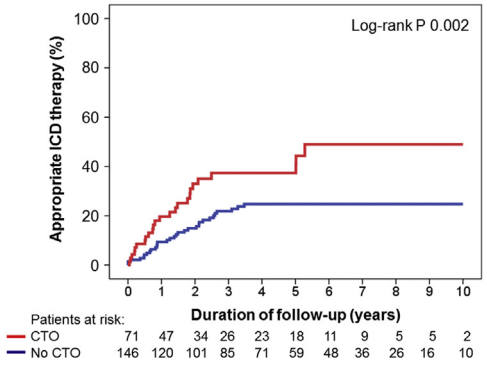

Figure 1 Cumulative event rate for appropriate ICD therapy in populations with CTO and without CTO. CTO = chronic total occlusion; ICD = implantable cardioverter-defibrillator.

Device programming

Devices were programmed with 2–3 consecutive zones (monitor zone, ventricular tachycardia zone, and ventricular fibrillation zone, usually 2 zones) with limits slightly varying per manufacturer. The cutoff rate for the VT zone was usually set at 171–182 beats/min, and the cutoff rate for the VF zone was usually set at 222–230 beats/min. In the VT zone, arrhythmias were initially treated with a series of antitachycardia pacing (ATP) bursts followed by shocks. In the VF zone, device shocks were the initial therapy or, when available, "ATP during charging." If a patient had a VAs with cycle length lower than the initially programmed cutoff, another detection zone for slow VT was added. Conventional programming was used for detection duration. Detection in the VF zone was usually programmed at 18 of 24 intervals or a 2.5-second delay depending on the manufacturer. Detection in the VT zone was usually programmed at 16–20 intervals or a 5-second delay depending on the manufacturer.

Follow-up and end points

Patients were usually followed every 3–6 months. The follow-up visits included clinical assessment and device

Table 2 Predictors of appropriate ICD therapy

	Univariate		Multivariate	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
CTO	2.20 (1.31–3.72)	.003	2.07 (1.23–3.50)	.007
LVEF <35%	2.07 (1.19–3.59)	.01	1.94 (1.11–3.38)	.02
Multivessel disease	1.64 (0.89–3.03)	.11		
CABG	1.35 (0.79–2.31)	.27		
Age >70 y	1.11 (0.62–1.98)	.73		
NYHA class III	1.06 (0.33–3.39)	.92		
Renal dysfunction	0.80 (0.42–1.51)	.49		

CABG = coronary artery bypass graft; CI = confidence interval; CTO = chronic total occlusion; HR = hazard ratio; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

interrogation. Unscheduled device interrogations were performed in the case of symptomatic episodes of arrhythmia and during unplanned hospitalization. All spontaneous VAs episodes were prospectively reviewed and classified (D.A.M.J.T.). The primary end point was *appropriate ICD therapy* defined as the delivery of ATP or shock for VAs (either ventricular tachycardia or ventricular fibrillation). The secondary end point was all-cause mortality.

Statistical analysis

Continuous data are presented as mean ± SD if the data were normally distributed or as median with interquartile range (25th and 75th percentile) otherwise. Categorical variables are presented as frequency and percentage. Differences in continuous variables between the 2 groups were analyzed using the unpaired Student *t* test or the Mann-Whitney *U* test, as appropriate. Differences in categorical variables were evaluated using the χ^2 test or the Fisher exact test in the case of small expected cell frequencies.

The cumulative event rate of appropriate ICD therapy was calculated using the Kaplan-Meier method. Predictors of appropriate ICD therapy were determined using univariate and multivariate Cox regression analysis. Potential predictors were presence of CTO, left ventricular ejection fraction (LVEF) <35%, coronary artery bypass graft, multivessel disease, age >70 years, New York Heart Association class III, and renal dysfunction (glomerular filtration rate <60 mL/min). Any variable with *P* value <.10 and CTO status were entered in the multivariate model. Data are presented as hazard ratios and 95% confidence intervals (CIs). A subgroup analysis was also performed where patients with unrevascularized CTO were compared with patients with recent (ie, between OHCA and ICD implantation) successful CTO revascularization (surgical or percutaneous). Statistical analyses were performed using SPSS version 21.0 (IBM Corporation, Armonk, NY). All statistical tests were 2-sided. *P* values <.05 were considered statistically significant.

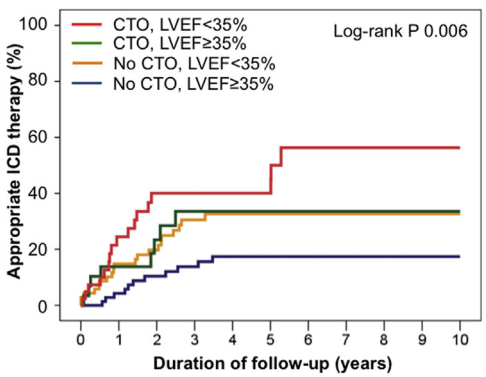

Figure 2 Cumulative event rate for appropriate ICD therapy in patients with CTO and without CTO stratified by LVEF <35% and ≥35%. CTO = chronic total occlusion; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction.

