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Impact of Chronic Total Coronary Occlusion on Recurrence of Ventricular Arrhythmias in Ischemic Secondary Prevention Implantable Cardioverter-Defibrillator Recipients (VACTO Secondary Study)

Insights From Coronary Angiogram and Electrogram Analysis

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ABSTRACT

OBJECTIVES This study sought to evaluate the incidence and clinical effect of coronary chronic total occlusions (CTOs) in patients with ischemic cardiomyopathy receiving an implantable cardioverter-defibrillator (ICD) for secondary prevention of sudden cardiac death (SCD).

BACKGROUND CTOs are common in patients with ischemic cardiomyopathy, which is the major cause of SCD. However, the impact of CTO in SCD survivors receiving an ICD is unknown.

METHODS A total of 425 patients who had survived an episode of ventricular arrhythmias and underwent ICD implantation for secondary prevention in 8 centers were included. Coronary angiogram, CTO angiographic characteristics, and ventricular arrhythmia pattern were centrally analyzed. Primary and secondary endpoints were appropriate ICD therapies and mortality during a median follow-up of 4.1 years, according to the presence of CTO in the baseline angiogram.

RESULTS Appropriate ICD therapies were higher in patients with CTO (51.7% vs. 36.3%; $p = 0.001$ at 4 years). Left ventricular ejection fraction (LVEF) ($p = 0.015$) and CTO ($p = 0.001$) were independent predictors of appropriate ICD therapy. Ventricular arrhythmia onset was associated to a shorter coupling interval and lower prematurity index in CTO patients. Defibrillator therapies were independently associated with worse LVEF ($p = 0.046$) and renal dysfunction ($p = 0.023$) among patients with CTO, and a tendency was observed in patients with better collateral flow ($p = 0.093$). Patients with poorer renal function ($p = 0.029$), LVEF ($p = 0.041$), and CTO ($p = 0.033$) experienced higher mortality rate.

CONCLUSIONS Among ICD recipients for secondary prevention of SCD, coronary CTO conferred a higher risk of VA recurrence and mortality in long-term follow-up. Angiographic and VA patterns could provide insights into the mechanisms of SCD and may have implications for the use of interventions designed to limit ICD shocks in this high-risk population. (J Am Coll Cardiol Intv 2017;10:879–88) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CI = confidence interval

CTO = chronic total occlusion

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

IQR = interquartile range

LVEF = left ventricular ejection fraction

PCI = percutaneous coronary intervention

PI = prematurity index

SCD = sudden cardiac death

VA = ventricular arrhythmia

VT = ventricular tachycardia

Sudden cardiac death (SCD), mainly related to ventricular arrhythmia (VA), is estimated to be responsible for ~15% of all deaths and coronary artery disease (CAD) is a frequent finding in VA survivors (1). An implantable cardioverter-defibrillator (ICD) has improved survival among patients that have experienced VA (2), and has become the standard of care for secondary prevention of SCD (3). Defibrillator therapies are common in this population (up to 47% at 4-year follow-up) (4). Despite the survival benefit conferred by ICD, appropriate and inappropriate shocks have a negative impact on prognosis and may impair quality of life, causing significant psychological effects. Thus, it is of utmost importance to determine predictors of ICD therapies, which might be different according to the baseline cardiac disease. However, previous studies assessing predictors of recurrent VA in secondary prevention patients have included different cardiac etiologies (5), with limited information in the specific group of ischemic patients.

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Chronic total coronary occlusion (CTO) is present in ~20% of the patients undergoing nonurgent coronary angiography (6), and even more frequently (~50%) in selected populations with CAD (7). There is growing interest in percutaneous treatment of CTO due to technical developments and observational evidence suggesting that successful CTO revascularization has the potential to improve left ventricle function and survival if myocardium is ischemic, but still viable (8,9). Previous studies have analyzed the impact of CTO on primary prevention ICD recipients or after ventricular tachycardia (VT) ablation (10–12) in single-center cohorts. However, the influence of CTO in VA recurrence among secondary prevention ICD recipients is unknown. Thus, the purpose of this multicenter study was to assess the incidence and clinical impact of CTO in a secondary prevention cohort of ischemic patients.

METHODS

STUDY POPULATION. This multicenter study collected data from 425 consecutive patients with CAD receiving an ICD for secondary prevention indication from 8 European centers. Life-threatening VA was defined as either VT or ventricular fibrillation causing hemodynamic instability requiring pharmacological or electrical cardioversion, or lasting more than 30 s with hemodynamic stability (2). Patients with an arrhythmic event in the context of an acute coronary syndrome were excluded. The indication for secondary prevention ICD implantation was determined at each center by local cardiologists or electrophysiologists following current European guidelines (2). All centers implanted multifunctional single-chamber, dual-chamber, or resynchronization ICDs. Clinical, electrocardiographic, echocardiographic, and procedural ICD data were prospectively gathered within a database at each participating center and were self-reported. Left ventricular ejection fraction (LVEF) was calculated from the biplane Simpson's method and if the echocardiography window from the apical 4-chamber view was not suitable, LVEF was visually estimated. Written informed consent was obtained from all patients before the procedure and the study was approved by the local Ethics Committees.

