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Prognostic impact of chronic total coronary occlusion on long-term outcomes in implantable cardioverter-defibrillator recipients with ischemic heart disease

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Abstract

Aims

The prognostic impact of chronic total coronary occlusion (CTO) on implantable cardioverter-defibrillator (ICD) recipients remains unclear.

Methods and Results

Eighty-four consecutive patients with ischemic heart disease who received ICD therapy for primary or secondary prevention were analyzed. We investigated all-cause mortality and major adverse cardiac events (MACEs) including cardiac death, appropriate device therapy, hospitalization for heart failure, and ventricular assist device implantation. Of the study patients (mean age 70 ± 8 years; 86% men), 34 (40%) had CTO. There were no significant differences in age, left ventricular ejection fraction (LVEF), NYHA functional class III or IV status, and proportion who underwent secondary prevention between patients with CTO (CTO group) and without CTO (non-CTO group). During a median follow-up of 3.8 years (interquartile range 2.7 to 5.4 years), the CTO group tended to have a higher MACE rate (log-rank P=0.054) than the non-CTO group. Within the CTO group, there was no difference in the MACE rate between patients with and without viable myocardium. In patients with ICD for secondary prevention (n=47), 16 patients (34%) with CTO had a higher MACE rate than patients without CTO (log-rank P<0.01). Cox proportional hazards regression analysis showed that the presence of CTO, but

not LVEF, was associated with a higher MACE rate. Multivariate analysis showed that the presence of CTO was a predictor of MACE (P<0.05).

Conclusion

In patients with ischemic heart disease receiving ICD implantation, the presence of CTO has an adverse impact on long-term prognosis, especially as secondary prevention.

Keywords: Chronic total occlusion, implantable cardioverter-defibrillator, ischemic heart disease, revascularization, myocardial viability

Introduction

In ischemic heart disease (IHD), left ventricular (LV) function, as reflected by ejection fraction (EF), is known to be a predictive factor for mortality and ventricular arrhythmic events. On the basis of the previous randomized trial[1,2], cardioverter-defibrillator (ICD) implantation may have benefits in terms of both primary and secondary prevention against sudden cardiac death in patients with prior myocardial infarction and a history of ventricular fibrillation, sustained ventricular tachycardia, or non-sustained ventricular tachycardia with syncope and severe LV dysfunction. International guidelines recommend ICD implantation for these particular patients as a class I recommendation.[3,4]

The SOLVD trial showed that revascularization significantly decreases the risk of sudden cardiac death in patients with coronary artery disease and LVEF <35%.[5] A meta-analysis showed that revascularization could potentially improve survival in patients with low LVEF and viable myocardium, but not in those without viable myocardium.[6] Indeed, the 2015 guidelines of the European Society of Cardiology recommended that patients with ischemic LV dysfunction (LVEF <35%) and indications for primary preventive ICD implantation should be evaluated for residual ischemia and potential revascularization targets because of the protective effect of revascularization against ventricular arrhythmias.[3]

The presence of chronic total coronary occlusion (CTO) is associated with long-term

mortality and further deterioration of LVEF. Recent studies have reported that patients who underwent successful percutaneous coronary intervention (PCI) for CTO have better prognosis than those who did not.[7] One study reported PCI has positive effects on LV remodeling and LVEF for up to 3 years in the CTO perfusion territory.[8] The COURAGE trial found that the prognostic impact of revascularization with PCI is enhanced if there is more than 5% reduction in ischemia.[9] Myocardial viability is indeed important when considering patient prognosis and indications for revascularization. However, in high-risk IHD patients with implanted ICDs, the association between CTO and/or myocardial viability with cardiac events remains to be fully investigated.

Therefore, the purpose of the present study was to evaluate the long-term prognostic impact of CTO in IHD patients with left ventricular dysfunction who received ICD for primary or secondary prevention.

Methods

Study patients and outcome measures

All patients with IHD who received ICDs for primary or secondary prevention at the National Cerebral and Cardiovascular Center in Japan between 2007 and 2012 were included in this study. IHD was defined as myocardial dysfunction secondary to occlusive or obstructive coronary artery disease. Baseline clinical data were obtained retrospectively from medical records. We

categorized patients into two groups according to the presence or absence of CTO on the basis of findings on coronary angiography performed most recently before ICD implantation. The presence of CTO was defined as total occlusion of a major epicardial artery with Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 for more than 3 months with or without retrograde filling through collateral vessels. Occluded vessels that were surgically revascularized were not considered to have CTO. Subgroup analysis was also performed, stratified by primary or secondary prevention, and the presence of viable myocardium in the CTO area.

The viability of the myocardium in the CTO area was determined by the presence of radionuclide uptake more than 50% of that in normal segments on myocardial scintigraphy, or by the absence of a thinned scar, dyskinesis, or left ventricular wall thickness greater than 6 mm during diastole based on echocardiography.[10, 11] Myocardial scintigraphy and echocardiography images were assessed by two expert cardiologists. LVEF was calculated with echocardiography using the biplane Simpson method. Estimated glomerular filtration rate was obtained using the formula previously reported by the Japan Association of Chronic Kidney Disease Initiative.[12] Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate less than 60 mL/min.

ICD implantation and data analysis

In the present study population, indications for ICD, including a cardiac resynchronization therapy defibrillator (CRT-D), were based on guidelines.[3, 4] All patients received a multifunctional single-chamber ICD, dual-chamber ICD, or CRT-D. All defibrillator systems were implanted transvenously without epicardial systems. Testing for the sensing, pacing, and defibrillation thresholds was performed during the implantation procedure and 3 to 5 days after implantation.

The records for ICD follow-up visits every 3 to 4 months were reviewed. Appropriate ICD therapy was detected from generator interrogation during an outpatient visit or hospital admission by expert electrophysiologists. Dates of death, admissions for heart failure, ICD therapy, and ventricular assist device (VAD) implantation were obtained from medical records.

