



**ORIGINAL RESEARCH**

# Reversible Cause of Cardiac Arrest and Secondary Prevention Implantable Cardioverter Defibrillators in Patients With Coronary Artery Disease: Value of Complete Revascularization and LGE-CMR

Anne-Lotte C. J. van der Lingen , MD\*; Marthe A. J. Becker, MD\*; Michiel J. B. Kemme, MD, PhD; Mischa T. Rijniere, MD, PhD; Eva M. Spoomans, MD; Stefan A. J. Timmer, MD, PhD; Albert C. van Rossum, MD, PhD; Vokko P. van Halm, MD, PhD; Tjeerd Germans, MD, PhD; Cornelis P. Allaart , MD, PhD

**BACKGROUND:** In survivors of sudden cardiac arrest with obstructive coronary artery disease, it remains challenging to distinguish ischemia as a reversible cause from irreversible scar-related ventricular arrhythmias. We aimed to evaluate the value of implantable cardioverter-defibrillator (ICD) implantation in sudden cardiac arrest survivors with presumably reversible ischemia and complete revascularization.

**METHODS AND RESULTS:** This multicenter retrospective cohort study included 276 patients (80% men, age 67±10 years) receiving ICD implantation for secondary prevention. Angiography was performed before ICD implantation. A subgroup of 166 (60%) patients underwent cardiac magnetic resonance imaging with late gadolinium enhancement before implantation. Patients were divided in 2 groups, (1) ICD-per-guideline, including 228 patients with incomplete revascularization or left ventricular ejection fraction ≤35%, and (2) ICD-off-label, including 48 patients with complete revascularization and left ventricular ejection fraction >35%. The primary outcome was time to appropriate device therapy (ADT). During 4.0 years (interquartile range, 3.5–4.6) of follow-up, ADT developed in 15% of the ICD-off-label group versus 43% of the ICD-per-guideline group. Time to ADT was comparable in the ICD-off-label and ICD-per-guideline groups (hazard ratio (HR), 0.46;  $P=0.08$ ). No difference in mortality was observed (HR, 0.95;  $P=0.93$ ). Independent predictors of ADT included age (HR, 1.03;  $P=0.01$ ), left ventricular end-diastolic volume HR, (1.05 per 10 mL increase;  $P<0.01$ ) and extent of transmural late gadolinium enhancement (HR, 1.12;  $P=0.04$ ).

**CONCLUSIONS:** This study demonstrates that sudden cardiac arrest survivors with coronary artery disease remain at high risk of recurrent ventricular arrhythmia, even after complete revascularization and with preserved left ventricular function. Late gadolinium enhancement–cardiac magnetic resonance imaging derived left ventricular volumes and extent of myocardial scar were independently associated with.

**Key Words:** secondary prevention implantable cardioverter defibrillator ■ sudden cardiac arrest ■ coronary artery disease ■ cardiac magnetic resonance ■ reversible underlying cause

Correspondence to: Cornelis P. Allaart, MD, PhD, Department of Cardiology, Amsterdam UMC, Vrije Universiteit Amsterdam, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands. E-mail: cp.allaart@amsterdamumc.nl

\*A.C.J. van der Lingen and M.A.J. Becker contributed equally.

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## CLINICAL PERSPECTIVE

### What is New?

- Survivors of sudden cardiac arrest with obstructive coronary artery disease and a presumably reversible ischemic cause receiving complete revascularization remain at risk of recurrent ventricular arrhythmias, as 15% of the patients with an off-label implantable cardioverter defibrillator (ICD) received appropriate device therapy during a median follow-up of 4 years.
- Higher age, increased end-diastolic volume, and larger extent of transmural late gadolinium enhancement assessed with cardiac magnetic resonance imaging are associated with appropriate device therapy in patients with a secondary prevention ICD with coronary artery disease.

### What Are the Clinical Implications?

- Patients with sudden cardiac arrest who are considered to be not eligible for secondary prevention ICD implantation according to the current guidelines are still at increased risk of ventricular arrhythmias.
- The incidence of appropriate device therapy in sudden cardiac arrest survivors with coronary artery disease and a presumably reversible cause is comparable to the incidence of appropriate device therapy in patients with a primary-prevention ICD, suggesting that ICD implantation can be justified.
- CMR with late gadolinium enhancement provides additional data to estimate the risk of recurrent arrhythmias in patients with a secondary prevention ICD with coronary artery disease; larger left ventricular end-diastolic volume and extent of transmural LGE are associated with recurrent ventricular arrhythmias.

### Nonstandard Abbreviations and Acronyms

<b>ADT</b>	appropriate device therapy
<b>CTO</b>	chronic total occlusion
<b>SCA</b>	sudden cardiac arrest
<b>VA</b>	ventricular arrhythmia

**G**uidelines recommend implantable cardioverter-defibrillator (ICD) implantation for secondary prevention of sudden cardiac death (SCD) in patients with ventricular fibrillation (VF) or hemodynamically unstable ventricular tachycardia (VT) without a reversible cause, regardless of left ventricular ejection fraction (LVEF).<sup>1</sup> Survivors of sudden cardiac arrest (SCA) with

a reversible cause, such as electrolyte abnormalities or myocardial ischemia, are considered to be at low risk of recurrent ventricular arrhythmias (VAs) after elimination of the primary cause and are therefore deemed not eligible for ICD implantation.<sup>2-4</sup>

A substantial number of patients surviving SCA suffer from obstructive coronary artery disease (CAD).<sup>5</sup> In these patients, it may be challenging to determine whether the arrest was caused by an acute ischemic event that may be restored by coronary revascularization, or by VA related to preexistent irreversible myocardial scar. The physician's decision whether SCA is primarily triggered by ischemia is typically guided by clinical information, including patient complaints and level of exercise before the arrest, electrocardiographic characteristics, troponin release, and coronary angiographic results.<sup>1</sup> Echocardiography is recommended for functional and structural assessment of the myocardium, whereas additional cardiac magnetic resonance (CMR) imaging with late gadolinium enhancement (LGE) is recommended by current guidelines for noninvasive tissue characterization.<sup>1,6</sup> Myocardial scar is an established substrate for VA.<sup>7</sup> Even after exclusion of obstructive CAD by invasive coronary angiography, occult myocardial infarction (MI) is seen on LGE-CMR in 8% of SCA survivors,<sup>6</sup> emphasizing the difficulty of clinical assessment of substrate reversibility. The same predicament applies in patients with VA caused by myocardial ischemia, treated with complete revascularization but with myocardial scar present on LGE-CMR. Although guidelines recommend otherwise, recent studies suggest a beneficial effect of secondary prevention ICD in SCA survivors with reversible cause, as these patients remain at high risk for recurrent VA.<sup>8-10</sup> The objectives of this study are to evaluate (1) if SCA survivors with obstructive CAD and a presumably reversible ischemic cause are at lower risk of appropriate device therapy (ADT) compared with survivors with an irreversible ischemic cause, and (2) to evaluate the value of clinical and imaging parameters associated with ADT in SCA survivors with CAD.

