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Substrate Ablation vs Antiarrhythmic Drug Therapy for Symptomatic Ventricular Tachycardia

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ABSTRACT

BACKGROUND In patients with ischemic cardiomyopathy and an implantable cardioverter-defibrillator (ICD), catheter ablation and antiarrhythmic drugs (AADs) reduce ICD shocks, but the most effective approach remains uncertain.

OBJECTIVES This trial compares the efficacy and safety of catheter ablation vs AAD as first-line therapy in ICD patients with symptomatic ventricular tachycardias (VTs).

METHODS The SURVIVE-VT (Substrate Ablation vs Antiarrhythmic Drug Therapy for Symptomatic Ventricular Tachycardia) is a prospective, multicenter, randomized trial including patients with ischemic cardiomyopathy and appropriated ICD shock. Patients were 1:1 randomized to complete endocardial substrate-based catheter ablation or antiarrhythmic therapy (amiodarone + beta-blockers, amiodarone alone, or sotalol ± beta-blockers). The primary outcome was a composite of cardiovascular death, appropriate ICD shock, unplanned hospitalization for worsening heart failure, or severe treatment-related complications.

RESULTS In this trial, 144 patients (median age, 70 years; 96% male) were randomized to catheter ablation (71 patients) or AAD (73 patients). After 24 months, the primary outcome occurred in 28.2% of patients in the ablation group and 46.6% of those in the AAD group (hazard ratio [HR]: 0.52; 95% CI: 0.30-0.90; $P = 0.021$). This difference was driven by a significant reduction in severe treatment-related complications (9.9% vs 28.8%, HR: 0.30; 95% CI: 0.13-0.71; $P = 0.006$). Eight patients were hospitalized for heart failure in the ablation group and 13 in the AAD group (HR: 0.56; 95% CI: 0.23-1.35; $P = 0.198$). There was no difference in cardiac mortality (HR: 0.93; 95% CI: 0.19-4.61; $P = 0.929$).

CONCLUSIONS In ICD patients with ischemic cardiomyopathy and symptomatic VT, catheter ablation reduced the composite endpoint of cardiovascular death, appropriate ICD shock, hospitalization due to heart failure, or severe treatment-related complications compared to AAD. (Substrate Ablation vs Antiarrhythmic Drug Therapy for Symptomatic Ventricular Tachycardia [SURVIVE-VT]: NCT03734562) (J Am Coll Cardiol 2022;79:1441–1453) © 2022 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug

ICD = implantable cardioverter-defibrillator

VT = ventricular tachycardia

Implantable cardioverter-defibrillators (ICDs) prevent sudden cardiac death, but appropriate shocks are painful, deteriorate the quality of life, reduce device longevity, and may increase mortality.[1-6] In patients with ischemic heart disease, randomized trials have shown that both catheter ablation and antiarrhythmic drugs (AADs) reduce appropriate ICD shocks.[7-9] Ablation seems better than escalating AADs in patients with ventricular tachycardia (VT) recurrences despite use of amiodarone, but no randomized studies have compared the efficacy and safety of both treatments in AAD-naïve patients.[10] AADs probably have fewer acute complications; however, they can also have significant adverse effects and in some subgroups of patients may increase mortality.[9,11] Ablation has acute complications and a not-negligible procedure-related mortality to which an ablation strategy based on repetitive induction and mapping during VT may contribute.[12] On the other hand, an ablation strategy based on substrate mapping during sinus rhythm is very effective and has few complications.[7,13,14]

The SURVIVE-VT (Substrate Ablation versus Antiarrhythmic Drug Therapy for Symptomatic Ventricular Tachycardia) was designed to compare substrate-based catheter ablation procedure with AADs as the first-line strategy in patients with ischemic cardiomyopathy and symptomatic VT or ICD shocks for a composite efficacy and safety outcome.