ANGIOGRAPHIC AND ARRHYTHMIA ANALYSES. Only patients with a coronary angiogram available within 6 months before ICD implantation were included in the study. Coronary angiograms were centrally reviewed offline in 2 participating centers blinded to primary and secondary endpoints. CAD was considered in the presence of significant coronary stenosis defined by a stenosis ≥50% in at least 1 major vessel or previous surgical or percutaneous coronary revascularization. The number and localization of lesions were recorded. The presence of multivessel CAD was defined as disease in 2 or more major epicardial coronary arteries. CTO was defined as the presence of a total coronary occlusion with or without antegrade or retrograde filling through collateral vessels in at least 1 major coronary artery with an estimated duration of ≥3 months. The duration of the occlusion was determined by clinical information or the results of previous angiogram. Angiographic CTO characteristics, collaterals assessment, and J-CTO (Multicenter CTO Registry in Japan) registry score were evaluated as previously described (13–15). Occluded vessels that were surgically or

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percutaneously revascularized before ICD implantation or occluded secondary vessels such as a diagonal branch or posterolateral branches were not considered as CTO.

Electrograms and VA patterns were centrally analyzed in a subgroup of patients with appropriate ICD therapy by an electrophysiologist (M.S.-G.) blinded to baseline and angiographic characteristics. For each sustained VA, 10 s of electrogram recordings were obtained at the onset of the tachycardia, in the period before therapy, and after therapy. The device also provides V sense-V sense intervals leading up to and including the tachycardia. Cycle lengths, tachycardia pattern onset, and number and success of antitachycardia pacing and shocks were analyzed and recorded. The onset of VT was also classified as extrasystolic or sudden according to whether it was preceded by a premature ventricular complex, which were subsequently classified as isolated, double, or multiple according to their number. The prematurity of the initiating beat was determined by the prematurity index (PI), defined as the coupling interval of the first premature depolarization initiating the VT normalized to the immediately preceding cycle length (16). If the PI was greater or lower than 0.5, the extrasystolic onset was considered as long coupled or short coupled, respectively.

FOLLOW-UP. Patients' visits were scheduled every 3 to 6 months within the first year after the implantation and yearly thereafter. In every follow-up visit, an expert electrophysiologist interrogated the device to obtain its present setting status, test for sensing, test pacing thresholds, and check for appropriate or inappropriate ICD therapy at each time point. Appropriate therapy was defined as either ICD shocks or antitachycardia pacing in response to VA, and the time to first appropriate therapy was considered the primary endpoint of the study. Therapy delivered for any issue other than VA (e.g., device malfunction, supraventricular tachycardia, T-wave oversensing) was considered inappropriate therapy and not included in the analysis. Details of subsequent clinical major adverse events (death, cardiac death, heart failure) were also collected as secondary endpoints. Complete follow-up information was achieved in 420 (98.5%) patients, with a median time of 4.1 (interquartile range [IQR]: 1.9 to 6.0) years.

STATISTICAL ANALYSIS. Categorical variables are expressed as number (percentage) and continuous variables as mean ± SD or median (IQR [25th to 75th percentile]) according to their distribution.

TABLE 1 Baseline Characteristics of the Study Population According to the Presence of a CTO

	All (N = 425)	No CTO (n = 210)	CTO (n = 215)	p Value
Clinical Data				
Age, yrs	69 (61–76)	69 (61–76)	69 (63–76)	0.350
Age ≥75 yrs	130 (30.6)	65 (31.0)	65 (30.2)	0.872
Male	392 (92.2)	187 (89.0)	205 (95.3)	0.015
BMI, kg/m^2	27.3 ± 3.7	26.9 ± 3.7	27.3 ± 3.7	0.347
Hypertension	308 (72.5)	149 (71.0)	159 (51.6)	0.489
Diabetes	140 (33.0)	64 (30.5)	76 (35.5)	0.270
Dyslipidemia	256 (60.2)	118 (56.2)	138 (64.2)	0.092
Smoking	261 (61.6)	125 (59.8)	136 (63.3)	0.466
Current	113 (26.7)	56 (26.9)	57 (26.5)	
Prior	148 (34.9)	68 (32.7)	79 (36.7)	
Atrial fibrillation	95 (22.4)	53 (25.2)	42 (19.6)	0.166
New York Heart Association functional class				0.246
I	145 (36.7)	80 (40.6)	65 (32.8)	
II	189 (47.8)	86 (43.7)	103 (52.0)	
III	61 (15.5)	31 (15.7)	30 (15.2)	
Prior MI	331 (78.1)	156 (74.3)	175 (81.8)	0.062
eGFR, ml/min	71.9 ± 37.8	71.9 ± 26.5	71.9 ± 46.3	0.996
eGFR <60 ml/min	160 (38.8)	75 (36.9)	85 (40.7)	0.438
Electro Cardiographic and Echocardiographic Data				
Rhythm				0.288
Sinus	318 (76.3)	153 (73.6)	165 (78.9)	
AF	72 (17.3)	38 (18.3)	34 (16.3)	
Pacemaker	27 (6.5)	17 (8.2)	10 (4.8)	
Q waves	242 (57.2)	114 (54.3)	129 (60.0)	0.234
QRS duration, ms	100 (90–120)	100 (90–120)	100 (90–130)	0.713
LBBB	78 (20.8)	37 (19.8)	41 (21.8)	0.629
LVEF, %	38.7 ± 12.6	39.9 ± 13.6	37.5 ± 11.2	0.044
LVEF ≤40	266 (63.2)	127 (61.1)	139 (65.3)	0.372
Mitral regurgitation ≥3–4	56 (15.2)	24 (12.3)	32 (18.3)	0.109
Clinical and ICD Data				
Clinical presentation				0.385
Sudden death	115 (27.3)	63 (30.1)	52 (24.4)	
Unstable VT	197 (46.7)	92 (44.0)	105 (49.3)	
Stable VT	110 (26.1)	54 (25.8)	56 (26.3)	
ICD type				0.824
Single chamber	282 (66.5)	142 (67.9)	140 (65.1)	
Dual chamber	98 (23.1)	46 (22.0)	52 (24.2)	
CRT-D	44 (10.4)	21 (10.0)	23 (10.7)	
Medications at hospital discharge				
Statins	372 (87.5)	181 (86.2)	191 (88.8)	0.398
Beta-blocker	339 (86.5)	164 (85.4)	175 (87.5)	0.546
ACEI/ARB	314 (80.5)	153 (80.5)	161 (80.5)	0.995
Antiarrhythmic agents	148 (34.9)	75 (35.9)	73 (34.0)	0.677
Dual antiplatelet therapy	107 (29.2)	61 (29.0)	46 (21.4)	0.069
Anticoagulation therapy	98 (27.1)	51 (28.7)	47 (25.5)	0.506