## METHODS

### Data Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Study Population and Study Design

This study was designed as a multicenter retrospective observational cohort study. Survivors of SCA attributable to either VT or VF with CAD who

received an ICD with or without resynchronization therapy for secondary prevention of SCD between January 2011 and June 2018 were included. The other inclusion criterion was invasive coronary angiography before ICD implantation. The local ethics committee approved data collection and management of this study. Because of the retrospective nature of this study, informed consent was waived by the local medical ethical committee. Clinical and demographic data regarding baseline characteristics were obtained from electronic medical records. Ischemic heart disease was defined as a history of significant obstructive CAD (coronary stenosis of >70% or fractional flow reserve <0.80), a history of MI or prior coronary revascularization with percutaneous coronary intervention or coronary artery bypass grafting, or if patients were diagnosed with CAD at time of cardiac arrest. Patients without ischemic heart disease, without invasive coronary angiography, or who were lost to follow-up immediately after device implantation were excluded. The study cohort was divided in 2 groups: the ICD-perguideline group consisted of SCA survivors with an irreversible ischemic substrate, defined as (1) incomplete revascularization, including untreated coronary chronic total occlusions (CTOs); (2) history of MI or coronary revascularization without newly developed obstructive coronary lesions at time of SCA; (3) recurrent VA >48 hours after MI; or (4) LVEF  $\leq$ 35% before ICD implantation, whereas the ICD-off-label group consisted of SCA survivors with CAD, treated with complete coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) before ICD implantation and LVEF >35%. Two clinical case examples of patients in the ICD-off-label group are presented in Figure S1.

### CMR With LGE Protocol

LGE-CMR was performed in a large subgroup of patients (N=166) for either diagnosis of underlying etiology or quantification of left ventricular (LV) function before ICD implantation. Two centers (Amsterdam UMC, Vrije Universiteit Amsterdam, the Netherlands; and Northwest Clinics, Alkmaar, the Netherlands) performed CMR on 1.5 Tesla whole body scanners (Siemens, Erlangen, Germany; and GE Healthcare, Chicago IL), with dedicated phased array cardiac receiver coil. Functional imaging was performed using retrospective ECG-gated steady-state free precession cine imaging with breath-holding in 3 standard long-axis views and a stack of short-axis slices covering both ventricles from base to apex. Contrast images were acquired approximately 10 to 15 minutes after intravenous gadolinium administration using a T1-weighted

inversion recovery-prepared gradient echo sequence with optimized inversion time.

The presence and pattern of gadolinium hyperenhancement were assessed visually. If present, LGE was localized according to the 16-segment model of the American Heart Association.<sup>11</sup> Ischemic LGE was defined as subendocardial or transmural hyperenhancement in the territory of a coronary artery, and scar transmural was assessed visually. Subendocardial scar was defined as  $\leq$ 50% and transmural scar defined as >50% hyperenhancement of LV wall thickness.<sup>12</sup> LV volumes and LVEF were quantified by delineation of the endocardial border at end diastole and end systole from short-axis cine image stacks, using dedicated software (Mass, Medis, Leiden, the Netherlands; and Argus Function, Siemens, Erlangen, Germany). Papillary muscles were excluded from the myocardium and included in the blood pool.

### Ventricular Arrhythmia and Coronary Angiographic Characteristics

Data on level of exercise before SCA were collected and classified as none (eg, sitting), moderate (eg, cycling to work) or extensive exercise (eg, competitive sports). Peak cardiac enzymes, including creatine kinase myocardial band and troponin T, were collected (available only for the patients of the Amsterdam UMC [N=190]). Patients underwent invasive coronary angiography after the index cardiac arrest, with immediate or delayed revascularization if necessary. Multivessel disease was defined as the presence of  $\geq$ 2 coronary arteries with a significant lesion at time of SCA. CTO was defined as a complete obstruction of a native coronary artery with or without filling through collateral vessels, for a duration of at least 3 months. A patent graft to a preexisting CTO was considered as revascularization of the coronary artery. Successful coronary artery bypass grafting after SCA was considered as complete revascularization therapy.

### ICD Eligibility and ICD Settings

Patients were evaluated by a multidisciplinary heart team and accepted for secondary prevention ICD implantation. Patients with an ICD-off-label received complete coronary revascularization but were deemed eligible for secondary prevention ICD therapy if preexisting irreversible substrate could not be excluded at the discretion of the treating physician. ICDs were typically programmed with detection rates of >150 beats/min (monitor zone), >182 beats/min (VT 1 zone), and >250 beats/min (VF zone) with extended detection intervals, but could be optimized in the outpatient clinic if this was required. Clinical

follow-up was obtained from regular visits at intervals of 6 months, and from event transmissions of patient devices connected to remote monitoring. Events with antitachycardia pacing and shocks were reviewed by specialized cardiac device technicians and electrophysiologists.

## End Points and Follow-up

The primary end point was time to first ADT. ADT was defined as antitachycardia pacing or shock for VT or VF. Date and type (antitachycardia pacing or shock) of ADT, as well as the cumulative number of ADTs, were collected. Secondary end points were time to all-cause mortality and VT ablation.

## Statistical Analysis

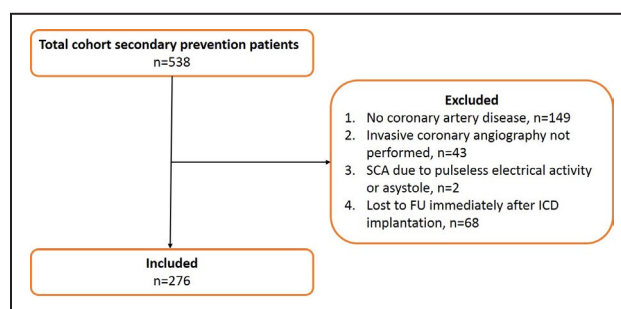
Continuous variables are presented as mean±SD if data were normally distributed or median and interquartile range (IQR) otherwise. Dichotomous and categorical data were expressed as frequencies and percentages. Kaplan–Meier curves, stratified by the 2 groups, were used to visualize differences in time-to-event. Median follow-up time was calculated using reverse Kaplan–Meier analysis. Hazard ratios (HRs) and 95% CIs were obtained using Cox regression. For comparison of the primary end point, patients without ADT were censored at end of follow-up or time of death. For comparison of overall survival, patients still alive at end of follow-up were censored at end of follow-up.

Based on the literature, the following variables were tested as potential confounders or effect modifiers: age, beta-blocker use, sex, LGE presence, LVEF, and resynchronization therapy. A variable was considered a confounder if the regression coefficient changed by >10%. Effect modification was evaluated by including an interaction term in the model. A variable was considered an effect modifier if the interaction term was statistically significant ( $P<0.05$ ).

Univariable Cox regression analyses were performed for clinical and imaging variables potentially associated with ADT. Next, variables with a  $P<0.10$  at univariable analysis were entered in a stepwise multivariable Cox regression analysis. Nonsignificant univariable variables were subsequently removed from the multivariable model using a backward elimination procedure. A 2-sided significance level of 5% was used for all analyses. All statistical analyses were performed using SPSS software package (version 26.0; IBM Corporation, Armonk, NY).