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METHODS

TRIAL DESIGN. The SURVIVE-VT was a phase IV, investigator-driven, academically sponsored, multicenter, randomized controlled trial conducted at 9 centers in Spain, all of them experienced in performing VT substrate catheter ablation. The Fundación de Investigación Biomédica Hospital Gregorio Marañón served as the coordinating center. The trial protocol was authorized by the Spanish Agency of Medicinal Products and Medical Devices. The Ethics Committee at each participating center approved the trial. All patients provided written informed consent. Randomization and clinical monitoring were performed by Alpha Bioresearch SL which also acted as the Data and Coordinating Centre. This study was supported by the Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación, and the EU-European Regional Development Fund (EC08/0296), with an additional unrestricted grant from Biosense Webster.

The executive committee designed and conducted the trial. Details about the trial committees are provided in the Supplemental Appendix. The first author wrote the first draft of the manuscript and all the authors made decisive contributions and agreed to submit the manuscript for publication. The funders of the trial had no role in the design or conduct of the trial, the analysis of the data, or in the authorship or submission of the manuscript. The first author had full access to all the data in the study and takes responsibility for its integrity and the data analysis. The study is registered in EudraCT (2009-011163-36) and ClinicalTrials.gov (NCT03734562).

PATIENTS. Patients were eligible for inclusion if they had a previous myocardial infarction (>6 weeks), optimal medical treatment (if ventricular dysfunction), and had an episode of very symptomatic VT defined as: 1) sustained VT treated using ICD shock (<6 months); and 2) sustained VTs with syncope, even if terminated with antitachycardia pacing. In 2013, the steering committee proposed a new qualifying criterion in order to promote enrollment, allowing the inclusion of patients with monomorphic VT necessitating ICD. It was implemented by previous acceptance by the ethics committee. Detailed inclusion and exclusion criteria are provided in the Supplemental Methods.

RANDOMIZATION AND INTERVENTIONS. Eligible patients were randomly assigned 1:1 to receive catheter ablation (ablation group) or AAD therapy (AAD group). Patients and treating physicians were aware of the treatment arm.

Randomization was performed with the use of prenumbered, opaque, sealed envelopes in permuted blocks of size 4 and a random number generator.

