Ventricular Arrhythmias Among Implantable Cardioverter-Defibrillator Recipients for Primary Prevention

Impact of Chronic Total Coronary Occlusion (VACTO Primary Study)

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Background—An implantable cardioverter-defibrillator (ICD) is the therapy of choice for primary prevention in patients with ischemia who are at risk for sudden cardiac death (SCD). One third of patients with significant coronary disease have chronic total coronary occlusion (CTO), which is associated with long-term mortality in patients with previous myocardial infarction. However, the impact of CTO on the occurrence of ventricular arrhythmias and long-term mortality in ICD recipients remains unknown.

Methods and Results—All consecutive patients with coronary artery disease receiving ICD therapy for the prevention of SCD were included in the study. Among other characteristics, the existence of CTO was assessed. During follow-up, the occurrence of appropriate device delivery because of ventricular arrhythmias as well as mortality were noted. A total of 162 patients (mean age, 62 ± 9 years; 93% men) with an ICD were included and followed for a median of 26 months (interquartile range, 12–42). At least 1 CTO was present in 71 (44%) patients. Appropriate device therapy was detected in 18% of the patients during the follow-up. The presence of CTO was associated with higher ventricular arrhythmia and mortality rates (log-rank test, <0.01). Multivariable analysis revealed that CTO was independently associated with appropriate ICD intervention (hazard ratio, 3.5; \( P = 0.003 \)).

Conclusions—In patients with ischemic heart disease receiving ICDs for primary prevention of SCD, CTO is an independent predictor for the occurrence of ventricular arrhythmias and has an adverse impact on long-term mortality. (Circ Arrhythm Electrophysiol. 2012;5:147-154.)

Key Words: coronary occlusion ▪ implantable cardioverter-defibrillators ▪ mortality ▪ arrhythmias cardiac

Sudden cardiac death (SCD) is a major cause of mortality, and ventricular arrhythmias (VA) are responsible for most cases. Implantable cardioverter-defibrillator (ICD) therapy was initially proven superior to antiarrhythmic drugs in patients experiencing life-threatening arrhythmias studied in large randomized trials. More recently, ICD prophylactic implantation has also been recommended for the primary prevention of SCD in patients with a prior myocardial infarction (MI) and advanced left ventricular dysfunction. This indication is exclusively based on a poor left ventricular ejection fraction (LVEF), so it has caused a notable increase in the number of implantations performed. However, a significant proportion (up to 75%) of these patients will never receive an ICD shock during their follow-up. Thus, identifying other variables that predict the need for ICD therapies could help in the better selection of ICD candidates.

Clinical Perspective on p 154

Chronic total coronary occlusion (CTO) is a very common condition among patients with coronary artery disease, with a reported prevalence between 20% to 50% in patients with ischemia referred to the catheterization laboratory. Additionally, the presence of a CTO is associated with further deterioration of LVEF during follow-up and with long-term mortality in patients with a previous MI. Several studies suggested that successful CTO recanalization may provide significant reduction of angina and an improvement in mortality rate and the occurrence of major adverse cardiac
events. Moreover, it has been proposed that an open artery may increase tolerance to future coronary events and provide electric stability.

Previous studies with ICD recipients have focused on global coronary artery disease, with no difference between CTO or non-CTO arteries. With an increase in the number of ICD implantations for ischemic cardiomyopathy, a great number of patients with CTO can be expected. The prevalence, follow-up, and prognostic implications of a history of CTO in patients with ICDs remain unknown. The purpose of the present study was to evaluate the prognostic importance of CTO in the occurrence of VA and mortality in patients with low LVEF receiving an ICD for primary prevention of SCD.