## RESULTS

Clinical data of 538 patients with a secondary prevention ICD were collected. Figure 1 presents the



**Figure 1. Consort diagram of the study inclusion process.** FU indicates follow-up, ICD, implantable cardioverter defibrillator, and SCA, sudden cardiac arrest.

consort diagram. A total of 276 patients met the inclusion criteria. Baseline characteristics are described in Table 1, stratified by ICD-per-guideline and ICD-off-label groups. Mean age was  $67\pm 10$  years, mean LVEF was  $38\pm 11\%$ , and the majority of the patients were men (80%). No significant differences were observed with respect to age, sex, medication use at time of ICD implantation, or device type between both groups.

## Clinical Outcomes

After a median follow-up of 4.0 years (IQR, 3.5–4.6), ADT occurred in 106 patients (38%), with an incidence rate of 14% per patient-year. There was no significant difference in follow-up time between the ICD-off-label and ICD-per-guideline groups (3.0 years [IQR 2.0–5.0] and 3.0 years [IQR 1.0–4.8], respectively;  $P=0.22$ ). VA developed in 15% of the ICD-off-label group versus 43% of the ICD-per-guideline group (Table 2), with an incidence rate of 5% per patient-year in the ICD-off-label group and an incidence rate of 16% per patient-year in the ICD-per-guideline group. Time to ADT was comparable in the ICD-off-label group and ICD-per-guideline group (HR, 0.46; 95% CI, 0.19–1.11;  $P=0.08$ ; Figure 2A). The median number of cumulative ADTs per patient was equally distributed between the groups ( $P=0.57$ ) (Table 2). No difference was observed in time to ADT between patients with LVEF  $\leq 35\%$  compared with patients with LVEF  $>35\%$  (HR, 1.35; 95% CI, 0.88–2.07;  $P=0.18$ ). The number of VT ablations was significantly higher in the ICD-per-guideline group ( $P<0.01$ ). A total of 40 patients died during follow-up (15%), without a significant difference in time to mortality between both groups (HR, 0.95; 95% CI, 0.30–2.98;  $P=0.93$ ; Figure 2B).

## Circumstances of SCA and Angiographic Findings

VF was the cause of the index arrest in the majority of patients (69%) and almost one-third of patients

**Table 1. Baseline Characteristics**

Characteristics	Total Cohort (n=276)	ICD-per-Guideline (n=228)	ICD-Off-Label (n=48)	P Value
Age, y	67±10	67±10	65±10	0.19
Male sex, n (%)	242 (80)	197 (86)	45 (94)	0.16
Cardiovascular risk factors				
Diabetes mellitus, n (%)	56 (20)	51 (22)	5 (10)	0.06
Hypertension, n (%)	120 (44)	98 (52)	22 (51)	0.91
Hyperlipidemia, n (%)	82 (30)	69 (38)	13 (32)	0.43
BMI, kg/m <sup>2</sup>	27±4	27±4	27±4	0.46
Medical history				
Prior MI, n (%)	180 (65)	159 (70)	21 (44)	<0.01
Prior PCI, n (%)	90 (33)	78 (34)	12 (25)	0.22
Prior CABG, n (%)	61 (22)	58 (25)	3 (6)	<0.01
LVEF, %*	38±11	36±11	48±8	<0.01
Atrial fibrillation, n (%)	89 (32)	79 (35)	10 (21)	0.06
Creatinine, µmol/L, median (IQR)	86 (76–102)	88 (77–103)	83 (71–95)	0.08§
QRS duration, ms, median (IQR)	108 (96–126)	110 (96–128)	98 (91–114)	<0.01§
Cardiac findings and intervention at index event				
VF at time of OHCA, n (%)	180 (65)	143 (63)	37 (77)	0.06
CK-MB†, µg/L	22 (8–45)	22 (8–56)	25 (8–40)	0.98§
Troponin T‡, µg/L, median (IQR)	0.33 (0.11–0.98)	0.32 (0.11–0.95)	0.37 (0.13–1.00)	0.72§
Moderate/extensive exercise before arrest, n (%)	69 (25)	52 (24)	17 (36)	0.08
Diffuse nonobstructive CAD, n (%)	74 (26)	73 (32)	1 (2)	<0.01
Multivessel disease, n (%)	163 (59)	133 (58)	30 (63)	0.59
CTO present (no prior CABG), n (%)	100 (36)	90 (40)	10 (21)	0.02
PCI performed, n (%)	102 (37)	67 (29)	35 (73)	<0.001
CABG performed, n (%)	26 (9)	12 (5)	14 (29)	<0.001
Complete revascularization, n (%)	143 (52)	95 (42)	48 (100)	<0.001
Medication at time of ICD implantation				
ACEi/ARB, n (%)	237 (86)	194 (85)	43 (90)	0.42
Beta-blockers, n (%)	251 (91)	205 (90)	46 (96)	0.27
Calcium channel blocker, n (%)	23 (8)	20 (9)	3 (6)	0.78
Amiodarone, n (%)	39 (14)	35 (15)	4 (8)	0.21
Device type				
ICD, n (%)	259 (94)	211 (93)	48 (100)	0.50
CRT-D, n (%)	17 (6)	17 (8)	0	0.50

Dichotomous variables compared using the chi-square test or Fischer's exact test. Continuous variables compared using *t*-tests unless otherwise indicated. \*Based on 199 patients; †Based on N=151; ‡Based on N=156; §Tested using Mann-Whitney U test. ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary arterial bypass graft surgery; CAD, coronary artery disease; CK-MB, creatine kinase myocardial band; CRT-D, resynchronisation therapy defibrillator; CTO, coronary chronic total occlusion; ICD, implantable cardioverter defibrillator; IQR, interquartile region; MI, myocardial infarction; OHCA, out-of-hospital cardiac arrest; PCI, percutaneous coronary intervention; and VF, ventricular fibrillation.

performed moderate to extensive exercise at time of SCA (Table 1). Median time between coronary angiography and ICD implantation was 5 days (IQR, 1-12). Overall, 59% of patients were diagnosed with multivessel CAD, and complete revascularization was performed in 143 (52%) patients. A total of 100 patients (36%) were diagnosed with a CTO at the time of the index event. During hospitalization, 15 (15%) of the patients with CTOs received CTO revascularization before ICD implantation. No differences

were observed in sex ( $P=0.90$ ), mean age ( $P=0.61$ ), or mean LVEF ( $P=0.69$ ) between patients with a CTO and without a CTO at index event (Table S1). There was no difference in time to ADT between patients with an untreated CTO compared with patients without a CTO or treated CTO (HR 1.34; 95% CI 0.88-2.02;  $P=0.17$ ; Figure 3A). However, in patients with incomplete revascularization (including untreated CTO), time to ADT was shorter compared with patients with complete coronary revascularization (HR

**Table 2. Outcomes**

Parameters	Total Cohort (n=276)	ICD-per-Guideline (n=228)	ICD-Off-Label (n=48)	P Value
ADT, n (%)	106 (38)	99 (43)	7 (15)	<0.001
Antitachycardia pacing only, n (%)	63 (23)	59 (26)	4 (8)	<0.01
ICD shock, n (%)	43 (16)	40 (18)	3 (6)	0.05
Cumulative number of ADTs per patient*, n (IQR)	2 (1–4)	2 (1–4)	3 (2–3)	0.57†
VT ablation, n (%)	27 (10)	27 (12)	0	<0.01
All-cause mortality, n (%)	40 (15)	36 (16)	4 (8)	0.18

Dichotomous variables compared using the chi-square test or Fischer's exact test. Continuous variables compared using Mann-Whitney U test. \*The cumulative number of ADTs per patient is computed only in patients who received  $\geq 1$  ADT; †Tested using the Mann-Whitney U test. ADT indicates appropriate device therapy; ICD, implantable cardioverter defibrillator; IQR, interquartile region; and VT ventricular tachycardia.