Values are median (interquartile range), n (%), or mean ± SD.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; CRT-D = cardiac resynchronization therapy with defibrillator; CTO = chronic total occlusion; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricle ejection fraction; MI = myocardial infarction; VT = ventricular tachycardia.

TABLE 2 Angiographic and Procedural Characteristic According to the Presence of a CTO

	All (N = 425)	No CTO (n = 210)	CTO (n = 215)	p Value
Angiographic Characteristic				
Right dominance	386 (92.3)	187 (90.3)	199 (94.3)	0.126
Number of narrowed coronary arteries				0.001
1	102 (24.0)	69 (32.9)	33 (15.3)	
2	148 (34.8)	80 (38.1)	68 (31.6)	
3	175 (41.2)	61 (29.0)	114 (53.0)	
LAD affected	312 (74.5)	149 (72.0)	163 (76.9)	0.250
Complete revascularization	128 (30.1)	128 (60.9)	0 (0.0)	0.001
Number of CTOs per patient		–	1.3	
Total number of CTO and localization			283	
LAD		–	58 (20.5)	
RCA		–	141 (49.8)	
LCX		–	84 (29.7)	
J-CTO registry score		–	2.08 ± 1.07	
J-CTO registry score ≥2			194 (70.3)	
Proximal cap ambiguity		–	150 (53.0)	
Collaterals		–		
Homocollateral		–	35 (14.5)	
Heterocollateral		–	107 (44.4)	
Homo- and heterocollateral			98 (40.7)	
Collateral flow assessment				
Rentrop grade ≤1		–	80 (28.8)	
Rentrop grade 2		–	55 (19.8)	
Rentrop grade 3		–	143 (51.4)	
Collateral channel grade 0		–	100 (36.1)	
Collateral channel grade 1		–	105 (37.9)	
Collateral channel grade 2		–	72 (26.0)	
Arrhythmia Analysis				
VT/VF	149 (85.6)/25 (14.4)	59 (89.4)/7 (10.6)	90 (83.3)/18 (16.7)	0.269
Cycle length, ms	289 (229–326)	300 (250–327)	279 (220–326)	0.139
Onset of VT				0.910
Extrasystolic	48 (71.6)	22 (71.0)	26 (72.2)	
Sudden	19 (28.4)	9 (29.0)	10 (27.8)	
Coupling interval, ms	445 (385–615)	546 (423–697)	430 (342–499)	0.024
Prematurity index	0.65 (0.53–0.81)	0.71 (0.52–0.92)	0.60 (0.54–0.70)	0.043
Premature ventricular complex				0.721
Isolated	15 (39.5)	8 (44.4)	7 (35.0)	
Double	10 (26.3)	5 (27.8)	5 (25.0)	
Multiple	13 (34.2)	5 (27.8)	8 (40.0)	
Morphology of PVC				
Same as VT	Not enough data	Not data	Not data	
Different as VT	Not enough data	Not data	Not data	

Values are n (%), mean ± SD, or median (interquartile range).

J-CTO = Multicenter CTO Registry in Japan; LAD = left anterior descending artery; LCX = left circumflex artery; PVC = premature ventricular complex; RCA = right coronary artery; VF = ventricular fibrillation; other abbreviations as in Table 1.