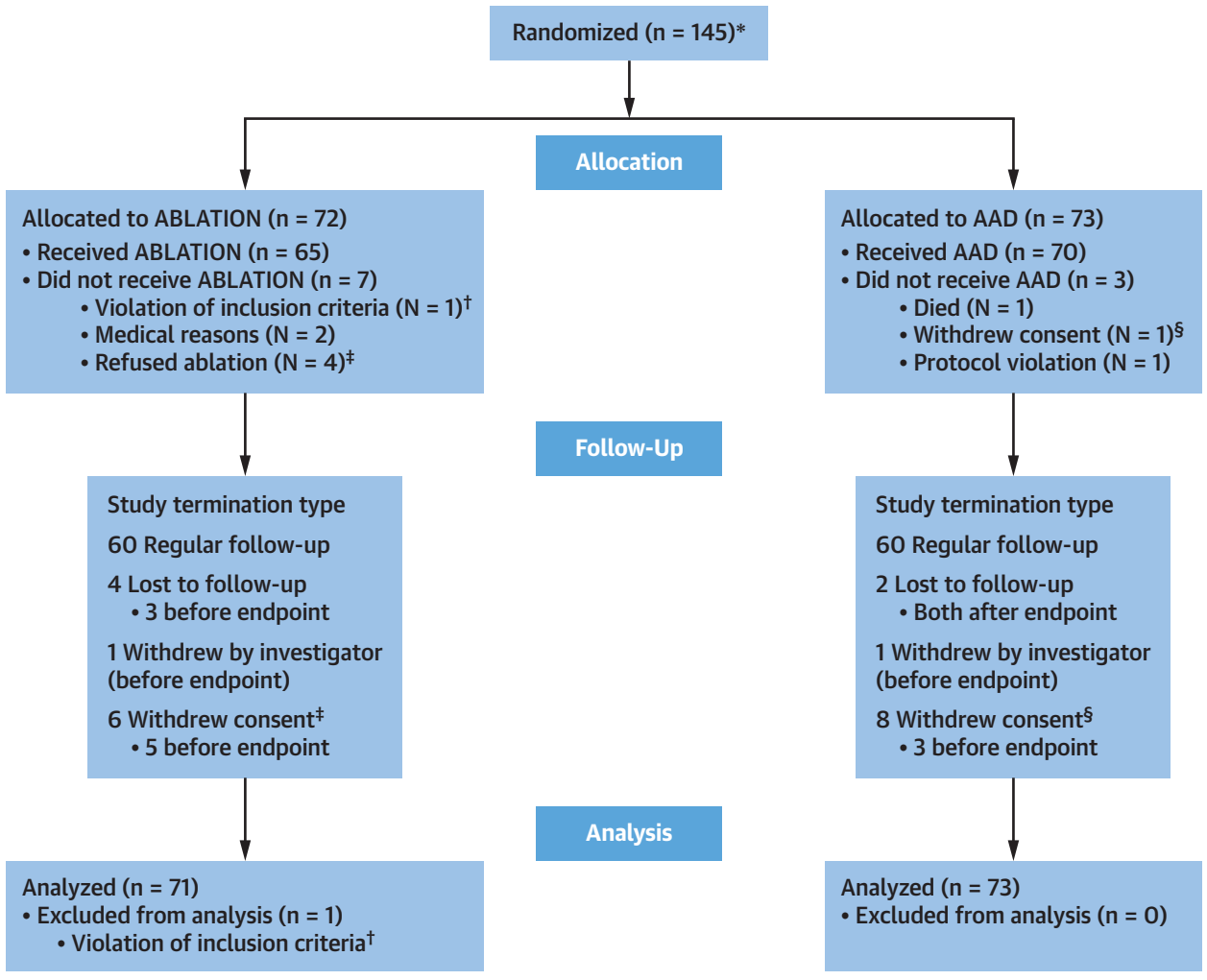
Subjects in the ablation group had their procedure scheduled within 15 days whereas subjects in the AAD group started with medical treatment immediately. The ablation procedures were performed using an endocardial substrate-based approach aimed at eliminating all the arrhythmogenic substrate avoiding VT induction.

Unless contraindicated, patients in the AAD group were treated with amiodarone + beta-blockers (strategy #1), those with contraindication to amiodarone were treated with sotalol ± beta-blockers (strategy #2), and those with contraindication or intolerance to beta-blockers received only amiodarone (strategy #3).

To minimize bias in arrhythmias detection, ICDs were programmed according to a standardized protocol after randomization.

Further details about ablation procedures, AAD therapy, and ICD programming are provided in the Supplemental Appendix.

FIGURE 1 Trial Flowchart



Randomization and allocation of patients are shown. Overall, 145 patients were randomized, 1 of them, allocated to catheter ablation, was excluded because the patient did not meet the inclusion criteria. The remaining 144 were included in the primary intention-to-treat analysis. *Sites were not required to provide screening logs during the recruitment phase. Thus, the number of patients assessed for eligibility is not available. †The patient was excluded from follow-up and further analysis. ‡3 patients refused ablation and withdrew consent. §1 patient withdrew consent before receiving AAD. AAD = antiarrhythmic drug.

OUTCOMES. The primary outcome was a composite of cardiovascular death, appropriate ICD shock, unplanned hospitalization for worsening heart failure, or severe treatment-related complications from enrollment up to the 24-month follow-up. Events eligible for the primary outcome were adjudicated by an independent arrhythmic event assessment committee blinded to the assigned treatment.

Prespecified secondary outcomes included each of the primary outcome components as well as sustained VT or ventricular fibrillation, appropriate and inappropriate ICD therapies, death from any cause, unplanned hospitalization for ventricular arrhythmias and cardiac events, change in ventricular ejection fraction, and quality of life.

Further information about the trial outcomes and follow-up are provided in the Supplemental Appendix.

STATISTICAL ANALYSIS. We estimated a cumulative incidence in the primary endpoint of 40% in the AAD group after 2 years of follow-up. Thus, we calculated that enrolling 180 patients would provide a power of 80% to detect a 20% absolute risk (50% relative risk) reduction in the primary outcome at a significance level of 0.05 (2-sided).