Results

Study population

A total of 217 patients received an ICD as secondary prevention after experiencing OHCA for VAs during the study period. The CTO group consisted of 71 patients (33%) with unrevascularized CTO before ICD implantation. The baseline characteristics are depicted in Table 1. The CTO group was older, had more multivessel disease, and had less coronary artery bypass grafts. Of the 71 patients with CTO, 23 patients (32%) underwent myocardial perfusion scintigraphy. Of the patients who underwent imaging stress testing, the majority (21 of 23 patients [91%]) demonstrated no or limited myocardial ischemia.

Appropriate ICD therapy

During a median follow-up of 61 months (28–97 months), 57 of 217 patients (26%) of the total group experienced an appropriate ICD therapy. The incidence of appropriate ICD therapy was higher in the CTO group than in the non-CTO group (log-rank, *P* = .002) (Figure 1). The cumulative event rates for appropriate ICD therapy (ATP and ICD shock) in the CTO group were 19.7%, 37.3%, and 37.3% at 1, 3, and 5 years, respectively. The cumulative event rates for appropriate ICD therapy in the non-CTO group were 9.4%, 21.9%, and 24.8% at 1, 3, and 5 years, respectively. Using univariate Cox regression analysis, the presence of CTO was associated with an increased risk of appropriate ICD therapy (hazard ratio 2.20; 95% CI 1.31–3.72; *P* = .003) (Table 2).

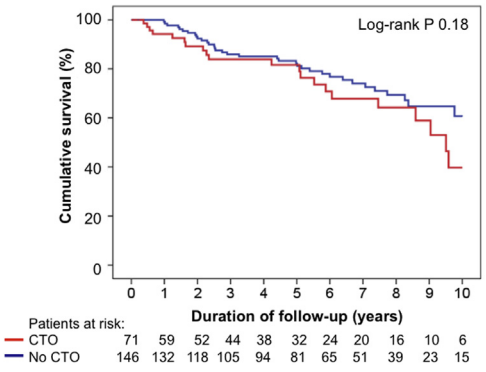

Figure 3 Cumulative survival rate in populations with CTO and without CTO. CTO = chronic total occlusion.

Multivariate Cox regression analysis demonstrated that CTO and LVEF <35% were independent predictors of appropriate ICD therapy (Table 2). The cumulative event rate for appropriate ICD therapy in the CTO and non-CTO groups stratified by LV function is depicted in Figure 2.

When restricting the outcome data to appropriate ICD therapy in the VF zone, the CTO group showed only a trend toward a higher rate of appropriate ICD therapy in comparison to the non-CTO cohort (log-rank, $P = .08$). The 5-year event rate of appropriate ICD therapy in the VF zone was 20.6% and 15.8% in the CTO and the non-CTO group, respectively.

Mortality

A total of 58 patients (27%) died during follow-up. The survival rate was similar between the CTO and non-CTO groups (log-rank, $P = .18$) (Figure 3). The cumulative survival rates in the CTO group were 94.2%, 83.9%, and 81.6% at 1, 3, and 5 years, respectively. The cumulative survival rates in the non-CTO group were 99.2%, 85.9%, and 82.2% at 1, 3, and 5 years, respectively. Univariate and multivariate Cox regression analysis demonstrated that the presence of CTO was not a predictor of all-cause mortality (Table 3). Univariate Cox regression analysis showed that LVEF <35%, age >70 years, and renal dysfunction were associated with an increased all-cause mortality. However, multivariate Cox regression analysis demonstrated that LVEF <35% and age >70 years were independent predictors of all-cause mortality.

Recent CTO revascularization and appropriate ICD therapy

There was a subgroup of patients (n = 25) who underwent successful CTO revascularization in the period between OHCA and ICD implantation. The cumulative event rate of appropriate ICD therapy within this group was similar to that of the unrevascularized CTO group (n = 71) (log-rank, $P = .48$).

Discussion

The present study demonstrates that CTO was an independent predictor of appropriate ICD therapy, but was not associated with all-cause mortality. This work also found that LVEF <35% was an independent predictor of both appropriate ICD therapy and all-cause mortality.

CTO and VAs

CTO is a common condition among patients with coronary artery disease, with a reported prevalence between 30% and 50% in patients with ischemia referred to the catheterization laboratory.[6,7] Therefore, it is not surprising that there was a high prevalence of CTO in our population of out-of-hospital cardiac survivors with coronary artery disease who received an ICD. The exact role of CTO in causing or triggering the initial ventricular fibrillation episode is not fully understood. However, there are several observations that may suggest that the presence of CTO play an important role in the development of VAs in patients with coronary artery disease.