The primary endpoint of this study was all-cause mortality. The secondary endpoint was the rate of major adverse cardiac events (MACEs) as an indicator of long-term prognosis. MACE was defined as cardiac death, hospital admission for heart failure, appropriate ICD therapy, and VAD implantation. Continuous data are presented as means ± SD. Comparison of continuous variables was performed using two-sided Student's t-tests. Categorical data were compared using the chi-square test or Fisher's exact test. All-cause mortality and survival free from MACEs were estimated using Kaplan-Meier time-to-event methodology, and patients groups were compared using the log-rank test. The risk of developing MACE was estimated by computing hazard ratios (HRs) and their 95% confidence intervals (CIs) based on Cox proportional hazards models. Any

variable with P <0.05 during univariate analysis was included in a multivariate model to identify independent predictors of MACE. P <0.05 was considered to be statistically significant for all statistical tests. All statistical analyses were performed using JMP (version 11.0, SAS Inc., Tokyo, Japan).

Results

Data from 534 consecutive patients with ICDs implanted between 2007 and 2012 were retrospectively collected. There were 87 patients with ischemic heart disease, 306 with non-ischemic cardiomyopathy, 21 with valvular heart disease, 10 with congenital heart disease, 85 with arrhythmias, 11 with vasospastic angina, and 14 with other cardiac diseases. We excluded one IHD patient who underwent VAD implantation before ICD implantation and two patients who were lost to follow-up. Ultimately, the study population consisted of 84 patients. The patients were classified into two groups according to presence of CTO (CTO group, n=34) and absence of CTO (non-CTO group, n=50) (**Figure 1**). Baseline clinical characteristics, medical history, and examination data are shown in **Table 1**. In the CTO group, the mean number of CTOs per patient was 1.3 ± 0.5, and 21 (62%) patients had CTO in the left anterior descending (LAD) artery. There were no significant differences in the baseline characteristics between the CTO and non-CTO groups.

During a median follow-up period of 3.8 years (interquartile range (IQR) 2.7–5.4 years), the primary outcome occurred in 20 (23.8%) patients (**Table 2**). The cumulative event rate for the primary outcome, all-cause mortality, was 4.8% at 1 year, 15.8% at 3 years, and 30.3% at 5 years of follow-up. Kaplan-Meier analysis revealed that the primary outcome tended to occur more frequently in the CTO group than in non-CTO group (log-rank test, *P*=0.06) (**Figure 1**). Cox proportional hazard regression revealed that the presence of CTO was not significantly related to all-cause mortality (unadjusted HR 2.30, 95% CI 0.95–5.88; *P*=0.06) (**Supplemental Table 1**). During the follow-up period, 47 (56%) patients developed MACE as a secondary endpoint. The cumulative incident rate for MACE was 27.4% at 1 year, 54.0% at 3 years, and 62.5% at 5 years of follow-up. Kaplan-Meier analysis revealed that the CTO group tended to have a higher MACE rate than the non-CTO group (log rank test, *P*=0.054) (**Figure 2**). Presence of CTO had a HR of 1.75 for MACE (95% CI 0.98–3.11; *P*=0.14) (**Supplemental Table 1**).

Baseline characteristics of the primary or secondary prevention subgroups are presented in **Supplemental Table 2** and **Supplemental Table 3**, respectively. In the 35 patients receiving ICD for primary prevention, there were no significant differences in mortality and MACE rates between the CTO and non-CTO groups (**Figures 2C** and **2D**, **Tables 2** and **Supplemental Table 4**). In the 47 patients receiving ICD as secondary prevention, mortality and MACE rates in the CTO group were significantly higher than those in the non-CTO group (**Figures 2E** and **2F**, **Table**

2 and **Supplemental Table 5**). Among the components of MACE, cardiac death was significantly associated with the presence of CTO in the secondary prevention group (**Table 2**). Cox proportional hazards regression analysis showed that the presence of CTO is an independent predictive factor for mortality and MACE, whereas LVEF was not.

We also assessed the viability of the CTO area in the CTO group, which was divided into the following two subgroups: CTO with viability (CTO/+viability group, *n*=21) and CTO without viability (CTO/-viability group, *n*=13). Kaplan-Meier analysis revealed that there was no significant difference between these subgroups in all-cause mortality (log-rank test, *P*=0.16) and MACEs (log-rank test, *P*=0.13) (**Figures 3A** and **3B**).

Before ICD implantation, revascularization for CTO was performed in 6 patients with PCI and 18 with CABG. There was no significant difference in all-cause mortality and MACE rates between these 24 patients with CTO revascularization and patients with CTOs who did not undergo revascularization (*n*=22) (HR 0.70; 95% CI 0.23–2.01; *P*=0.50 and HR 0.80; 95% CI 0.39–1.63; *P*=0.80, respectively).

Discussion

The major findings of this study are as follows: (1) 40% of patients with IHD and ICD implantation had CTO, (2) the CTO group tended to have a higher all-cause mortality and MACE rates than the non-CTO group, and (3) in a subgroup of patients with ICD for secondary

prevention, the presence of CTO was associated with high mortality and adverse clinical events, whereas LVEF was not.

High prevalence of CTO in IHD patients with ICDs

In previous studies of patients with IHD, there was a range in the prevalence of CTO. The CREDO-Kyoto Registry Cohort-2 study showed that 19% of patients (2,491 of 13,087 patients) in the PCI arm had CTO.[13] Jeroudi *et al.* reported that the prevalence of CTO was 31% (319 of 1,015) in patients with coronary artery disease in a tertiary Veterans Affairs Hospital.[14] In the National Cardiovascular Data Registry CathPCI Registry, the big data of PCI in the United States, PCI was performed for CTO in 3.8% of patients (22,365 of 594,510).[15] This registry showed that the percentage of PCIs for CTO increased from 3.2% in 2009 to 4.8% in 2013. There have been two studies in IHD patients with ICD, which showed a CTO prevalence rate of 44% and 69%, respectively.[16, 17] The present study showed that 40% of IHD patients with ICDs had CTO, which is consistent with previous studies.