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TABLE 1 Baseline Demographic Characteristics

	Ablation (n = 71)	AAD (n = 73)
Age, y	70 (63-75)	71 (64-76)
Male	70 (98.6)	68 (93.2)
BMI, kg/m^2	27.3 (25.2-31.6)	27.6 (25.9-30.0)
Hypertension	56 (78.9)	47 (64.4)
Diabetes	21 (29.6)	15 (20.5)
Renal insufficiency	8 (11.3)	7 (9.6)
Creatinine, mg/dL	1.05 (0.87-1.28)	1.02 (0.88-1.15)
Creatinine ≥1.5 mg/dL	11 (16.2)	7 (9.7)
Time since last myocardial infarction, y	14 (6-24)	14 (7-23)
Infarction location		
Anterior	25 (35.2)	31 (42.5)
Inferior	46 (64.8)	40 (54.8)
Lateral	6 (8.5)	12 (16.4)
Previous CABG	18 (26.5)	12 (17.1)
Previous PCI	26 (38.2)	26 (37.1)
No revascularization	25 (36.8)	33 (47.1)
Ejection fraction, %	35 (26-41)	33 (25-40)
LVEF ≤30%	31 (43.7)	36 (49.3)
NYHA functional class		
I	31 (44.3)	31 (42.5)
II	33 (47.1)	37 (50.7)
III	6 (8.6)	5 (6.8)
AF or atrial flutter	9 (13.6)	8 (12.3)
Medical therapy		
Beta-blockers	69 (97.2)	62 (86.1)
ACE inhibitors or ARBs	70 (98.6)	65 (90.3)
RAAS inhibitors	39 (55.7)	42 (60.9)
Follow-up, mo	23.8 (16.6-24.0)	23.3 (9.4-23.9)

Values are median (25th-75th percentile) or n (%).

AAD = antiarrhythmic drugs; ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin-receptor blocker; BMI = body mass index; CABG = coronary artery bypass grafting; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RAAS = renin-angiotensin-aldosterone system.

Enrollment started in September 2010. In July 2017, 145 patients (80.6% of the 180 projected) had been included in the trial. Considering the enrollment rate, achieving the calculated sample size would take at least 2 more years. For these reasons, the steering committee decided to stop recruitment and analyze the results.

Analyses were conducted according to the intention-to-treat principle.

Continuous variables are summarized as mean ± SD or median and 25th-75th percentiles depending on data distribution, whereas categorical variables are represented as frequencies and percentages.

Kaplan-Meier analysis was used to estimate the event-free survival rates, and log-rank tests were used to compare event-free survival differences. Hazard ratios (HRs) and CIs were calculated with Cox proportional hazards models. The proportional hazards assumption was checked and confirmed by plotting log-log survival curves against (log) time and by testing the Schoenfeld residuals. All other secondary outcomes and descriptive variables were tested with the Mann-Whitney rank-sum test, the Student's *t*-test (paired or unpaired), the chi-square, or the Fisher exact test, as appropriate.

There were no missing values in the main baseline variables (age, sex, and left ventricular ejection fraction [LVEF]). No imputation was performed for any missing values.

All tests were 2-tailed, and a $P < 0.05$ was considered statistically significant.

Statistical analysis was conducted with R software version 4.0.0 (R Foundation for Statistical Computing).

Several post hoc sensitivity analyses were performed including: 1) a covariate-adjusted Cox regression model including age, LVEF, and VT cycle length to assess heterogeneity of treatment effect; 2) a mixed-model analysis of the primary outcome adjusting the assigned treatment (fixed effect) for enrolling site (random effect) to assess the potential treatment effect variations among the different enrolling sites; 3) a "modified-intention-to-treat" analysis, including those patients who received at least 1 dose of the AAD or underwent catheter ablation; 4) an "as-treated" analysis, including patients according to the treatment they actually received; 5) an "as-treated_2" analysis, the same as before but censoring the patients who crossed over before reaching the primary outcome at the time of the crossover; and 6) a "per protocol" analysis, including patients who received the treatment they were initially assigned.