Methods

Study Population
Between 2002 and 2009, all consecutive patients receiving an ICD for primary prevention indication at the Puerta de Hierro University Hospital in Madrid, Spain, were studied. Baseline clinical and echocardiography data, characteristics of the implant procedure, and data for all follow-up visits were prospectively recorded in a dedicated database. Coronary status was categorized as having coronary artery disease with or without CTO. To assess the presence or absence of CTO, we retrospectively reviewed all coronary angiograms. In 29% of the patients who were referred for ICD implantation from different hospitals, interventional cardiology reports were used as a surrogate for angiograms. The CTO group was defined as a total occlusion with or without antegrade or retrograde filling through collateral vessels in at least 1 major coronary artery. Neither occluded vessels that were surgically or percutaneously revascularized nor secondary occluded vessels, such as diagonal branch, posterior descending artery, or posterolateral branches, were classified as CTO. Renal dysfunction was defined as a creatinine clearance <60 mL/min as calculated by the Cockroft-Gault formula. LVEF was calculated from the biplane Simpson method, and if the echocardiography window from the apical 4-chamber view was not suitable, LVEF was visually estimated.

Defibrillator Systems and Implantation Procedures
Defibrillator implantation in the study population was based on international guidelines; therefore, we selected patients with an ICD implanted for primary prevention after 2002, when the MADITT II (Multicenter Automatic Defibrillator Implantation Trial) was published. All patients received a multifunctional single-chamber, dual-chamber, or resynchronization ICD from one of the main manufacturers (St Jude Medical, Medtronic, Biotronik, or Boston Scientific). All defibrillator systems were implanted transvenously and without thoracotomy, excluding patients with epicardial systems. We performed testing of the sensing, pacing, and defibrillation thresholds during the implantation procedure.

Long-Term Follow-Up
Patient visits were scheduled every 3 to 8 months. In every follow-up visit, the ICD was interrogated to obtain its present setting status, to test the sensing and pacing thresholds, and to obtain data on its operation to look for appropriate or inappropriate ICD therapy. The ICD interrogation and event reviews were always done by an expert electrophysiologist (I.F.L.), keeping the same criteria for ICD settings. Therapies were recorded as appropriate when shocks or antitachycardia pacing took place in response to VA (either ventricular tachycardia or ventricular fibrillation). Therapy delivered for anything other than VA (device malfunction, supraventricular tachycardia, or T-wave oversensing) was not included. Details of subsequent clinical deterioration, death, or heart transplantation were documented. Urgent heart transplantation was considered equivalent to death in the analysis.

Statistical Analysis
The primary end point of the study was the occurrence of VA in patients with CTO compared to that in patients without CTO. The secondary end points included total mortality in the CTO and non-CTO groups at long-term follow-up. Qualitative variables are expressed as percentages and quantitative variables as mean±SD or median (25th–75th interquartile range), depending on variable distribution. The normality distribution for continuous data were examined with the Shapiro-Wilk test. Comparison of numeric variables was performed using the 2-sided Student t-test or Wilcoxon rank sum test, and the χ² or Fisher exact tests were used to compare qualitative variables. Freedom from VA and mortality curves were calculated using the Kaplan-Meier method, and comparison between patient 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.

The risk of developing VA was estimated by computing hazard ratios (HRs) and their 95% CIs by the Cox regression method. The validity of the proportionality assumption was verified for all covariates by a visual examination of the log (−log) curves and a test based on Schoenfeld residuals. After checking for colinearity, we included any variable with P<0.1 in a univariable analysis as well as the coronary status (CTO or non-CTO) in a multivariable logistic regression model. We entered age, LVEF, and QRS as continuous variables in the regression model and calculated an HR for age that was calibrated for each 5-year increase. P<0.05 was considered significant for all statistical tests. All analyses were done using SPSS version 18.0 for Windows statistical software.