Assessment of normality for continuous data was performed using the Shapiro-Wilk test. Comparison of qualitative variables was performed with the chi-square or Fisher exact test. Quantitative variables with a normal or non-normal distribution were analyzed with a 2-sided, Student *t* test or Wilcoxon rank sum or median test, respectively. Freedom from recurrence of VA and mortality curves was calculated using the Kaplan-Meier method, and comparison between groups was obtained with the log-rank test. Patients missing their follow-up were considered at risk until the date of last contact, at which point they were censored. Clinically relevant variables (even without differences between groups) and variables with a p value < 0.10 in the univariate analysis were entered into a mixed Cox regression analysis to determine the independent predictors of appropriate ICD therapy and secondary outcomes. The model was adjusted by center variability to determine significant changes in the outcomes. A secondary analysis was performed to determine the associated factors to appropriate ICD therapies in the CTO group in a patient level analysis. Among patients with multiple CTO, the occluded artery with the worse collateral flow was selected for this analysis. A p value < 0.05 was considered significant for all statistical tests. All analyses were performed with the Statistical Package for Social Sciences for Windows version 20.0 (IBM, Armonk, New York).

RESULTS

Baseline characteristics, electrocardiographic, echocardiographic and clinical data of the study population (n = 425 patients) are listed in Table 1. Median age was 69 (IQR: 61 to 69) years and 392 (92.2%) patients were men. A total of 215 (50.6%) patients had at least 1 CTO in the baseline coronary angiogram. The prevalence of men, previous myocardial infarction, and surgical revascularization was higher among CTO patients. Clinical presentation at the time of ICD implantation was similar between groups and most patients (66.5%) received a single-chamber ICD. Patients with CTO were more likely to have more extensive CAD (3-vessel coronary disease) and incomplete revascularization (Table 2).

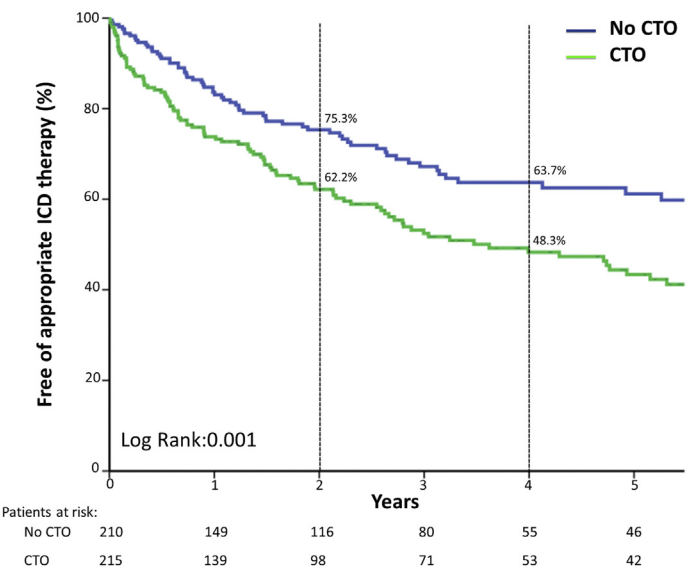
CLINICAL OUTCOMES. A total of 180 (42.3%) patients had at least 1 episode of sustained VA with an appropriate ICD therapy (either antitachycardia pacing or shock) during the follow-up period, with a median time from the ICD implant to first therapy of 397 (IQR: 140 to 959) days. Ventricular fibrillation and VT were observed in 155 (86.1%) and 25 (13.9%) patients, respectively. Patients with CTO were more likely to receive an appropriate ICD therapy (51.7%; 95% confidence interval [CI]: 43.9% to 59.5%) compared to those without CTO (36.3%; 95% CI: 34.3% to 38.3%; log-rank p = 0.001, rate at 4 years) (Figure 1). The presence of a CTO was associated with higher rate of ICD therapy (hazard ratio [HR]: 1.73; 95% CI: 1.28 to 2.34; p = 0.001) and this association

persisted after adjusting for baseline characteristics and confounding factors in multivariable analysis (Table 3). Patients with multivessel CAD without a CTO had similar events rates compared to patients with single-vessel disease (Figure 2A). However, patients with incomplete revascularization without a CTO experienced higher rates of ICD therapy compared to those with complete revascularization, but lower rates compared to patients with CTO (p = 0.002) (Figure 2B).

A total of 59 (32.8%) patients died during the follow-up period, and 35 (19.4%) had a cardiac origin. Survival rate was lower in patients with CTO (73.9%; 95% CI: 67.0% to 80.8%) compared to those without CTO (81.0%; 95% CI: 74.7% to 87.3%; log-rank p = 0.014) at 4 years (Figure 3A), mainly driven by a higher cardiac mortality (Figures 3B and 3C). Renal dysfunction (HR: 1.67; 95% CI: 1.05 to 2.66; p = 0.029), lower LVEF at baseline (HR: 1.12; 95% CI: 1.00 to 1.24; p = 0.041), and presence of CTO (HR: 1.69; 95% CI: 1.04 to 2.73; p = 0.033) were independent predictors of mortality (Table 4).