Prognostic impact of CTO in IHD patients with ICDs

The present study showed that the rates of all-cause mortality and MACE were not significantly different between the two groups, but they tended to be higher in the CTO group. There have been two previous studies regarding the impact of CTO in patients with ICD. However, these studies

were limited to patients who received ICD for primary prevention and their results seem to be conflicting.[16, 17] Nombela-Franco *et al.* reported that the presence of CTO was significantly associated with mortality and ventricular arrhythmias in patients with ICDs implanted for primary prevention.[16] On the contrary, Raja *et al*. reported that the presence of CTO was not associated with mortality or the incidence of ventricular arrhythmias in patients with ICDs implanted for primary prevention.[17] In our subgroup analysis, there was no association between the presence of CTO and clinical outcomes in patients with ICD for primary prevention. The prevalence of previous MI was much higher in our study (99%) and the study by Raja *et al*. (79%) than the study by Nombela-Franco *et al*. (51%), although LVEF in the three studies were not obviously different (Nombela-Franco *et al*.; 29%, Raja *et al*. 30%, our study; 25%). The study population in our study and the study by Raja *et al.* might have reflected more selected IHD patients. Another explanation of the discrepancy in results in the primary prevention population might be related to the prevalence of CKD, a known predictor of prognosis in patients with IHD. [18] In the previous two studies, the prevalence of CKD ranged from 27% to 40%. However, in our study, all patients in the CTO group and 94% of patients in the non-CTO group had CKD.

Importantly, to the best of our knowledge, our study revealed for the first time the negative impact of CTO on long-term mortality and the MACE rate in IHD patients with ICDs implanted for secondary prevention. In patients who received ICD for secondary prevention, the presence of

CTO was an independent predictor of all-cause mortality and MACE, while LVEF was not. It should be noted that our study population had reduced LV function, with mean LVEF of 24 ± 8%. Among these particularly high-risk patients with severe cardiac dysfunction, LVEF might no longer be a statistically significant predictor of long-term prognosis. However, the small study size might be a limitation. The reason why the presence of CTO affects prognosis only in the secondary prevention group of our study should be investigated. Amiodarone was not significantly related to mortality and the rate of MACE. This was also the same results when the population was limited to the patients with ICD for primary or secondary prevention. In our study, there was no significant difference in LVEF between the primary and secondary prevention groups. However, the primary prevention group had larger LV end-diastolic and end-systolic diameters than the secondary prevention group. There were no differences in clinical characteristics other than the prevalence of CRT-D between the two groups (primary prevention group 62% vs. secondary prevention group 30%). These findings suggest that LV remodeling was rather developed in the primary prevention group and that there must be other confounders impacting the prognosis of the secondary prevention group.

Implications of the present study and revascularization for CTO

In clinical practice, the importance of revascularization for vessels with CTO that have territories with viable myocardium is frequently discussed. In our study, 44% of patients in the CTO group

had viable tissue in the CTO area. However, only one patient underwent revascularization with PCI. This patient experienced sudden cardiac death without any events 4.1 years after PCI. Our study population might have had some characteristics that made them not suitable for PCI or CABG, such as CKD, anatomically complex lesions, or small viable area. Another possible reason for the low rate of revascularization might be that revascularization with PCI was performed for suitable lesions before ICD implantation. Indeed, revascularization for CTO was performed in 24 patients in this study (6 with PCI and 18 with CABG), but revascularization for CTO had no beneficial impact on clinical outcomes. This might be mainly because our sample size was small. The STICH trial could not identify patients with differences in survival benefit from CABG based on assessment of myocardial viability using single-photon emission computed tomography, dobutamine echocardiography, or both.[19] Furthermore, studies quantifying ventricular function using MRI have shown that the improvement in ventricular function as a result of opening CTOs is very modest.[8, 20] There was a large multicenter prospective cohort study (IRCTO registry [21]) showing that the successful rate of CTO PCI was 75.4%, which was consistent with that in other studies (ref). In the IRCTO registry study, the patients who underwent PCI for CTO had better survival and lower major adverse cardiac and cerebrovascular events compared to those who had medical therapy only. However, it is difficult to clarify the effects of PCI to CTO due to the variety of patient backgrounds and clinical settings. Also, in the IRCTO registry, the rate of peri-

procedural complication was not significantly different between the patients with and without successful PCI. Because of the improved devices and techniques, CTO PCI is getting safer. Consequently, interventionists are now seeking patients with good indications for PCI. Our study suggests that the revascularization of CTOs in patients with ICD as secondary prevention may provide some benefit.

Study limitations

There were several limitations in the present study. First, this was a retrospective observational study, although the baseline patient characteristics of the two groups were similar. Second, the study population was relatively small. The present study was obviously underpowered for evaluating long-term clinical outcomes. Third, assessment of myocardial was not performed in all patients with CTO. Finally, our findings do not warrant revascularization of CTO in ischemic heart disease with ICD. Although hibernating myocardium was associated with arrhythmogenesis in animal models [22], it is inevitable to assess myocardial ischemia/viability in the territory of the CTO in the previous clinical studies. Further large and randomized studies with standardized evaluation of viable myocardium are necessary to elucidate this issue. Furthermore, contemporary interventions for CTO including retrograde approach have dramatically improved. However, the previous studies of the US and Japanese registries demonstrated that procedural success was

associated with several patient factors and operator experience. [23, 24]

Acknowledgements

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Figure Legends

Figure 1. Study flow chart

CTO, chronic total coronary occlusion; ICD, implantable cardioverter-defibrillator; VAD, ventricular assist device.