Detailed information about post hoc analysis is provided in the Supplemental Appendix.

RESULTS

PATIENTS. From September 2010 through July 2017, 145 patients were enrolled. After randomization, 72 were allocated to undergo catheter ablation and 73 to receive AAD; 1 patient in the ablation group was excluded after randomization because the patient did not meet the inclusion criteria (Figure 1). The baseline demographic and clinical characteristics of the patients included were well balanced (Table 1). The index arrhythmia was an appropriate shock in 115 patients, VT with syncope in 7, nontolerated VT without syncope in 22, and 112 (78%) patients have had ≥2 VTs. More information about the index VT episode, device types, and ICD programming at discharge are provided in Table 2.

TABLE 2 Baseline ECG, Index Episode, and ICD Programming

	Ablation (n = 71)	AAD (n = 73)
AF or atrial flutter	9 (13.6)	8 (12.3)
Heart rate, beats/min	69 ± 20	68 ± 20
QRS morphology		
Paced rhythm	5 (7.0)	4 (5.4)
LBBB	8 (11.3)	14 (19.2)
RBBB	10 (14.1)	5 (6.8)
ICD before inclusion	68 (95.8)	70 (95.9)
ICD after inclusion	2 (2.8)	3 (4.1)
Device type		
Single-chamber	55 (77.5)	54 (75.0)
Dual-chamber	5 (7.0)	5 (6.9)
CRT	11 (15.5)	13 (18.1)
Index episode		
Cycle length, ms	313 ± 63	317 ± 61
Fast VT (<320 ms)	38 (55.1)	40 (57.1)
Appropriated shocks	58 (85.3)	57 (81.4)
Appropriated ATP	55 (80.9)	53 (75.7)
ICD programming at discharge		
VF zone cutoff, ms	290 (270-300)	283 (260-300)
VT 2 zone cutoff, ms	320 (320-335)	324 (320-353)
VT 1 zone cutoff, ms	375 (353-390)	370 (357-395)

Values are n (%), mean ± SD, or median (25th-75th percentile).

AF = atrial fibrillation; ATP = antitachycardia pacing; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; RBBB = right bundle branch block; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviation as in Table 1.

TABLE 3 Composite Primary and Secondary Outcomes

	Ablation (n = 71)	AAD (n = 73)	HR (95% CI)	*P* Value
Composite primary endpoint	20 (28.2)	34 (46.6)	0.52 (0.30-0.90)	0.021
Primary endpoint components				
Cardiovascular mortality	3 (4.2)	3 (4.1)	0.93 (0.19-4.61)	0.929
Appropriate ICD shocks	12 (16.9)	13 (17.8)	0.88 (0.40-1.93)	0.749
Hear failure hospitalization	8 (11.3)	13 (17.8)	0.56 (0.23-1.35)	0.198
Severe treatment-related complications	7 (9.9)	21 (28.8)	0.30 (0.13-0.71)	0.006
Other outcomes				
Total mortality	3 (4.2)	4 (5.5)	0.69 (0.15-3.08)	0.624
Appropriate ICD therapies	18 (25.4)	16 (21.9)	1.02 (0.52-2.01)	0.950
Appropriate ATP	8 (11.4)	12 (16.4)	0.54 (0.22-1.34)	0.186
Any documented VT[a]	19 (26.8)	21 (28.8)	0.79 (0.43-1.49)	0.417
Hospitalization for VA[a]	5 (7.0)	20 (27.4)	0.21 (0.08-0.57)	0.002
Cardiac hospitalization	13 (18.3)	27 (37.0)	0.42 (0.22-0.82)	0.011
Incessant/undetected VT/electric storm[a]	3 (4.2)	15 (20.5)	0.17 (0.05-0.58)	0.005
VT storm[a]	2 (2.8)	5 (6.8)	0.38 (0.07-1.98)	0.252
Slow undetected VT[a]	2 (1.4)	10 (13.7)	0.18 (0.04-0.84)	0.028
Inappropriate ICD therapies	2 (2.8)	4 (5.5)	0.45 (0.08-2.48)	0.362
Inappropriate ICD shocks	2 (2.8)	4 (5.5)	0.45 (0.08-2.48)	0.362
Inappropriate ATP	2 (2.8)	1 (1.4)	1.84 (0.17-20.3)	0.618

Values are n (%) unless otherwise stated. [a]Post hoc analyses.