A recent study showed that patients with previously failed or not attempted CTO recanalization had a higher incidence of sudden cardiac death (2.7% vs 0.5% at 4 years of follow-up) than did those with successful CTO recanalization.[1] These observations may imply that ischemia associated with CTO renders a patient vulnerable to VAs. This is strengthened by the observation that CTOs are an independent predictor of VAs in patients with ischemic cardiomyopathy and ICDs for primary prevention.[2,3] Our study

Table 3 Predictors of all-cause mortality

	Univariate		Multivariate	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
CTO	1.44 (0.85–2.45)	.18	0.97 (0.51–1.87)	.93
Age >70 y	3.19 (1.90–5.38)	<.001	2.84 (1.64–4.92)	<.001
LVEF <35%	2.20 (1.23–3.92)	.008	2.07 (1.15–3.73)	.02
Renal dysfunction	2.19 (1.29–3.72)	.004	1.63 (0.94–2.81)	.08
Multivessel disease	1.76 (0.97–3.19)	.06	1.35 (0.65–2.80)	.42
NYHA class III	1.75 (0.70–4.39)	.24		
CABG	1.23 (0.72–2.09)	.45		

CABG = coronary artery bypass graft; CI = confidence interval; CTO = chronic total occlusion; HR = hazard ratio; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

is, to our knowledge, the first study that shows that CTO is also an independent predictor of VAs in survivors of OHCA with coronary artery disease who receive an ICD.

There are several explanations for the increased risk of VAs in patients with CTO. The substrate of VAs in patients with ischemic cardiomyopathy is usually a myocardial scar.[8] Channels of slow conduction, a prerequisite for reentry, can be found within the scar or, more commonly, in the scar-border zone.[8–10] It is known that the presence of CTO is associated with ischemia, as measured by fractional flow reserve, even in the presence of well-developed collaterals.[11,12] Ischemia around the postinfarction necrotic core may increase electrical instability and the development of VAs.

CTO and all-cause mortality in ICD recipients

Prior studies in patients with ischemic cardiomyopathy who received an ICD as primary prevention have shown conflicting results of the effect of CTO on all-cause mortality.[2,13] It is important to realize that patients who received an ICD for primary prevention have a low ejection fraction, which is a strong predictor of all-cause mortality. In our study cohort of patients who received an ICD for secondary prevention, of which approximately half (52%) had LVEF <35%, the presence of CTO was not associated with a higher mortality rate.

The lack of a clear adverse effect of CTO on all-cause mortality in ICD recipients (either primary or secondary prevention) is in contrast to data from non-ICD carriers. A recent meta-analysis, not specifically including ICD recipients, showed that failed CTO recanalization was associated with a higher risk of all-cause mortality in comparison to those with successful CTO recanalization (odds ratio 1.92; 95% CI 1.59–2.33).[14] This discrepancy in the effect of CTO on all-cause mortality may be partially explained by the prevention of sudden cardiac death due to VAs in ICD recipients.

Clinical implications and future directions

The results of the present study may have several implications. First, owing to technical advances in percutaneous coronary intervention techniques, CTO recanalization can be achieved with high success rates and low complication rates.[15] At this moment, there is no compelling evidence that successful CTO recanalization during the initial hospitalization may reduce VAs burden in survivors of OHCA. In the small substudy in our cohort, there was no reduction in appropriate ICD therapy in patients who underwent recent CTO revascularization before ICD implantation. However, this analysis is hampered by the small sample size (n = 25, underpowered) and the observational nature of the study design. Appropriately designed prospective randomized trials can elucidate this issue.

Second, our study supports the causative role of CTO in the development of VAs irrespective of the LV function. Interestingly, patients with CTO with LVEF >35% had an incidence of VAs similar to that of patients without CTO with severe LV dysfunction (LVEF <35%). Previous studies have shown that severe LV dysfunction is an important predictor of sudden cardiac death and ICDs are indicated as primary prevention in patients with ischemic cardiomyopathy with severe LV dysfunction primarily on the basis of the results of the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (median LVEF 23%–24%).[16–18] Previous CTO studies demonstrated a higher risk of all-cause mortality and sudden cardiac death rate in patients with failed CTO recanalization despite the fact that only a minority (7%–11%) had severe LV dysfunction.[1,19] In our study, the presence of CTO had predictive power similar to that of severe LV dysfunction. More research is needed to investigate the incidence of VAs and the role of a prophylactic ICD in patients with failed CTO recanalization and preserved LV function.

Study limitations

There are several limitations. The current guidelines recommend prolonged detection settings and higher tachycardia therapy zone limits to reduce ICD therapy primarily based on the Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT) trial.[20] These guidelines were published in 2015, and we changed our clinical practice in 2016 (these patients are not included in this study). We do not know whether these new settings will change the conclusions of our study, as they will probably lower the incidence of appropriate ICD therapy in both CTO and non-CTO groups. In addition, we have no complete data on the extent of ischemia in the population with CTO and thus cannot make a distinction between those with small and moderate/large ischemic burden. One can imagine that patients with moderate or large ischemic burden are more prone to VAs. Finally, the single-center design may limit generalizability of the data. However, the 3-year mortality rate in our study (15%) was similar to that in the ICD arms of secondary prevention randomized controlled trials.[21–23]

Conclusion

In OHCA survivors with coronary artery disease, the presence of CTO is common and is an independent predictor of future VAs. CTO was not associated with a higher mortality rate in this secondary prevention ICD group. The data support the causative role of CTO in the development of VAs. Further studies are needed to investigate whether CTO revascularization can reduce the arrhythmic risk in OHCA survivors.

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