1.54; 95% CI 1.05–2.26;  $P=0.03$ ; Figure 3B). In the ICD-off-label group, VF at index event was associated with less ADT, whereas VT at the index event was associated with more ADT during follow-up ( $P=0.04$ ). Creatine kinase myocardial band values ( $P=0.73$ ), troponin T values ( $P=0.22$ ), and moderate to extensive exercise before SCA ( $P>0.99$ ) were not associated with ADT at follow-up.

### CMR Characteristics

A total of 166 patients received CMR with LGE imaging before ICD implantation (60% of the total cohort). Patients who received CMR were younger and were more often diagnosed with single-vessel CAD. There were no differences with respect to sex, LVEF, prior MI, or end points in patients with and without CMR (Table S2). Median time interval between CMR and ICD implantation was 6 days (IQR 3–13). Table 3 depicts the CMR results, stratified by both groups. The majority of patients demonstrated LGE on CMR (93%), primarily with an ischemic pattern (90%) and with a median extent of 5 (IQR 3–7) segments. LV volumes were significantly larger in the ICD-per-guideline group compared with the ICD-off-label group (eg, LV end-diastolic volume [LVEDV]  $240\pm 84$  mL versus  $197\pm 45$  mL, respectively;  $P<0.01$ ), and LVEF was significantly lower ( $36\pm 22\%$  versus  $48\pm 8\%$ , respectively;  $P<0.01$ ). There was no significant difference between the extent of LGE in the ICD-per-guideline group and the ICD-off-label group, although the extent of LGE with  $>50\%$  transmural extent tended to be larger in the ICD-per-guideline group (3 [IQR, 1–5] segments versus 2 [IQR, 0–4] segments;  $P=0.13$ , respectively). Table S3 presents the outcome of the ICD-per-guideline group and ICD-off-label group with CMR.

### Parameters Associated With ADT

Table 4 presents the univariable and multivariable analyses of clinical and imaging parameters for the association with time to ADT in patients receiving LGE-CMR

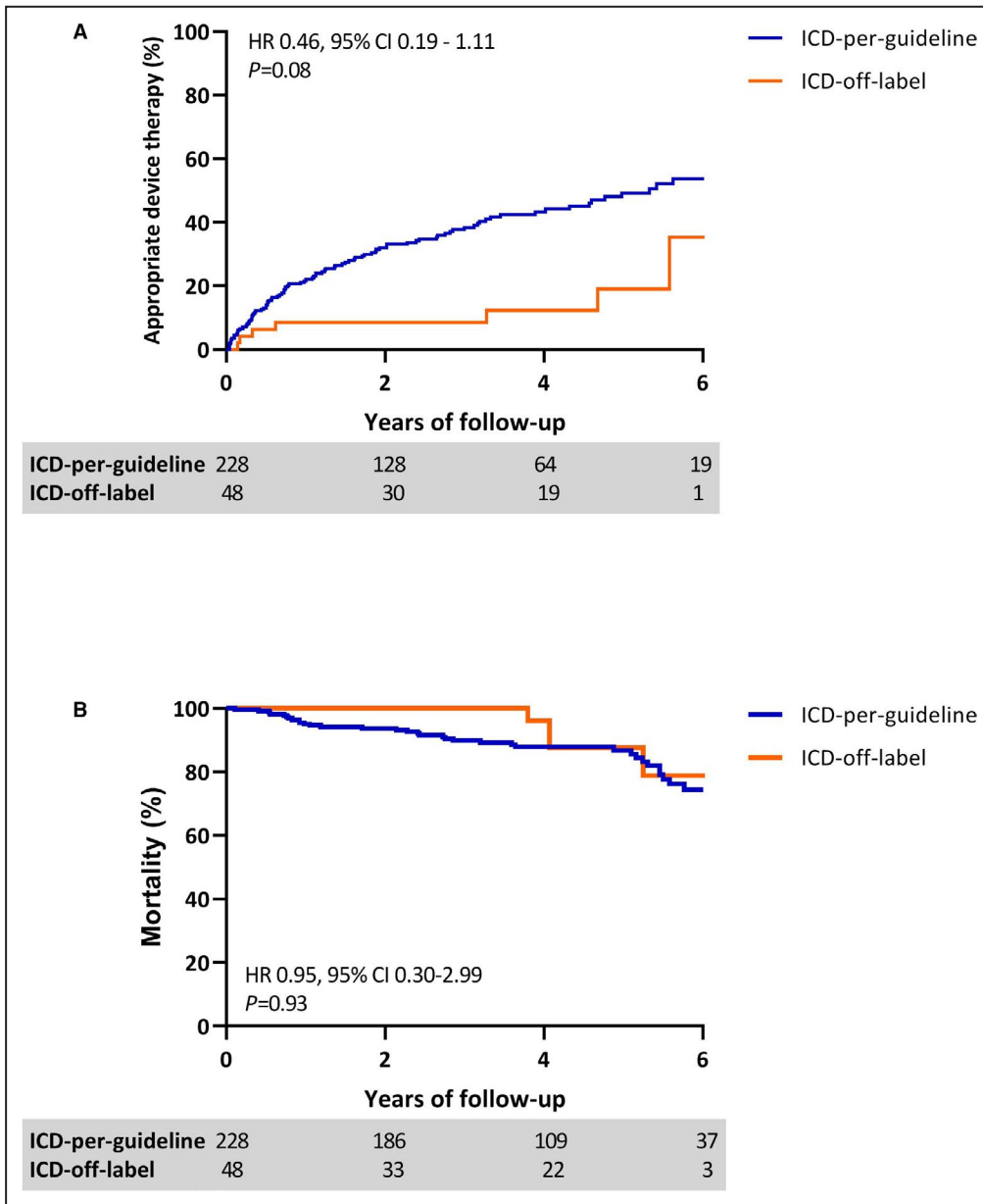
imaging (N=166). Parameters associated with time to ADT at univariable analysis were higher age ( $P=0.02$ ), male sex ( $P=0.08$ ), prior MI ( $P=0.04$ ), larger LVEDV ( $P<0.01$ ), lower LVEF ( $P=0.01$ ), number of segments with ischemic LGE with  $>50\%$  transmural extent ( $P<0.01$ ), incomplete revascularization ( $P=0.05$ ), untreated CTO ( $P=0.09$ ), and an ICD-per-guideline indication ( $P=0.04$ ). Interestingly, LGE presence was not significantly associated with time to ADT ( $P=0.17$ ). Multivariable Cox regression analyses using backward selection showed that higher age ( $P=0.02$ ), larger LVEDV ( $P<0.01$ ), and higher number of segments with LGE with  $>50\%$  transmural extent ( $P=0.04$ ) remained independently associated with time to ADT. Univariable and multivariable analyses without imaging parameters of the total study cohort (N=276) are presented in Table S4.