Results
Data from 718 consecutive patients with an ICD were prospectively collected. After excluding nonischemic cardiomyopathy (n=387), secondary prevention indication (n=155), and primary prevention before 2002 (n=11), a total of 165 patients received an ICD because of ischemic cardiomyopathy and were followed up for 26 months (interquartile range, 12–42 months). Of these 165 patients, 3 were excluded from the analysis because of limited angiogram data. The remaining 162 (98%) patients were included in the study and classified into 2 groups according to the presence or absence of CTO. One (1%) patient in the non-CTO group was lost to follow-up. The study flow diagram is shown in Figure 1.
Baseline clinical, echocardiographic, and device characteristics of the 162 patients included in the analysis are presented in Table 1. The patients had a mean age of 62±9 years and a low LVEF (29±9%), and the majority (93%) of patients were men. Eighty-two of the 162 (51%) patients had a history of MI. Electrocardiographic rhythm was sinus rhythm in 133 (82%) patients, atrial fibrillation in 21 (13%), and pacemaker dependent in 8 (5%). Single- and dual-chamber ICDs were implanted in 102 (63%) and 14 (9%) patients, respectively, whereas biventricular ICDs were implanted in 46 (28%). At least 1 CTO was found in 71 (44%) patients. There were no differences in baseline characteristics between the 2 groups, except that patients with CTO were more likely to be younger and to have diabetes and less likely to have atrial fibrillation compared to patients without CTO. Patients with CTO more frequently had 3-vessel coronary disease (Table 1). There were 92 CTOs in 71 patients (1.29 CTOs per patient), and the right coronary artery was the site of the most frequent CTO (48/92 [52%]) followed by the left anterior descending artery (23/92 [23%]). Collaterals with Rentrop grade ≥2 were present in 71% of the patients with CTO. Q waves in the CTO territory were present in 30% of the patients. Only 6% of the patients with CTO had a dyskinesia in the myocardium supplied by the occluded artery, and 58% had hypokinesia or normal regional function by echocardiogram. None of the patients with CTO underwent coronary revascularization after ICD implantation.

**Impact of CTO on VA**

Of the 162 patients, appropriate ICD-delivered therapy (antitachycardia pacing or shock) because of VA occurrence was detected in 29 (18%) during follow-up, with a median time from the implant of 257 days (interquartile range, 60–644 days). A total of 1400 (range, 1–1002) episodes in 29 patients were noted, exclusively terminated with antitachycardia pacing in 8 patients, with ICD shock in 2, and with both therapies in 19. The cumulative incidences of appropriate device delivery were 13% (95% CI, 8%–19%) at 1 year, 16% (95% CI, 10%–22%) at 2 years, and 23% (95% CI, 15%–31%) at 3 years of follow-up. The rate of appropri-
ICD therapy was higher in the CTO group than in the non-CTO group (Table 2).

Kaplan-Meier analysis for the primary end point revealed progressive divergence of the curves for survival free from ICD therapy as shown (CTO 74±12% versus non-CTO 91±6%, \( P < 0.05 \) after 2 years of follow-up) (Figure 2). There were no differences between the CTO and non-CTO groups in the cycle length of the VA (276 and 288 ms, respectively; \( P = 0.24 \)). Antitachycardia pacing therapies were successful in 46 of 62 (74%) patients with CTO and in 20 of 30 (67%) patients without CTO (\( P = 0.45 \)).

Five variables were related to appropriate ICD therapy: presence of CTO, older age, 3-vessel disease, previous MI, and hypercholesterolemia. The Cox regression method for the multivariable analysis showed that age (adjusted HR, 1.3 per 5-year increase; 95% CI, 1.1–1.7 years; \( P = 0.015 \)) and the presence of CTO (adjusted HR, 3.5; 95% CI, 1.5–8.3; \( P = 0.003 \)) were independent predictors of VA occurrence in the overall population (Table 3). Patients with CTO had a >2-fold risk of appropriate ICD therapy compared with patients without CTO. After adjusting for CTO in the multivariate model, 3-vessel disease was no longer an independent predictor for ICD therapy (Figure 3).