ANGIOGRAPHIC AND ARRHYTHMIA FINDINGS. A total of 283 coronary arteries with a CTO were encountered in 215 patients, as depicted in Table 2. The right coronary artery was the most frequent occluded artery and the mean J-CTO registry score was 2.08 ± 1.07. Poor distal flow (Rentrop grade ≤1) and collateral channel (collateral channel grade 0) were observed in 80 (28.8%) and 100 (36.1%) CTOs, respectively. Patients with ≥2 CTOs had a tendency toward a higher cumulative appropriate ICD therapy (HR: 1.38; 95% CI: 0.92 to 2.08; p = 0.123) (Figure 4). Although Rentrop collateral flow was associated with higher incidence of VA (Rentrop grade 3 versus Rentrop grade ≤2; HR: 1.54; 95% CI: 1.04 to 2.26; p = 0.029), there was no association with collateral channels (collateral channel grade 2 versus collateral channel grade ≤1; HR: 1.35; 95% CI: 0.88 to 2.07; p = 0.170). In multivariable analysis for predictors of ICD therapies among CTO patients, Rentrop grade 3 showed a tendency toward a higher risk of VA recurrence (Table 5). There were no differences in the VA presentation (VT vs. ventricular fibrillation) and tachycardia cycle length between patients with and without CTO (Table 2). In the subgroup of 74 (41%) patients with electrogram tracings available, the median coupling interval of the initiating beat was 445 ms (IQR: 385 to 615 ms) with a median PI of 0.65 (IQR: 0.53 to 0.81). Most of the episodes (87.5%) were initiated by long-coupled premature ventricular complexes (PI >0.5). Patients with CTO had a shorter coupling interval (p = 0.024) and lower PI (p = 0.043) (Table 2).

FIGURE 1 Freedom From Appropriate ICD Therapy According to the Presence of CTO



Kaplan-Meier survival curves for freedom from first appropriate device therapy according to the presence or absence of a chronic total occlusion (CTO).

DISCUSSION

One-half of the VA survivors with CAD receiving an ICD for secondary prevention presented a CTO in the baseline coronary angiogram. This finding was associated with higher rates of appropriate ICD therapy and mortality during the follow-up. No definitive angiographic findings were related with higher VA recurrence, although better collaterals flow in the CTO artery had a tendency toward a

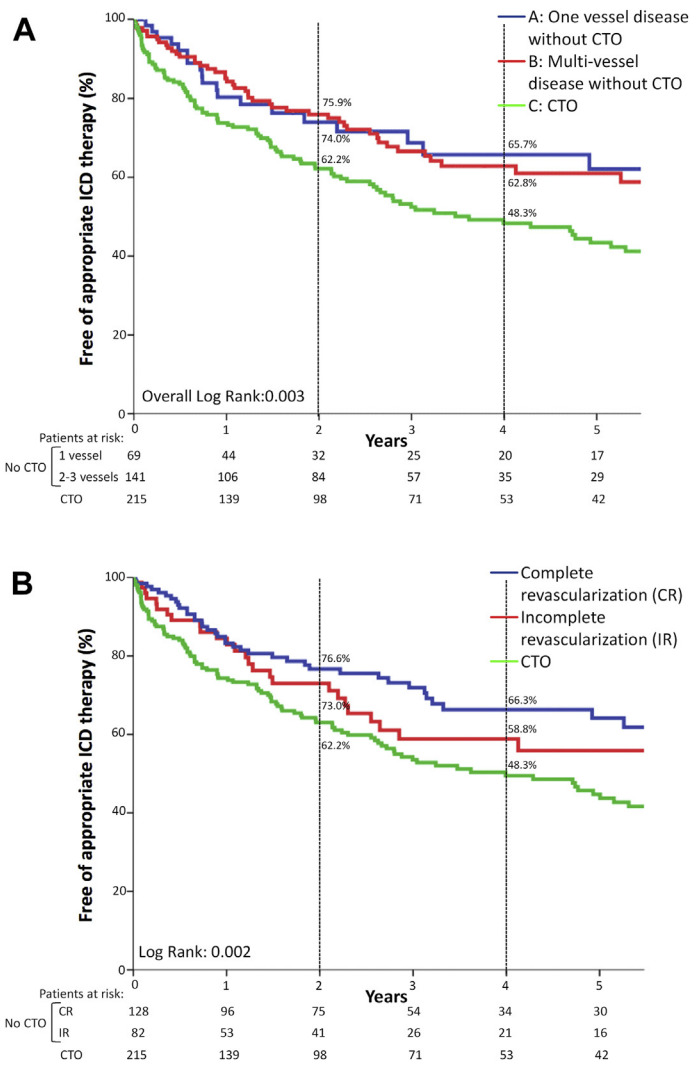
TABLE 3 Univariate and Multivariate Predictors of Appropriate ICD Therapy

	Univariable Analysis HR (95% CI)	p Value	Multivariable Analysis* HR (95% CI)	p Value
CTO	1.73 (1.28–2.34)	0.001	1.80 (1.30–2.50)	0.001
Age*	1.06 (0.98–1.15)	0.128	1.02 (0.93–1.11)	0.666
Female	1.14 (0.67–1.94)	0.626	1.54 (0.87–2.73)	0.138
Dyslipidemia	0.96 (0.71–1.30)	0.801	0.89 (0.64–1.25)	0.503
Diabetes	1.15 (0.84–1.57)	0.393	1.04 (0.73–1.48)	0.823
Atrial fibrillation	1.11 (0.79–1.57)	0.550	0.99 (0.68–1.45)	0.975
Prior MI	1.14 (0.79–1.65)	0.472	0.84 (0.55–1.27)	0.395
NYHA functional class ≥II	1.37 (0.99–1.91)	0.060	1.18 (0.82–1.69)	0.366
eGFR <60 ml/min	1.33 (0.98–1.79)	0.066	1.15 (0.82–1.60)	0.411
LVEF†	1.10 (1.04–1.17)	0.002	1.09 (1.02–1.17)	0.015
Q wave	1.28 (0.94–1.73)	0.111	1.25 (0.89–1.75)	0.205

*For each increase of 5 years. †For each decrease of 5%.