## DISCUSSION

This study shows that survivors of SCA with CAD remain at high risk of recurrent VA during follow-up. Even patients with a presumably reversible ischemic cause, with LVEF  $>35\%$  and complete revascularization, remain at risk of recurrent VA. SCA survivors with CAD with increased LVEDV and high number of segments with LGE with  $>50\%$  transmural extent are at high risk of ADT. In addition, this study suggests that incomplete revascularization increases the risk of ADT, emphasizing the need to strive for complete revascularization before ICD implantation.

### Reversible Causes and ICD Eligibility

ICD implantation is an established therapy to improve survival rates of SCA, but SCA survivors with a reversible and correctable cause are not eligible for ICD therapy according to current guidelines.<sup>1</sup> However, this recommendation is based on a paucity of data, since previous randomized secondary prevention ICD trials excluded SCA survivors with reversible causes.<sup>2–4</sup> The present study demonstrates that patients with a secondary prevention ICD with CAD and a preserved LVEF and

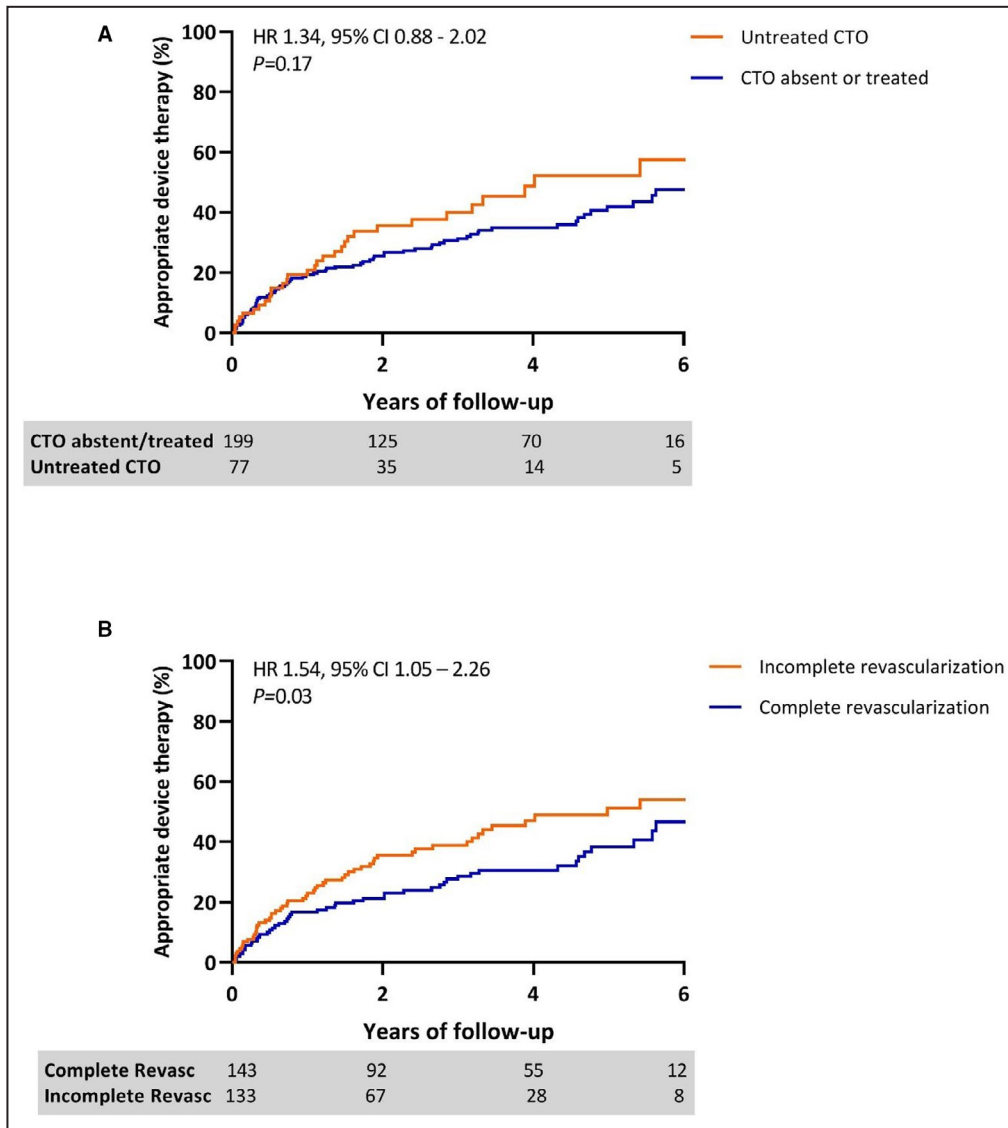


**Figure 2. The primary and secondary end points during follow-up.**

Kaplan-Meier curves depicting differences in (A) appropriate device therapy and (B) all-cause mortality between the ICD-per-guideline and ICD-off-label groups during 6 years of follow-up. Unadjusted values appropriate device therapy: HR, 0.30; 95% CI, 0.14–0.65;  $P < 0.01$ . Unadjusted values mortality: HR, 0.65; 95% CI, 0.23–1.83;  $P = 0.41$ . \*The HRs in Figure 2 are adjusted for LVEF. HR indicates hazard ratio; and ICD, implantable cardioverter defibrillator.

complete revascularization, suggesting removal of the identifiable underlying cause, remain at increased risk of VA during follow-up. This indicates that ICD implantation might be justified in this group of patients. Concerning the recurrence of arrhythmias in SCA survivors with CAD, previous studies found conflicting results. Several studies reported a negligible benefit of ICD therapy in this subgroup,<sup>8,13</sup> whereas others are in line with the current study and report that SCA survivors with CAD remain at risk of VA after complete revascularization and may

benefit from ICD implantation.<sup>9,14,15</sup> This inconsistency in results is not well elucidated. Several studies included a substantial group of patients with a nonshockable rhythm at the index event,<sup>8,13</sup> in whom the expected beneficial effect of ICD therapy might be reduced. Moreover, differences in primary outcome measure, including all-cause mortality,<sup>13,14</sup> cardiac mortality,<sup>9</sup> and ADT,<sup>8,15</sup> might explain the ambiguous results. The AVID (Antiarrhythmic Versus Implantable Defibrillators) registry, including patients screened but deemed not eligible for the AVID trial,



**Figure 3. The value of CTO and revascularization on appropriate device therapy during follow-up.** Kaplan–Meier curves depicting differences in appropriate device therapy in (A) patients with or without CTO present, and in (B) patients with complete versus incomplete revascularization during 6 years of follow-up. CTO indicates chronic total occlusion; ICD, implantable cardioverter defibrillator; and HR, hazard ratio.

indicated that mortality rates were higher in SCA survivors with a reversible cause compared with patients with an irreversible cause.<sup>14</sup> Although the current study shows that the ADT rate was lower in the ICD-off-label group compared with the ICD-per-guideline group (15% versus 43% after 4 years of follow-up), the event rate of ADT in the ICD-off-label group is comparable to event rates seen in the current primary prevention ICD population. Primary prevention ICD registries reported ADT in approximately 10% to 20% of patients during 3 years of follow-up,<sup>16,17</sup> suggesting that secondary prevention ICD implantation based on reversible ischemic causes is justifiable.