Impact of CTO on Mortality

Over a median follow-up of 26 months (interquartile range, 12–42 months), 15 (9%) patients died (including 1 patient with an urgent heart transplantation). The cumulative event rates for mortality were 5% (95% CI, 2%–9%) at 1 year, 8% (95% CI, 3%–13%) at 2 years, and 12% (95% CI, 7%–18%) at 3 years of follow-up.

Comparing the 2 groups, survival analysis showed a 2-year cumulative event rate for mortality of 15% (95% CI, 6%–24%) for patients with CTO and 4% (95% CI, 1%–8%) for patients without CTO (\( P < 0.01 \)) (Figure 4). Multivariable analysis revealed that the presence of a CTO was an independent predictor of mortality (adjusted HR, 5.6; 95% CI, 1.4–21). Absence of β-blocker, older age, and New York Heart Association functional class III or IV were also predictors of mortality (Table 4).

### Table 2. Cumulative Event Rates for Appropriate ICD Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary Prevention, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global (n=161)</td>
<td>No CTO (n=90)</td>
</tr>
<tr>
<td>1 y</td>
<td>13 (8–19)</td>
</tr>
<tr>
<td>2 y</td>
<td>16 (10–22)</td>
</tr>
<tr>
<td>3 y</td>
<td>23 (15–31)</td>
</tr>
</tbody>
</table>

ICD indicates implantable cardioverter-defibrillator; CTO, chronic total coronary occlusion.

### Table 3. Univariable and Multivariable Predictors of ICD Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTO</td>
<td>2.9 (1.3–6.2)</td>
<td>3.5 (1.5–8.3)</td>
</tr>
<tr>
<td>Age (per 5-y increase)</td>
<td>1.1 (1.0–1.2)</td>
<td>1.3 (1.1–1.7)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>2.2 (1.0–5.1)</td>
<td>0.050</td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>1.9 (0.9–4.1)</td>
<td>0.066</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.8 (0.9–4.3)</td>
<td>0.080</td>
</tr>
</tbody>
</table>

ICD indicates implantable cardioverter-defibrillator; HR, hazard ratio; CTO, chronic total coronary occlusion; MI, myocardial infarction.

*HR adjusted for age, sinus rhythm, 3-vessel disease, previous MI, diabetes, renal dysfunction, and hypercholesterolemia.

patients with Rentrop grade >2 collaterals had a tendency toward a lower rate of more VA than those with Rentrop grade <2 collaterals (22% versus 38%, \( P = 0.162 \)).

![Figure 2. Kaplan-Meier survival curves for freedom from first appropriate device therapy in CTO and non-CTO populations. CTO indicates chronic total coronary occlusion; ICD, implantable cardioverter-defibrillator.](http://circep.ahajournals.org/Downloaded from)
In the VACTO (Ventricular Arrhythmias and Chronic Total Coronary Occlusion) Primary Study, we assessed the prognostic importance of CTO in the incidence of appropriate ICD therapy for VA and its impact on mortality in a cohort of patients receiving ICD treatment for primary prevention of ischemic cardiomyopathy. The main findings can be summarized as follows: (1) CTO was very frequent (44%) in this population, and (2) the presence of a CTO had a negative impact on VA incidence and mortality at long-term follow-up.

**Impact of CTO on VA**

In the present cohort, the 16% incidence of VA at 2 years seemed comparable to previous studies.6–8,18,19 Previously described predictors of appropriate ICD therapy, such as age, smoking status, ICD indication, QRS width, sex, New York Heart Association class, renal dysfunction, LVEF, and β-blocker use,18–21 were included.
in the present analysis. As in other studies, we found that age was an independent predictor of ICD therapy. However, even after adjusting for all these factors, patients with CTO exhibited a significantly higher risk of device delivery.