Figure 2. All-cause mortality and MACE-free survival in all patients (*n*=84) (A)(B), patients with ICD for primary prevention (*n*=37) (C)(D), and in patients with ICD for secondary prevention (*n*=47) (E)(F).

MACE includes cardiac death, appropriate device therapy, hospitalization due to heart failure, and ventricular assist device implantation. The data of the CTO and non-CTO groups were compared. MACE, major adverse cardiac event.

Figure 3. Kaplan-Meier analysis of all-cause mortality (A) and MACE-free survival (B) in patients with CTO by myocardial viability.

The viability of the myocardium in the CTO area was determined by the presence of radionuclide uptake on myocardial scintigraphy, or the absence of a thinned scar, dyskinesis, or left ventricular wall thinning on echocardiography.

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Figure 1

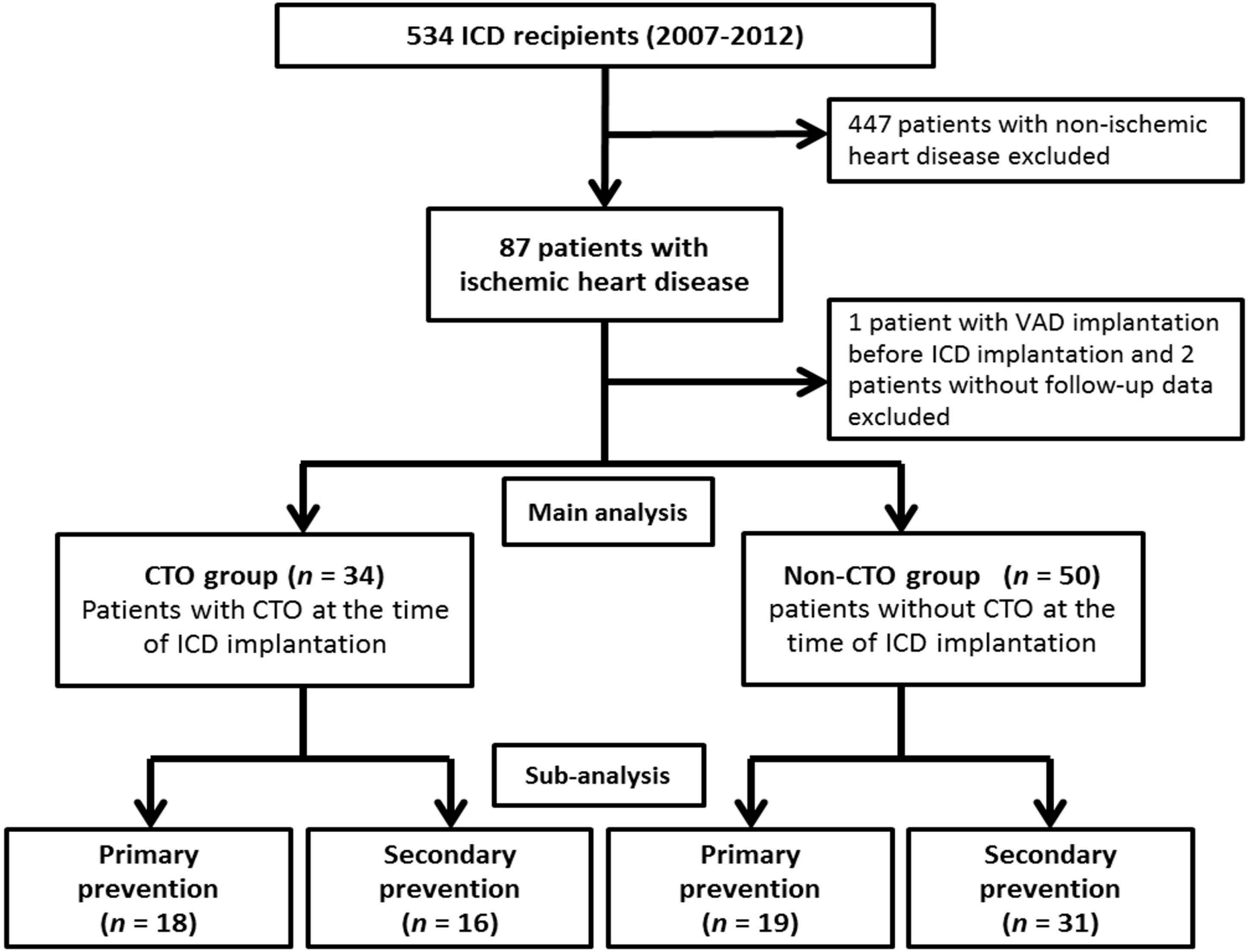
534 ICD recipients (2007-2012)
447 patients with non-ischemic heart disease excluded
87 patients with ischemic heart disease
1 patient with VAD implantation before ICD implantation and 2 patients without follow-up data excluded
Main analysis
CTO group (n = 34)
Patients with CTO at the time of ICD implantation
Non-CTO group (n = 50)
patients without CTO at the time of ICD implantation
Sub-analysis
Primary prevention (n = 18)
Secondary prevention (n = 16)
Primary prevention (n = 19)
Secondary prevention (n = 31)