It can be argued that the underlying pathophysiology of CAD is not entirely correctible or reversible by revascularization of the obstructive (culprit) lesion, since CAD has a progressive nature. Although percutaneous coronary intervention would temporarily resolve a critical coronary stenosis, new lesions may develop over time.<sup>18</sup> Furthermore, studies have shown an important genetic predisposition of developing VA during ischemia in MI. A familial history of SCD was an independent risk factor for VA in MI.<sup>19,20</sup> This suggests that patients developing VF or VT during an ischemic event are at increased risk of SCD when new ischemia occurs at follow-up.



**Table 3. CMR Values**

	Cohort With CMR (n=166)	ICD-per-Guideline with CMR (n=134)	ICD-Off-Label With CMR (n=32)	P Value
End-diastolic volume, mL	231±80	240±84	197±45	<0.01
End-systolic volume, mL	147±73	157±76	104±35	<0.01
LVEF, %	39±12	36±22	48±8	<0.01
LVEF ≥50%, n (%)	31 (19)	17 (13)	14 (44)	<0.01
Any LGE present, n (%)	155 (93)	127 (95)	28 (88)	0.23
Presence ischemic LGE, n (%)	149 (90)	123 (92)	26 (81)	0.32
No. of segments with ischemic LGE, median n (IQR)	5 (3–7)	5 (3–7)	5 (3–6)	0.36*
No. transmural segments (LGE >50%), median n (IQR)	3 (1–5)	3 (1–5)	2 (0–4)	0.13*
No. subendocardial segments, median n (IQR)	1 (0–3)	1 (0–3)	1 (0–4)	0.59*

Dichotomous variables compared using the chi-square test or Fischer's exact test. Continuous variables compared using *t*-tests unless otherwise indicated. \*Tested using the Mann-Whitney U test. CMR indicates cardiac magnetic resonance; ICD, implantable cardioverter defibrillator; IQR, interquartile region; LGE, late gadolinium enhancement; and LVEF, left ventricular ejection fraction.

### Value of CMR

This study demonstrates that increased LV volume, expressed as LVEDV, is independently associated with ADT, which is in line with previous reports.<sup>21</sup> LV dilation increases wall stress, which was found to increase the risk of VA.<sup>22,23</sup> Interestingly, LVEF, currently used in guidelines for risk assessment of VA, is in the present study only univariably associated with ADT. The current study shows that the extent of LGE with >50% transmural is also independently associated with the

primary end point. Myocardial scar is an established substrate for VA,<sup>6</sup> and previous studies demonstrated that additional CMR with LGE imaging was able to detect myocardial scar in the majority of SCA survivors,<sup>24,25</sup> even after exclusion of obstructive CAD.<sup>6</sup> A recently published consensus paper on risk assessment of arrhythmias recommends LGE-CMR for imaging of myocardial scar.<sup>26</sup>

Scar after an ischemic event is typically seen in a subendocardial or transmural pattern.<sup>27</sup> LGE

**Table 4. Univariable and Multivariable Cox Regression Analysis of Clinical and Imaging Parameters for Predicting Appropriate Device Therapy in Patients Receiving CMR**

Parameter	HR (95% CI)	P Value	HR (95% CI)	P Value
Univariable analysis			Multivariable analysis	
Age (years)*	1.03 (1.00–1.06)	0.02	1.04 (1.01–1.06)	0.01
Male sex*	2.49 (0.90–6.86)	0.08	...	...
Diabetes mellitus*	0.93 (0.49–1.79)	0.83	...	...
Prior MI*	1.88 (1.04–3.42)	0.04	...	...
Atrial fibrillation*	0.88 (0.50–1.56)	0.67	...	...
Beta-blocking therapy*	0.88 (0.35–2.21)	0.79	...	...
Creatinine (μmol/L)†	1.00 (0.99–1.01)	0.75	...	...
LVEF per 10%‡	0.76 (0.62–0.94)	0.01	...	...
LVEDV per 10 mL§	1.05 (1.02–1.08)	<0.01	1.06 (1.02–1.09)	<0.01
LGE presence*	2.66 (0.65–10.91)	0.17	...	...
No. transmural LGE segments*	1.17 (1.06–1.29)	<0.01	1.12 (1.01–1.25)	0.04
Moderate-intensive exercise*	1.14 (0.66–1.95)	0.64	...	...
CK-MB	1.00 (0.99–1.00)	0.68	...	...
Multivessel CAD*	1.13 (0.68–1.85)	0.64	...	...
Incomplete revascularization*	1.67 (1.01–2.76)	0.05	...	...
CTO treated conservatively*	1.57 (0.94–2.64)	0.09	...	...
ICD-per-guideline indication*	2.48 (1.07–5.76)	0.04	...	...
CRT-D*	1.79 (0.71–4.47)	0.22	...	...

\*Based on 166 patients; †Based on N=158; ‡Based on N=162; §Based on N=165; ||Based on N=106. CAD, coronary artery disease; CK-MB, creatinine kinase myocardial band; CMR, cardiac magnetic resonance; CRT-D, resynchronization therapy defibrillator; CTO, coronary chronic total occlusion; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; and MI, myocardial infarction.

transmurality of >50% of wall thickness is in general considered as nonviable, based on in previous studies in which LGE >50% was associated with no or limited functional recovery after revascularization.<sup>12</sup> However, this may have affected the choice of a conservative treatment in patients with incomplete revascularization or untreated CTO in the present cohort. Although the infarcted segments were classified as nonviable based on LGE transmurality, viable myocardium with electrical activity can still be present in the border zone and the residual noninfarcted myocardial wall. Previous studies demonstrated a significant association between border zone and VA.<sup>28,29</sup> The continuing ischemia in the residual viable myocardium and border zone attributable to untreated coronary stenosis can cause recurrence of VA.<sup>30</sup> The results of the present study suggest that complete coronary revascularization might reduce the burden of VA, as revascularization decreases the ischemic burden and therewith the associated electrical instability and VAs, irrespective of scar extent and potential functional recovery.

### Limitations

Several limitations should be kept in mind when interpreting these data. First, this is a retrospective observational study suffering from the biases inherent to this design. Moreover, the study population is rather small, and results should therefore be interpreted with caution. Second, selection of patients in the ICD-off-label group is biased by indication, since the clinical decision to implant an off-label ICD for secondary prevention in this group was based on expert opinion. However, in both clinics, every patient is discussed in a dedicated heart team meeting before acceptance for ICD implantation. Unfortunately, a control group including SCA survivors with CAD without an ICD for secondary prevention was not available for comparison. Third, in the assessment of myocardial substrate, T2-weighted CMR imaging may be valuable, since it visualizes myocardial edema. The presence of edema suggests recent myocardial injury,<sup>24</sup> allowing differentiation of newly developed scar from preexisting old substrate. However, this was not routinely performed, and data are therefore missing in the current evaluation. The value of distinguishing recent myocardial damage with edema from old preexisting myocardial scar on the prognosis in patients with CAD after SCA may be of interest for future studies. Fourth, the value of echocardiography was not analyzed in this study, as only a minority of patients received a complete echocardiography examination including LVEF quantification.