CI = confidence interval; HR = hazard ratio; NYHA = New York Heart Association; other abbreviations as in Table 1.

FIGURE 2 Freedom From Appropriate ICD Therapy According to the Extent of Coronary Artery Disease and Revascularization Status



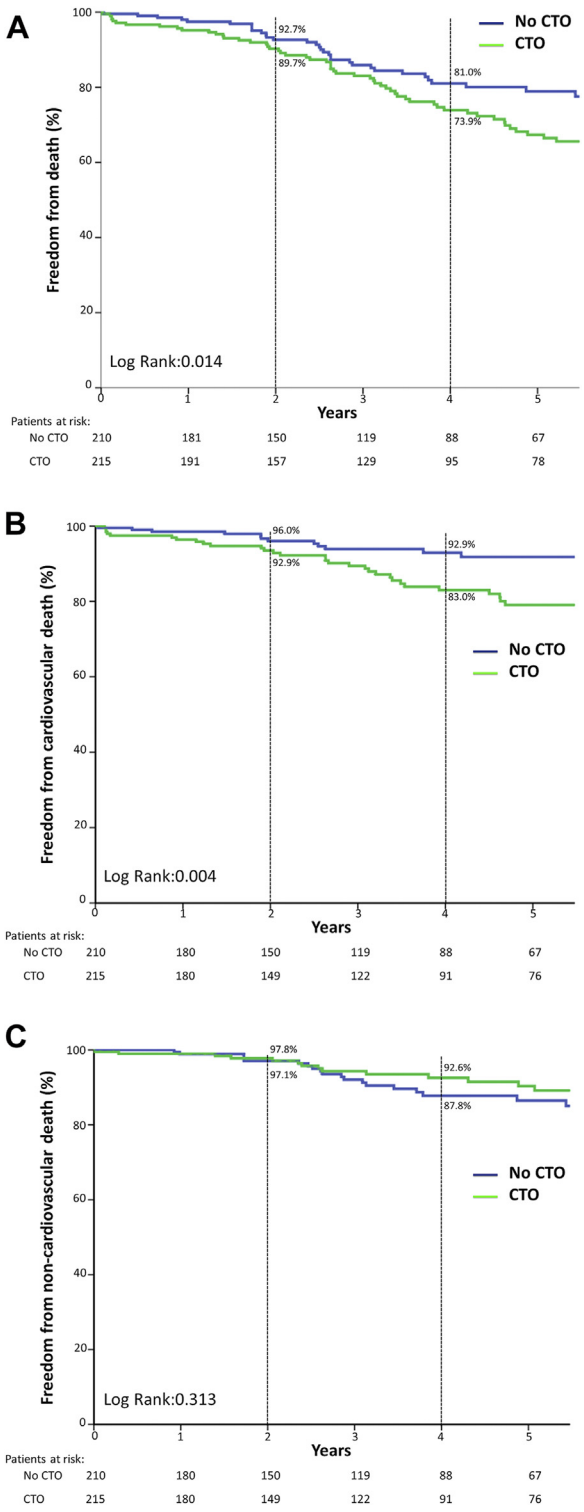
Kaplan-Meier survival curves for freedom from first appropriate device therapy according to **(A)** one-vessel or multivessel or chronic total occlusion diseases or chronic total occlusion (CTO) and **(B)** complete revascularization (CR), incomplete revascularization (IR), or CTO.

higher VA recurrence. Although the arrhythmia and cycle length were similar in patients with and without CTO, the onset of the premature ventricular complex was shorter in the CTO group.