Figure 2

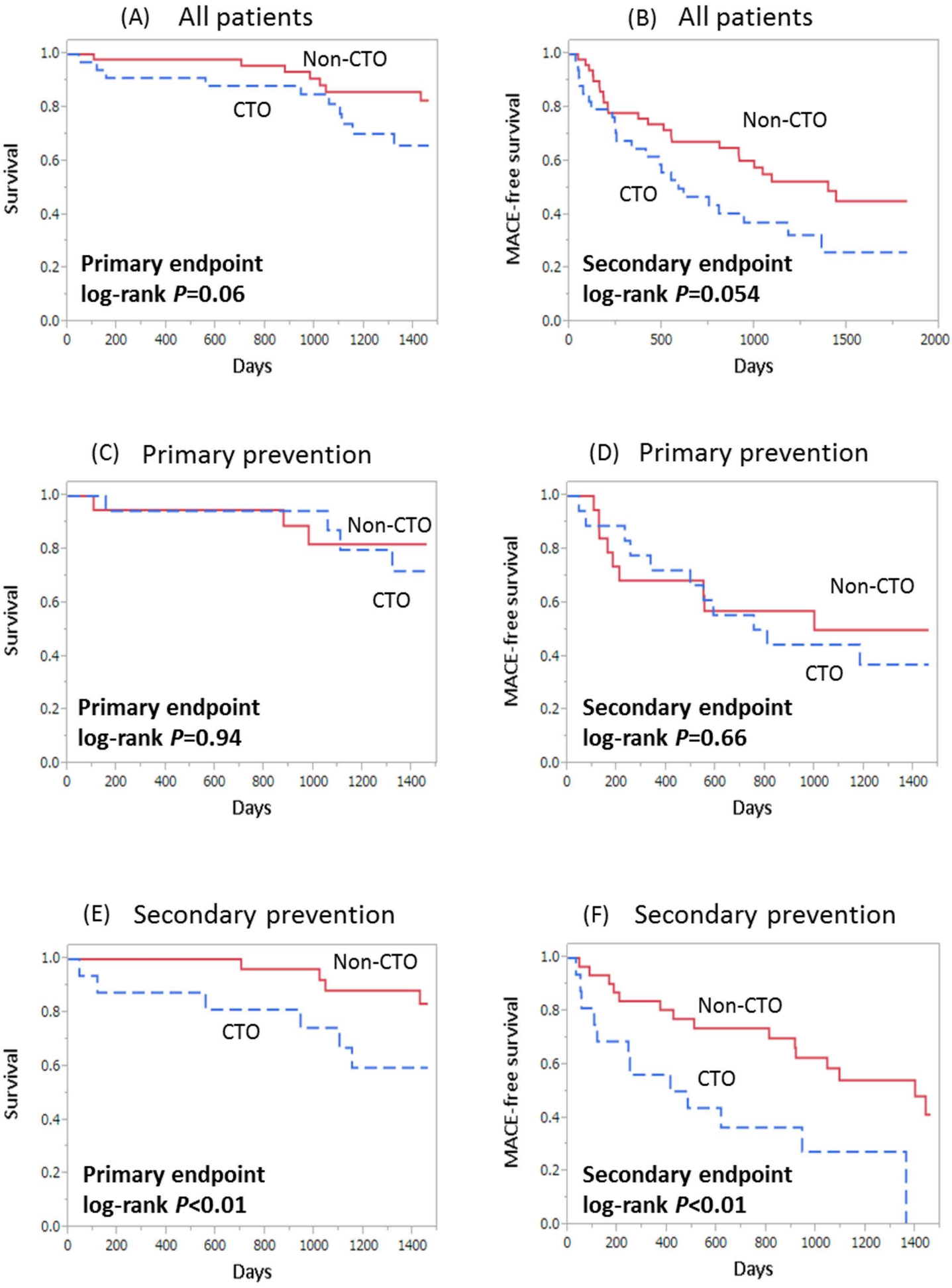
(A) All patients
Survival
Non-CTO
CTO
Primary endpoint
log-rank P=0.06
Days
(B) All patients
MACE-free survival
Non-CTO
CTO
Secondary endpoint
log-rank P=0.054
Days
(C) Primary prevention
Survival
Non-CTO
CTO
Primary endpoint
log-rank P=0.94
Days
(D) Primary prevention
MACE-free survival
Non-CTO
CTO
Secondary endpoint
log-rank P=0.66
Days
(E) Secondary prevention
Survival
Non-CTO
CTO
Primary endpoint
log-rank P<0.01
Days
(F) Secondary prevention
MACE-free survival
Non-CTO
CTO
Secondary endpoint
log-rank P<0.01
Days