## CONCLUSIONS

In conclusion, survivors of SCA with CAD are at high risk of recurrent VA during follow-up. Even in patients with a presumably reversible ischemic cause, with complete revascularization and LVEF  $\geq 35\%$ , the risk of recurrent VA is substantial. Hence, secondary prevention ICD therapy might be justified in this off-label patient subgroup, since the event rate of ADT is comparable to the event rate seen in the primary prevention ICD population. Moreover, the current study shows that higher age, larger LVEDV, and increased extent of LGE with >50% transmurality are independent predictors for recurrence of VA, suggesting that LGE-CMR should be incorporated in a patient-guided risk assessment for survivors of SCA. Since our study and other observational studies are suggesting that SCA patients with a reversible cause based on CAD might benefit from ICD therapy, a randomized study is required to further clarify this vexing problem.

## ARTICLE INFORMATION

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### Affiliations

From the Department of Cardiology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Cardiovascular Sciences, Amsterdam, Netherlands (A.C.v.d.L., M.A.B., M.J.K., M.T.R., E.M.S., A.C.v.R., V.P.v.H., T.G., C.P.A.); and Department of Cardiology, Northwest Clinics, Alkmaar, The Netherlands (M.A.B., S.A.T., T.G.).

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None.

### Supplementary Material

Tables S1–S4

Figure S1

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# **SUPPLEMENTAL MATERIAL**

**Table S1. Patient characteristics with and without a CTO.**

<b>Characteristics</b>	<b>CTO absent (n=176)</b>	<b>CTO present (n=100)</b>	<b>P- value</b>
Age (years)	67 ± 10	66 ± 10	0.61
Male sex	154 (88%)	88 (88%)	0.90
Diabetes mellitus	28 (16%)	28 (28%)	0.02
Hypertension	76 (54%)	44 (49%)	0.46
Hyperlipidemia	49 (37%)	33 (38%)	0.84
BMI (kg/m <sup>2</sup> )	27 ± 4	27 ± 5	0.92
Prior MI	113 (64%)	67 (67%)	0.64
Prior PCI	62 (35%)	28 (28%)	0.22
Prior CABG	61 (35%)	N/A	N/A
Atrial fibrillation	56 (32%)	33 (33%)	0.84
Creatinine (µmol/L)	85 (76 - 99)	87 (75 - 103)	0.99†
QRS duration (ms)	114 ± 26	111 ± 20	0.30
LVEF (%)	38 ± 12	38 ± 11	0.69
No. of segments with ischemic LGE*	4 (2-6)	6 (5-7)	<0.01†
No. transmural ischemic segments*	3 (0 – 4)	4 (2 – 6)	0.03†
No. subendocardial segments*	1 (0 – 3)	1 (0 – 4)	0.61†
ACEi/ARB	150 (85%)	87 (87%)	0.68
Beta-blockers	163 (93%)	88 (88%)	0.20
Amiodarone	24 (14%)	15 (15%)	0.76

ICD	162 (92%)	97 (97%)	0.10
CRT-D	14 (8%)	3 (3%)	0.10

Dichotomous variables compared using the chi-square test or Fischer's exact test. Continuous variables compared using t-tests unless otherwise indicated. \* based on 166 patients; † tested using Mann-Whitney U test. ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; BMI; body mass index; CABG, coronary arterial bypass graft surgery; CRT-D, resynchronisation therapy; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MI; myocardial infarction; PCI, percutaneous coronary intervention.

**Table S2. Patient characteristics with and without LGE-CMR.**

<b>Characteristics</b>	<b>Total Cohort (n=276)</b>	<b>Patients without CMR (n=110)</b>	<b>Patients with CMR (n=166)</b>	<b>P-value</b>
ICD-off-label group	48 (17%)	16 (15%)	32 (19%)	0.31
Age (years)	67 ± 10	70 ± 8	65 ± 10	<0.01
Male sex	242 (80%)	97 (82%)	145 (87%)	0.84
Amsterdam UMC, Vrije Universiteit	190 (69%)	66 (60%)	124 (75%)	0.10
Northwest Clinics Alkmaar	86 (31%)	44 (40%)	42 (25%)	0.10
<b><i>Cardiovascular risk factors</i></b>				
Diabetes mellitus	56 (20%)	22 (20%)	34 (21%)	0.92
Hypertension	120 (44%)	47 (57%)	73 (49%)	0.29
Hyperlipidemia	82 (30%)	27 (35%)	55 (38%)	0.65
BMI (kg/m <sup>2</sup> )	27 ± 4	27 ± 4	27 ± 4	0.55
<b><i>Medical history</i></b>				
Prior MI	180 (65%)	66 (60%)	114 (69%)	0.14
Prior PCI	90 (33%)	40 (36%)	50 (30%)	0.28
Prior CABG	61 (22%)	36 (33%)	25 (15%)	<0.01
LVEF (%)*	38 ± 11	36 ± 9	39 ± 12	0.17
Atrial fibrillation	89 (32%)	39 (36%)	50 (30%)	0.35
Creatinine (µmol/L)	86 (76 – 102)	91 (77 – 103)	85 (75 – 99)	0.34§
QRS duration (ms)	108 (96 – 126)	110 (96 – 130)	106 (96 – 122)	0.24§
<b><i>Cardiac findings and intervention at index event</i></b>				
VF at time of OHCA	180 (65%)	65 (59%)	115 (69%)	0.08

CK-MB † (ug/L)	22 (8 - 45)	37 (12 – 73)	19 (7 – 39)	0.01§
Troponine T ‡ (ug/L)	0.33 (0.11 – 0.98)	0.43 (0.10 – 1.37)	0.31 (0.12 – 0.87)	0.74§
Moderate/extensive exercise prior to arrest	69 (25%)	22 (22%)	47 (28%)	0.27
Diffuse non-obstructive CAD	74 (26%)	32 (29%)	42 (25%)	0.49
Multivessel disease	163 (59%)	76 (69%)	87 (52%)	<0.01
CTO present (no prior CABG)	100 (36%)	35 (32%)	65 (39%)	0.21
PCI performed	102 (37%)	37 (34%)	65 (39%)	0.35
CABG performed	26 (9%)	12 (11%)	14 (8%)	0.49
Complete revascularization	143 (52%)	57 (52%)	86 (52%)	0.99

***Medication at time of ICD implantation***

ACEi/ARB	237 (86%)	93 (85%)	144 (87%)	0.61
Beta-blockers	251 (91%)	97 (88%)	154 (93%)	0.19
Ca channel blocker	23 (8%)	10 (9%)	13 (8%)	0.71
Amiodarone	39 (14%)	20 (18%)	19 (11%)	0.12

***Device Type and procedures***

Upgrade procedures	15 (5%)	15 (14%)	0 (0%)	<0.001
ICD	259 (94%)	103 (94%)	156 (94%)	0.91
CRT-D	17 (6%)	7 (6%)	10 (6%)	0.91

***End points***

Appropriate device therapy	106 (38%)	43 (39%)	63 (38%)	0.85
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All-cause mortality	40 (15%)	18 (16%)	22 (13%)	0.47
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Dichotomous variables compared using the chi-square test or Fischer's exact test. Continuous variables compared using t-tests unless otherwise indicated.\* based on 199 patients; † based on N=151; ‡ based on N=156; § tested using Mann-Whitney U test. ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; BMI, body mass index; Ca, calcium; CABG, coronary arterial bypass graft surgery; CAD, coronary artery disease; CK-MB, creatinine kinase myocardial band, CRT-D, resynchronisation therapy; CTO, coronary chronic total occlusion; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; VF, ventricular fibrillation.