CTO incidence was high (up to 40%) in the study population. This percentage is analogous to that previously described by Christofferson et al.9 Recent studies, however, reported a prevalence of ~15% to 30%.10,22 The higher prevalence in the present population could be explained by a negative selection as a result of ICD implantation in patients with very low LVEF because of more-extensive coronary disease. Usually, CTOS are medically treated instead of being surgically or percutaneously revascularized. Large areas of residual or silent ischemia in a CTO territory were observed by Werner and Figulla23 and Werner et al, 24 and even in the presence of collaterals, myocardial blood supply in the CTO territory did not prevent exercise-induced ischemia. Ischemia could be a trigger for VA occurrence, whereas chronic scarring is another possible mechanism for the genesis of VA.25 In fact, a great proportion of the present cohort had a previous MI, but this did not differ between patients in the CTO and non-CTO groups. The significant proportion in the CTO study population with possible myocardial viability indicates theoretically that an interaction of ischemia superimposed on a chronic MI scar may lead to arrhythmic events in these patients, which could be considered and assessed in future studies.

More than 30% of the patients with CTO had arrhythmic events after 3 years of follow-up, which puts them in a high-risk subgroup for receiving ICD discharges. In this scenario, it might be useful to either perform a prophylactic ventricular tachycardia catheter ablation26 or intensify antiarrhythmic treatment before the ICD implantation in patients with CTO to reduce the ICD therapies and improve quality of life.27 On the contrary, 90% of the patients without CTO with primary prevention indication for an ICD remained free from VA at 2 years follow-up. Expanding the indication after the MADIT II trial to more-permissive uses of ICD has resulted in the acceptance of patients who are less likely to benefit from an ICD. This new predictor of appropriate ICD therapy in primary prevention could help the physician to be more selective of ICD candidates. Thus, the current study suggests that CTO may be one of the most important predictors of therapy and raises the question of whether this variable should be emphasized to select appropriate ICD candidates.

Although previous studies showed an improvement in arrhythmic markers after late reperfusion of an infarct-related artery,28,29 more recently, Rashba et al,30 in a sub-study of the OAT (Occluded Artery Trial), found no differences in heart rate variability between percutaneous coronary intervention with stenting of a persistently occluded infarct-related artery and medical treatment. However, this study included patients with subacute MI and a mean LVEF of 47% compared to an LVEF of 30% in the present study population with only 50% of the patients with chronic MI and 30% with Q waves in the CTO territory. Patients included in CTO registries had not been represented in the OAT,31 so whether CTO revascularization could provide electric stability and reduce a predisposition to future VA remains unknown.32

Impact of CTO on Mortality

Previous studies demonstrated the impact of CTO on mortality.14 The difference in mortality might be related to a deterioration of LVEF and VA occurrence. It has been shown that in patients with acute MI, the presence of a CTO in the noninfarct-related artery increases mortality.11 These findings seem comparable to the 4-fold increased risk of mortality for patients with CTO in the present study, independent of the number of coronary arteries affected.

In addition, several studies have shown that reopening CTOS improves prognosis.13,33–35 However, the findings in the current literature regarding the potential relationship between CTO revascularization in patients with very low LVEF and improvement in mortality are inconsistent, as are the criteria for candidacy for ICD implantation. Otherwise, the possibility of LVEF improvement with its beneficial effect on survival provides the rationale for the technically demanding attempt to revascularize a CTO. Finally, as ICD indications continue to expand along with the financial impact on the healthcare system, future real-world studies may help to further risk stratify patients who would most benefit from ICD treatment and CTO revascularization.

Study Limitations

Several limitations of the present study should be mentioned. To begin with, this observational and nonrandomized cohort study was performed to assess the role of CTO in long-term follow-up in ICD recipients. We have only considered the coronary status immediately before ICD implantation. Hence, patients who developed a new CTO after implantation could have been misclassified. None of the patients underwent CTO revascularization during follow-up; thus, we could not assess a possible benefit of revascularization in VA occurrence. Furthermore, we did not routinely perform an ischemia test; thus, information about reversible ischemia or viability in patients with CTO is limited. However, indirect data, such as absence of electrocardiographic Q waves or dyskinesia in the myocardium supplied by the occluded artery, support a viable myocardium or a possible recovery after recanalization.36