Figure 3

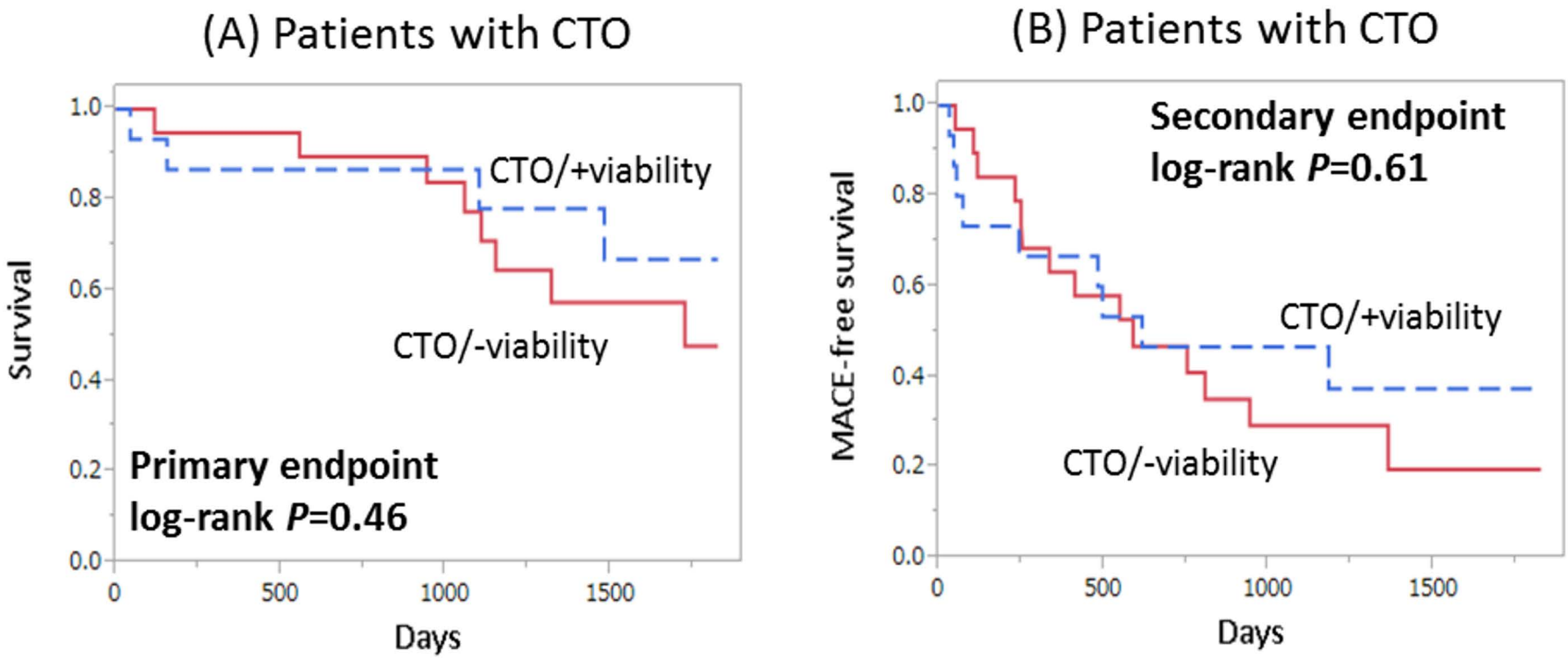
(A) Patients with CTO
Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
500
1000
1500
Days
CTO/+viability
CTO/-viability
Primary endpoint
log-rank P=0.46
(B) Patients with CTO
MACE-free survival
1.0
0.8
0.6
0.4
0.2
0.0
0
500
1000
1500
Days
Secondary endpoint
log-rank P=0.61
CTO/+viability
CTO/-viability

Table 1. Baseline characteristics of patients by CTO status

	All patients (*n*=84)	CTO (*n*=34)	Non-CTO (*n*=50)	*P* value
Age (years)	70 ± 8	71 ± 1	69 ± 1	0.90
Male	72(86)	32(94)	40(80)	0.11
Body mass index (kg/m^2)	22 ± 3	22 ± 1	22 ± 1	0.42
CRT-D	37(44)	17(50)	20(40)	0.36
ICD for secondary prevention	47(56)	16(47)	31(62)	0.18
NYHA functional class ≥3	26(31)	12(35)	14(28)	0.48
Diabetes mellitus	38(45)	15(44)	23(46)	0.86
Hypertension	59(70)	24(71)	35(70)	0.95
Dyslipidaemia	62(74)	24(71)	38(76)	0.58
Current smoking	15(18)	7(21)	8(16)	0.59
Chronic kidney disease	81(96)	34(100)	47(94)	0.29
Previous myocardial infarction	83(99)	33(97)	50(100)	0.40
Multivessels disease	70(83)	31(91)	39(78)	0.14
Previous CABG	34(40)	13(38)	21(42)	0.73
Previous PCI	62(74)	24(71)	38(76)	0.58
QRS width (msec)	142 ± 29	142 ± 5	143 ± 4	0.39
Chronic AF	17(20)	10(29)	7(14)	0.08
History of non-sustained VT	73(87)	29(85)	44(88)	0.75
LV end diastolic diameter (mm)	65 ± 9	66 ± 2	64 ± 1	0.73
LV end systolic diameter (mm)	55 ± 11	57 ± 2	54 ± 2	0.86
LVEF (%)	24 ± 8	23 ± 1	25 ± 1	0.13
Mitral regurgitation ≥grade 3	13(15)	5(15)	8(16)	1.00
β -blocker	69(82)	27(79)	42(84)	0.59
ACE-I or ARB	57(68)	21(62)	36(72)	0.32
Statin	61(73)	21(62)	40(80)	0.07
Oral inotropes	13(15)	7(14)	6(18)	0.65
Amiodarone	44(52)	17(50)	27(54)	0.72
No. of CTOs/case (/patient)	-	1.3 ± 0.5	-	-
CTO in LAD	-	21(62)	-	-
Viability in CTO area	-	15(44)	-	-

Data are presented as means ± SD, *n* (%), or medians (interquartile range). *P* values are for CTO group vs. non-CTO group. CTO, chronic total coronary occlusion; CRT-D, cardiac resynchronization

therapy-defibrillator; ICD, implantable cardioverter-defibrillator; NYHA, New York Heart Association; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; AF, atrial fibrillation; VT, ventricular tachycardia; LV, left ventricular; EF, ejection fraction; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LAD, left anterior descending artery.

Table 2. Follow-up event rates for all patients and by prevention subgroup

	All patients (*n*=84)			Patients with ICD for primary prevention (*n*=37)			Patients with ICD for secondary prevention (*n*=47)		
	CTO group	Non-CTO group	*P* value	CTO group	Non-CTO group	*P* value	CTO group	Non-CTO group	*P* value
All-cause mortality	12 (35.3%)	8 (16%)	0.07	4 (22.2%)	4 (21.1%)	1.00	8 (50.0%)	4 (12.9%)	0.01
MACE	23 (67.6%)	24 (48%)	0.12	11 (61.1%)	9 (47.4%)	0.51	12 (75.0%)	15 (48.4%)	0.12
Cardiac death	10 (29.4%)	6 (12%)	0.05	3 (16.7%)	3 (15.8%)	1.00	7 (43.8%)	3 (9.7%)	0.02
Appropriate ICD therapy	13 (38.2%)	12 (24%)	0.22	5 (27.8%)	2 (10.5%)	0.23	8 (50.0%)	10 (32.3%)	0.34
Hospital admission for heart failure	16 (47.1%)	17 (34%)	0.26	8 (44.4%)	8 (42.1%)	1.00	8 (50.0%)	9 (29.0%)	0.21
Ventricular assist device implantation	0 (0%)	1 (2%)	1.00	0 (0%)	1 (5.3%)	1.00	0 (0%)	0 (0%)	-

MACE, major adverse cardiovascular events. Other abbreviations as in Table 1.