The presence of a coronary CTO has been associated with worse clinical outcomes in several scenarios, such as stable angina, acute coronary syndromes and heart failure (17,18). It has been hypothesized that an occluded artery could be related to lower myocardial reserve for future events, electrical instability and subsequently higher incidence of VA. The present study showed a high incidence (~50%) of CTO in patients with ICD for secondary prevention. No previous studies assessing the incidence of a CTO in this setting exist, although this high incidence was in accordance to previous reports in other scenarios (7). The impact and the mechanism of a CTO in the first VA episode causing a SCD remain undetermined. In the VACTO primary study (10), we observed a higher risk for appropriate ICD therapies in primary prevention patients with CTO. Later, Di Marco et al. (11) also reported that a CTO in an infarct-related artery was an independent predictor of VT recurrence after a successful VT ablation. On the contrary, in a recent large cohort of primary prevention ICD recipients, the presence of a CTO was not associated with VA occurrence (12). Only the absence of a left circumflex CTO was a protective factor for ICD therapies. Survivors of SCD are a highly susceptible population for having VA recurrence in the follow-up, indeed, more than other ICD recipients' population (5,19). In our cohort, VA rates were as high as 31% and 44% at 2- and 4-year follow-up, respectively, which is in accordance with previous studies (4,5). However, patients with CTO had almost twice the risk of VA recurrence. It has been shown that CTO in an infarct-related artery is associated with greater scar and, above all, greater border zone (11). The post-infarction scar is recognized as the main substrate for VA in patients with ischemic cardiomyopathy and, within the scar, the border zone where surviving cardiomyocytes are interposed among fibrotic cells, seems to be critically associated with VA. It often hosts the channels of slow conduction that are an essential part of VT re-entrant circuit (20) and it has been associated with increased arrhythmic events in cardiac magnetic resonance studies (21). For example, Robbers et al. (21) found that larger amounts of partially necrotic areas (25% to 50% of myocardium thickness visualized by cardiac magnetic resonance with late gadolinium enhancement) were associated with increased risk of developing VT 1 month after a primary PCI. Although in a totally different population, in our study CTO patients with better collateral flow had a tendency toward higher VA recurrence. This could be explained by a greater amount of hibernating myocardium, especially in the border zone of a previous infarction (22) or in partially viable areas. Better collateral flow assessed by Rentrop classification was associated with less transmurality (≤75%) in late gadolinium enhancement studies (23), and this could be translated into more electrical instability especially in the border zone of partially necrotic areas. Moreover, well-developed collaterals in CTO arteries did not prevent ischemia (22,24,25), which is the most important trigger for VA. Importantly the extent of CAD was

not associated with ICD therapies, which was more related to the revascularization status. Incomplete revascularization had a negative impact on clinical outcomes (26,27) and similarly we observed an incremental risk of ICD therapies according to complete or incomplete revascularization status, being patients with CTO in the highest risk. This study highlights the importance of evaluating the presence of a CTO at the time of ICD implantation to better ascertain a more vulnerable group of patients with poorer outcomes at follow-up. The possible additional therapeutic actions for these patients are coronary revascularization and VA ablation. The latter is useful to reduce recurrences of VA and might improve survival (28). However, Di Marco et al. (11) reported a high incidence of VA recurrence despite successful catheter ablation in patients with a CTO in an infarct related artery. Coronary flow restoration in a CTO artery is a modifiable factor in the current era of PCI. Angiographic CTO complexity in our cohort was considered difficult by J-CTO score assessment in a high proportion of patients (~70%). However, current PCI success rate is high (~85%) even in difficult cases if performed by experienced operators (15,29). An adequate perfusion of the occluded artery could translate into diminishing the ischemic burden in the noninfarcted myocardium border, formation of a more stable myocardium tissue, and a beneficial influence on the remodeling process. Several studies have shown an improvement of LVEF after successful CTO revascularization (30,31), and a better remodeling process might be translated into lower future VA. In accordance with this hypothesis, Cetin et al. (32) found a significant decrease in some electrocardiographic markers (such as QTc dispersion or T-wave peak-to-end interval) of ventricular repolarization after successful CTO revascularization, indicating a reduction of arrhythmic vulnerability. These may account for the long-term electrophysiological stability that follows a late opening of an occluded coronary artery. However, whether CTO revascularization may decrease or not the VA recurrence is unknown. Importantly, Raja et al. (12) did not find a significant decrease in ICD therapies in primary prevention patients with a revascularized CTO. Similarly to previous studies (4,11,12), LVEF was independently associated with VA recurrence. Ventricular function has been the major parameter to guide ICD implantation for primary prevention of SCD, and continues to have an impact in secondary prevention patients. Even more, CTO was a strong predictor of mortality in patients with heart failure and low LVEF (18). Optimal medical treatment and coronary revascularization to maintain or improve LVEF would be of utmost importance for these patients.

FIGURE 3 Survival Curves According to the Presence of CTO



Kaplan-Meier survival curves for **(A)** all-cause, **(B)** cardiovascular, and **(C)** noncardiovascular mortality according to the presence or absence of a chronic total occlusion (CTO).

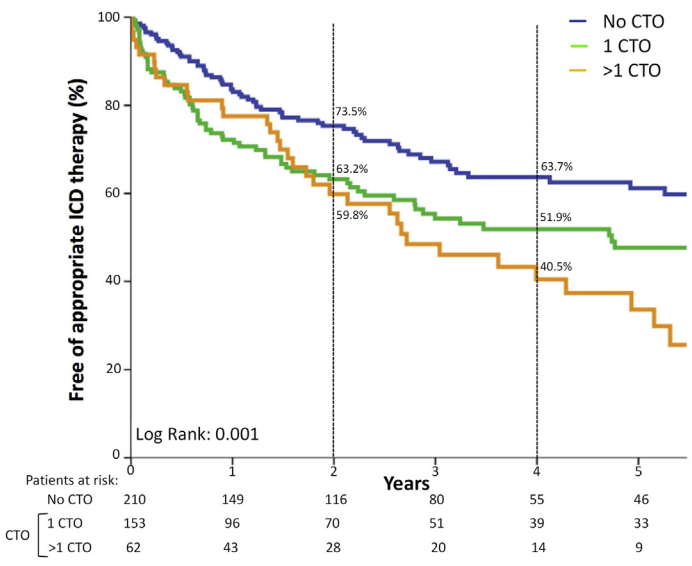
TABLE 4 Univariate and Multivariate Predictors of Cumulative Mortality