**Table S3. Outcomes in the LGE-CMR-subgroup.**

Parameters	Study cohort with CMR (n=166)	ICD-per-guideline with CMR (n=134)	ICD-off-label with CMR (n=32)	P-value
Appropriate ICD therapy	63 (38%)	57 (43%)	6 (19%)	0.01
ATP only	34 (20%)	31 (23%)	3 (9%)	0.08
ICD Shock	29 (17%)	26 (19%)	3 (9%)	0.18
Cumulative number of ICD therapy per patient	2 (1-4)	2 (1-4)	3 (2-3)	0.92*
VT ablation	15 (9%)	15 (11%)	0	0.08
All-cause mortality	22 (13%)	18 (13%)	4 (13%)	0.89

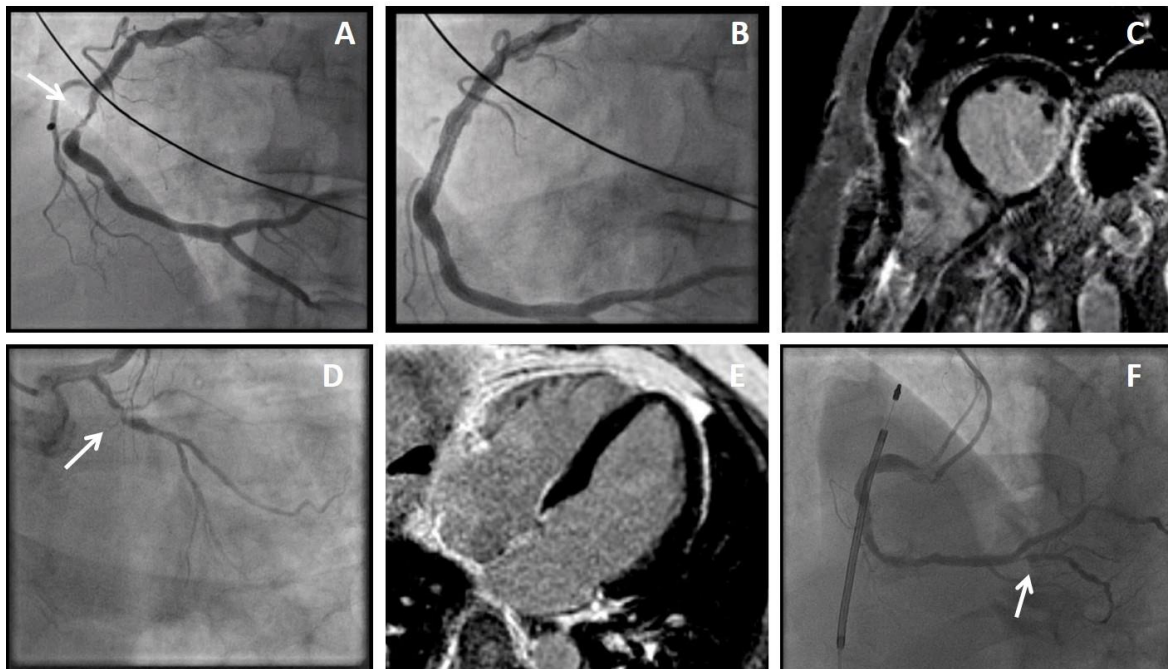
Dichotomous variables compared using the chi-square test or Fischer's exact test. Continuous variables compared using the Mann-Whitney U test. \* tested using Mann-Whitney U test. ATP, anti-tachycardia pacing; CMR, cardiac magnetic resonance; ICD, implantable cardioverter defibrillator; VT ventricular tachycardia.

**Table S4. Univariable and multivariable Cox regression analysis of clinical parameters for predicting appropriate device therapy in the total study cohort.**

Parameter	HR (95% CI)	P-value	HR (95% CI)	P-value
<b>N=276</b>				
<b>Univariable analysis</b>			<b>Multivariable analysis</b>	
Age (years)	1.03 (1.01 – 1.05)	0.01	1.02 (1.01 – 1.04)	0.04
Male sex	2.10 (1.02 – 4.33)	0.04	2.39 (1.16 – 4.94)	0.02
Diabetes mellitus	1.15 (0.72 – 1.85)	0.55		
Prior MI	1.95 (1.25 – 3.05)	<0.01	1.64 (1.04 – 2.60)	0.03
Atrial fibrillation	1.20 (0.80 – 1.80)	0.38		
Beta-blocking therapy	1.00 (0.49 – 2.07)	0.99		
Creatinine (μmol/L)	1.00 (0.99 – 1.00)	0.66		
LVEF<35%	1.48 (0.90 – 2.43)	0.13		
Moderate-Intensive exercise	0.83 (0.52 – 1.32)	0.43		
CK-MB	1.00 (0.99 – 1.00)	0.53		
Multivessel CAD	1.24 (0.84 – 1.82)	0.29		
Incomplete revascularization	1.54 (1.05 – 2.26)	0.03	-	-
Untreated CTO	1.34 (0.88 – 2.02)	0.17		
ICD-Per-Guideline	3.30 (1.53 – 7.11)	<0.01	2.99 (1.40 – 6.47)	<0.01
CRT-D	1.73 (0.87 – 3.44)	0.12		

CAD, coronary artery disease; CK-MB, creatinine kinase myocardial band, CRT-D, resynchronization therapy defibrillator; CTO, coronary chronic total occlusion, ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

**Figure S1. Case examples of ICD-off-label patients.**



Case examples of two off-label patients. Case example 1 (A-C) is a patient with a history of a inferoposterolateral myocardial infarction. Acute angiography revealed a significant stenosis of the RCA (A), which was successfully treated with PCI (B). LGE-CMR showed a large transmural infarction in the inferolateral wall and a moderate LV function (LVEF 39%) (C). At follow-up the patient received two ICD shocks for VT. Case example 2 (D-F) is a patient without a cardiac history. After index cardiac arrest the angiography showed two significant stenosis of the RCX and RCA (D), which were both successfully stented. CMR revealed a good cardiac function (LVEF 55%) and without LGE. During follow-up, the patient developed VF and received an ICD shock. Repeated angiography revealed a newly developed stenosis of the RCA (F).