Table 3. Univariate and multivariate analysis of predictors of all-cause mortality and MACE

Variable	All patients (*n*=84)											
	All-cause mortality						MACE					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
CTO	2.30	(0.95-5.88)	0.06	1.79	(0.71-4.72)	0.22	1.75	(0.98-3.11)	0.06	1.56	(0.86-2.82)	0.14
Age (per one-year increase)	1.02	(0.97-1.09)	0.44				1.01	(0.98-1.05)	0.51			
Male	3.27	(0.68-58.7)	0.16				1.20	(0.55-3.15)	0.67			
CRT-D	0.91	(0.36-2.22)	0.85				1.28	(0.72-2.27)	0.40			
Secondary prevention	1.21	(0.50-3.10)	0.67				1.10	(0.62-2.00)	0.74			
NYHA functional class ≥3	2.81	(1.15-6.87)	0.02	2.31	(0.92-5.78)	0.07	2.50	(1.37-4.48)	< 0.01	2.32	(1.15-4.69)	0.02
Diabetes mellitus	0.97	(0.39-2.34)	0.94				1.18	(0.66-2.11)	0.56			
Hypertension	0.55	(0.23-1.40)	0.20				0.73	(0.40-1.36)	0.31			
Dyslipidaemia	0.86	(0.34-2.43)	0.76				1.32	(0.69-2.72)	0.41			
Current smoking	0.68	(0.16-2.03)	0.52				1.20	(0.54-2.39)	0.63			
Multivessel disease	0.17	(0.39-5.03)	0.80				1.55	(0.71-4.06)	0.29			
LVEF	0.97	(0.92-1.02)	0.28				0.96	(0.92-0.99)	0.02	0.98	(0.93-1.02)	0.23
Mitral regurgitation ≥grade 3	1.22	(0.35-3.35)	0.72				1.68	(0.79-3.25)	0.17			
β-blocker	0.45	(0.17-1.40)	0.15				0.46	(0.24-0.95)	0.04	0.37	(0.18-0.81)	0.01
Amiodarone	1.86	(0.76-4.96)	0.17				1.56	(0.88-2.84)	0.13			
Statin	0.36	(0.15-0.91)	0.03	0.47	(0.19-1.24)	0.13	1.31	(0.69-2.70)	0.43			
ACE-I or ARB	0.46	(0.19-1.13)	0.09				0.53	(0.30-0.97)	0.04	0.69	(0.38-1.31)	0.25

Abbreviations as in Table 1.

Table 4. Baseline characteristics of patients with ICD implantation for secondary prevention

	Secondary prevention (*n*=47)		
	CTO (*n* =16)	Non-CTO (*n* =31)	*P* value
Age (years)	73 ± 9	69 ± 8	0.17
Male	15 (94)	23 (74)	0.14
Body mass index (kg/m^2)	22 ± 3	22 ± 4	0.55
CRT-D	5 (31)	9 (29)	1.00
NYHA functional class ≥3	6 (38)	7 (23)	0.32
Diabetes mellitus	6 (38)	12 (40)	1.00
Hypertension	20 (65)	20 (65)	1.00
Dyslipidaemia	13 (81)	22 (71)	0.51
Current smoking	6 (19)	6 (19)	1.00
Chronic kidney disease	29 (94)	29 (94)	0.54
Previous myocardial infarction	16 (100)	31 (100)	-
Multivessel disease	14 (88)	25 (81)	0.70
Previous CABG	4 (25)	13 (42)	0.34
Previous PCI	13 (81)	21 (68)	0.49
QRS width	137 ± 29	142 ± 33	0.61
Chronic AF	4 (25)	3 (10)	0.21
History of non-sustained VT	16 (100)	31 (100)	-
LV end diastolic diameter (mm)	63 ± 13	63 ± 8	0.86
LV end systolic diameter (mm)	56 ± 14	51 ± 10	0.25
LVEF (%)	21 ± 7	25 ± 7	0.09
Mitral regurgitation ≥grade 3	4 (25)	5 (16)	0.47
β-blocker	12 (80)	27 (90)	0.21
ACE-I or ARB	6 (38)	22 (71)	0.03
Statin	11 (69)	24 (77)	0.73
Oral inotropes	3 (19)	1 (3)	0.11
Amiodarone	11 (69)	18 (58)	0.54
No. of CTOs/case (/patient)	1.1 ± 0.3	-	
CTO in LAD	9 (56)	-	
Viability in CTO area	8 (50)	-	

Abbreviations as in Table 1.