	Univariable Analysis HR (95% CI)	p Value	Multivariable Analysis HR (95% CI)	p Value
CTO	1.65 (1.11–2.45)	0.013	1.69 (1.04–2.73)	0.033
Age*	1.16 (1.04–1.130)	0.006	1.06 (0.93–1.21)	0.373
Female	0.69 (0.30–1.58)	0.386	0.65 (0.24–1.82)	0.415
Dyslipidemia	0.92 (0.63–1.36)	0.683	0.70 (0.43–1.14)	0.152
Diabetes	1.58 (1.07–2.34)	0.020	1.62 (1.00–2.64)	0.051
Atrial fibrillation	1.23 (0.80–1.89)	0.342	0.84 (0.49–1.46)	0.548
Prior MI	1.06 (0.66–1.69)	0.812	0.80 (0.46–1.38)	0.418
eGFR <60 ml/min	1.92 (1.30–2.84)	0.001	1.67 (1.05–2.66)	0.029
Left bundle branch block	1.75 (1.11–2.77)	0.016	1.21 (0.72–2.04)	0.464
LVEF†	1.14 (1.05–1.24)	0.002	1.12 (1.00–1.24)	0.041
Mitral regurgitation ≥2–4	1.61 (1.06–2.43)	0.025	1.10 (0.67–1.79)	0.712

*For each increase of 5 years. †For each decrease of 5%.

Also in the present study, the CTO group experienced higher overall and cardiac mortality compared to the non-CTO group, in addition to poorer renal function and LVEF. However, whether CTO revascularization has a beneficial impact on survival is still controversial (33,34). All the studies assessing the effect of CTO revascularization are observational and no randomized controlled clinical trials are currently available. Pooled results of observational studies showed a favorable effect of CTO revascularization (33), though recent studies reported no additional benefit (34). Future studies will have to determine the beneficial effect of CTO revascularization, on VA recurrence, left ventricle function and mortality in this population. In the meantime, this study could help in the identification of clinical and angiographic factors that influence the rate of VA recurrence and may improve risk stratification and management after ICD implantation in patients with CAD.

FIGURE 4 Freedom of Appropriate ICD Therapy According to the Number of CTO



Kaplan-Meier survival curves for freedom from first appropriate device therapy according to the absence or presence of 1 or ≥2 chronic total occlusions (CTOs).

TABLE 5 Univariate and Multivariate Predictors of Appropriate ICD Therapy Among Patients With CTO

	Univariable Analysis HR (95% CI)	p Value	Multivariable Analysis HR (95% CI)	p Value
Rentrop grade 3	1.54 (1.04–2.26)	0.029	1.40 (0.95–2.07)	0.093
eGFR <60 ml/min	1.71 (1.23–2.38)	0.001	1.57 (1.07–2.32)	0.023
LVEF <40%	1.43 (1.01–2.02)	0.042	1.51 (1.01–2.26)	0.046

Abbreviations as in Tables 1 and 3.

STUDY LIMITATIONS. This is an observational study and results should be interpreted with caution. Although patients were consecutive, data and events were reported by each participating center without an event adjudication committee. Noninvasive functional tests were not systematically performed in all the patients, and information about viability and ischemia extension are limited. Although all the patients underwent ICD interrogation, electrograms retrieved and analyzed from ICDs were limited to one-half of the patients that had an ICD therapy. This could bias the results of arrhythmia analysis and should be interpreted with caution until further investigations are available. Coronary anatomy was assessed before ICD implantation and repeated coronary angiograms were limited and not analyzed.

CONCLUSIONS

Chronic total coronary occlusion is present in a high percentage of SCD survivors with CAD. The presence of CTO was an independent predictor of VA recurrence in secondary prevention ICD recipients and was associated with poorer survival in long-term follow-up. Differences in VA onset were detected between patients with and without CTO, although the association between VA and specific angiographic characteristics of the CTO remained uncertain. Future studies should evaluate whether specific therapeutic strategies targeting CTO may decrease the risk of VA recurrence and cardiac death.

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PERSPECTIVES

WHAT IS KNOWN? CTO is a marker of worse prognosis in several clinical scenarios such as acute coronary syndrome, stable angina, and ischemic cardiomyopathy. However, its impact on ICD recipients for secondary prevention of SCD is unknown.

WHAT IS NEW? CTO was a frequent finding (~50%) in patients with ischemic cardiomyopathy who received an ICD for secondary prevention and was independently associated with appropriated ICD therapies. VA onset was associated with a shorter coupling interval and a lower PI in CTO patients, and better collateral flow was associated with more appropriate ICD therapies among CTO patients.

WHAT IS NEXT? Future studies will have to determine the beneficial effect of CTO revascularization on VA recurrence, left ventricle function, and mortality in this population.

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