Device setting was not done by an independent core laboratory and was left to the physician’s discretion. However, all arrhythmic events were reviewed by the same electrophysiologist in a second stage and classified subsequently. Moreover, the occurrence of appropriate ICD delivery is an imperfect surrogate for SCD and probably overestimates the risk of SCD. Nevertheless, we analyzed the

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Table 4. Multivariable Predictors of Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of β-blocker</td>
<td>6.3 (1.4–28.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>CTO</td>
<td>5.6 (1.4–21.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>NYHA class =III</td>
<td>4.7 (1.3–17.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age (per 5-y increase)</td>
<td>1.5 (1.0–2.3)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CTO, chronic total coronary occlusion; NYHA, New York Heart Association.
occurrence of VA only, which are life-threatening events, and the proportion of ventricular tachycardia that would have been fatal in the absence of appropriate ICD therapy is still unknown. Finally, this was a single-center study, and as such, the biases of the local center and population may have influenced the CTO incidence and predictors of ICD delivery.

Conclusions
CTO is present in a high percentage of patients with ischemic heart disease receiving an ICD for primary prevention of SCD. The data suggest that CTO is an independent predictor for occurrences of VA in primary prevention, and it has an adverse impact on long-term mortality. Our findings may further help to select appropriate ICD candidates and open new lines of investigation regarding the impact of CTO recanalization on future VA.

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Disclosures
Dr Fernández Lozano has served on advisory boards for Boston Scientific and Sorin Group and is on a steering committee or study advisory committee for Medtronic and St Jude Medical.

References
Coronary artery disease remains the most important cause of left ventricular dysfunction. Patients with ischemic cardiomyopathy are at high risk of sudden cardiac death. The implantable cardioverter-defibrillator is now a common therapy for primary prevention in these patients. However, this indication is based exclusively on a poor left ventricular ejection fraction. Chronic total coronary occlusion (CTO) has been reported to be present in as many as 30% of patients with ischemia and has an adverse impact in long-term survival. In the present VACTO (Impact of Chronic Total Coronary Occlusion) Primary Study, we included real-world patients who underwent implantable cardioverter-defibrillator implantation for primary prevention and assessed the prognostic value of prior angiographic evidence of at least 1 CTO on ventricular arrhythmias and their additive impact on mortality in such patients. At 2 years, the cumulative incidence of appropriate implantable cardioverter-defibrillator therapy was higher in the CTO group than in the non-CTO group (26% versus 9%, \( P = 0.01 \)). The findings support that CTO is a strong independent predictive factor for the occurrence of ventricular arrhythmias (hazard ratio, 3.5; 95% CI, 1.5%–8.3%).

**CLINICAL PERSPECTIVE**

Coronary artery disease remains the most important cause of left ventricular dysfunction. Patients with ischemic cardiomyopathy are at high risk of sudden cardiac death. The implantable cardioverter-defibrillator is now a common therapy for primary prevention in these patients. However, this indication is based exclusively on a poor left ventricular ejection fraction. Chronic total coronary occlusion (CTO) has been reported to be present in as many as 30% of patients with ischemia and has an adverse impact in long-term survival. In the present VACTO (Impact of Chronic Total Coronary Occlusion) Primary Study, we included real-world patients who underwent implantable cardioverter-defibrillator implantation for primary prevention and assessed the prognostic value of prior angiographic evidence of at least 1 CTO on ventricular arrhythmias and their additive impact on mortality in such patients. At 2 years, the cumulative incidence of appropriate implantable cardioverter-defibrillator therapy was higher in the CTO group than in the non-CTO group (26% versus 9%, \( P = 0.01 \)). The findings support that CTO is a strong independent predictive factor for the occurrence of ventricular arrhythmias (hazard ratio, 3.5; 95% CI, 1.5%–8.3%).
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