Table 5. Univariate and multivariate analysis of predictors of all-cause mortality and MACE in patients who received ICD for secondary prevention

variable	Secondary prevention group (*n*=47)											
	All-cause mortality						MACE					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
CTO	4.69	(1.47–17.7)	0.01	3.70	(1.12–14.3)	0.03	2.86	(1.27–6.41)	0.01	2.59	(1.10–5.93)	0.03
Age (years)	1.09	(1.00–1.18)	0.04	1.06	(0.98–1.16)	0.16	1.02	(0.98–1.07)	0.38			
Male	3.02	(0.59–555)	0.22				1.14	(0.47–3.40)	0.79			
CRT-D	0.88	(0.19–2.97)	0.22				1.36	(0.58–3.00)	0.46			
NYHA functional class ≥3	1.51	(0.40–4.83)	0.51				2.23	(0.98–4.84)	0.06			
Diabetes mellitus	1.86	(0.59–6.29)	0.29				2.25	(1.05–4.92)	0.04	2.41	(1.09–5.45)	0.03
Hypertension	1.06	(0.33–3.96)	0.76				1.11	(0.51–2.59)	0.80			
Dyslipidaemia	0.82	(0.26–3.09)	0.76				1.68	(0.71–4.65)	0.25			
Current smoking	0.30	(0.02–1.56)	0.18				0.91	(0.30–2.26)	0.86			
Multivessel disease	1.25	(0.33–8.17)	0.77				2.25	(0.78–9.50)	0.14			
LVEF	1.03	(0.95–1.11)	0.50				0.97	(0.92–1.02)	0.24			
Mitral regurgitation ≥grade 3	1.34	(0.30–4.50)	0.67				2.25	(0.92–1.02)	0.07			
β-blocker	0.35	(0.10–1.59)	0.15				0.27	(0.11–0.67)	0.02	0.34	(0.13–0.95)	0.04
Amiodarone	1.92	(0.57-8.67)	0.31				1.33	(0.61-3.10)	0.48			
statin	0.33	(0.10–1.06)	0.06				1.51	(0.64–4.12)	0.36			
ACE-I or ARB	0.33	(0.09–1.06)	0.06				0.52	(0.24–1.12)	0.09			

Abbreviations as in Table 1.

SUPPLEMENTAL MATERIAL

Supplemental Table 1. Baseline characteristics of patients with ICD implantation for primary prevention

	Primary prevention (*n*=37)				
	CTO (*n* =18)		Non-CTO (*n* =19)		*P* value
Age (years)	70	± 7	68	± 9	0.58
Male	17	(94)	17	(89)	1.00
Body mass index (kg/m^2)	23	± 3	23	± 4	0.84
CRT-D	12	(67)	11	(58)	0.74
NYHA functional class ≥3	6	(33)	7	(37)	1.00
Diabetes mellitus	9	(50)	10	(53)	1.00
Hypertension	13	(72)	15	(79)	0.71
Dyslipidaemia	11	(61)	16	(84)	0.15
Current smoking	4	(22)	2	(11)	0.40
Chronic kidney disease	18	(100)	18	(95)	1.00
Previous myocardial infarction	17	(94)	19	(100)	0.49
Multivessel disease	17	(94)	14	(74)	0.18
Previous CABG	9	(50)	8	(42)	0.75
Previous PCI	11	(61)	17	(89)	0.06
QRS width	145	± 30	145	± 22	0.99
Chronic AF	6	(33)	4	(21)	0.48
History of non-sustained VT	13	(72)	13	(68)	1.00
LV end diastolic diameter (mm)	68	± 2	67	± 2	0.80
LV end systolic diameter (mm)	58	± 2	58	± 2	0,92
LVEF (%)	24	± 8	25	± 11	0,83
Mitral regurgitation ≥grade 3	1	(6)	3	(16)	0.60
β-blocker	15	(83)	14	(74)	0.69
ACE-I or ARB	15	(83)	14	(74)	0.69
Statin	10	(56)	16	(84)	0.08
Oral inotropes	3	(17)	6	(32)	0.45
Amiodarone	6	(33)	9	(47)	0.51
No. of CTOs/case (/patient)	1.2	± 0.4	-		
CTO in LAD	12	(67)	-		
Viability in CTO area	7	(39)	-		

Abbreviations as in Table 1.

Supplemental Table 2. Univariate and multivariate analysis of predictors of all-cause mortality and MACE in patients who received ICD for primary prevention

Variable	Primary prevention group (*n*=37)											
	All-cause mortality						MACE					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value	HR	(95% CI)	*P* value
CTO	0.95	(0.22–4.02)	0.94	0.47	(0.07–2.47)	0.38	1.22	(0.50–3.07)	0.66	1.27	(0.52–3.16)	0.60
Age (years)	0.94	(0.88–1.03)	0.18				0.99	(0.94–1.06)	0.80			
Male	NA						1.71	(0.35–30.8)	0.54			
CRT-D	1.11	(0.27–5.44)	0.88				1.34	(0.54–3.79)	0.54			
NYHA functional class ≥3	7.43	(1.70–50.9)	< 0.01	4.12	(0.60–46.9)	0.16	2.78	(1.12–6.92)	0.03	2.82	(1.13–7.03)	0.03
Diabetes mellitus	0.35	(0.05–1.53)	0.17				0.53	(0.21–1.29)	0.16			
Hypertension	0.20	(0.05–0.86)	0.03	0.20	(0.04–1.04)	0.06	2.36	(0.17–1.13)	0.08			
Dyslipidaemia	0.94	(0.21–6.44)	0.94				1.21	(0.47–3.73)	0.70			
Current smoking	1.45	(0.21–6.33)	0.66				1.59	(0.45–4.33)	0.43			
Multivessel disease	1.10	(0.19–20.7)	0.93				1.05	(0.35–4.52)	0.93			
LVEF	0.91	(0.82–0.99)	0.03	0.95	(0.83–1.08)	0.45	0.95	(0.90–1.00)	0.06			
Mitral regurgitation ≥grade 3	0.94	(0.05–5.31)	0.95				0.86	(0.14–3.00)	0.84			
β-blocker	0.58	(0.13–3.99)	0.53				0.64	(0.25–1.97)	0.40			
Amiodarone	1.67	(0.39-7.09)	0.47				1.77	(0.72-4.33)	0.21			
Statin	0.43	(0.10–2.27)	0.28				1.24	(0.48–3.82)	0.67			
ACE-I or ARB	0.83	(0.19–5.69)	0.83				0.59	(0.23–1.82)	0.33			

Abbreviations as in Table 1.