HR = hazard ratio; VA = ventricular arrhythmia; other abbreviations as in Tables 1 and 2.

Among the 71 patients in the ablation group, 6 did not undergo ablation. Procedural characteristics of the ablations performed are described in Supplemental Table 1. Among the 73 patients in the AAD group, 3 did not receive the assigned treatment. Of the 70 subjects treated with AAD, 61 (86%) received amiodarone alone (n = 34) or in combination with beta-blockers (n = 27), whereas 10 (14%) were treated with sotalol (Supplemental Table 2).

Throughout the trial, 8 patients (10.1%) in the ablation group crossed over to antiarrhythmic therapy, whereas 18 (24.3%) in the AAD group underwent catheter ablation, all of them after experiencing VT recurrence (HR: 0.40; 95% CI: 0.17-0.92; $P = 0.031$). Crossovers occurred before reaching a primary outcome in 4 patients in the ablation group and 1 patient in the AAD group. Furthermore, 3 patients (4.3%) in the ablation group underwent a second procedure for recurrent VT.

PRIMARY OUTCOME AND COMPONENTS. After 24 months of follow-up, the primary outcome occurred in 20 of 71 patients (28.2%) in the ablation group and 34 of 73 patients (46.6%) in the ADD group (HR: 0.52; 95% CI: 0.30-0.90; $P = 0.021$ by Cox regression) (Table 3). Kaplan-Meier composite primary outcome-free survival estimates were 68.5% in the ablation group and 46.2% in the AAD group (primary and secondary outcomes are shown in Table 4). Kaplan-Meier curves comparing the primary outcome and its components in the 2 trial groups are shown in the Central Illustration and Figure 2. The number of patients who would need to be treated to prevent a primary endpoint was 4.6 (95% CI: 2.5-25).

Sensitivity analyses were all robust and consistent with the results of the primary analysis (Supplemental Table 3). Adjustment for enrolling site as a random effect did not change the estimated treatment effect (HR: 0.51; 95% CI: 0.30-0.90; $P = 0.019$).

The heterogeneity of the treatment effect according to age, LVEF, and VT cycle length is shown in Supplemental Figure 1. There was a significant interaction between the treatment and the VT cycle length. The 2-year primary endpoint-free survival estimates decreased for the AAD group with increasing cycle length ($P = 0.038$ for the cycle length and $P = 0.05$ for the interaction). The interactions between the treatment and age or LVEF were not statistically significant.

There was a similar incidence of cardiovascular mortality or ICD shocks. The difference in the primary

TABLE 4 2-Year Kaplan-Meier Event-Free Survival Estimates and Log-Rank Test of the Study Primary and Secondary Outcomes

	2-Year (95% CI) KM Event-Free Survival Estimates		
	Ablation (n = 71)	AAD (n = 73)	Log-Rank *P* Value
Composite primary endpoint	68.5 (57.8-81.1)	46.2 (35.1-60.8)	0.019
Primary endpoint components			
Cardiovascular mortality	94.3 (88.2-100)	95.3 (90.3-100)	0.930
Appropriate ICD shocks	80.3 (70.8-91.0)	77.4 (67.1-89.2)	0.750
Hear failure hospitalization	86.6 (78.3-95.8)	77.6 (67.4-89.3)	0.190
Severe treatment-related complications	89.5 (82.4-97.2)	67.0 (56.1-79.8)	0.003
Other outcomes			
Total mortality	94.3 (88.2-100)	92.9 (86.2-100)	0.622
Appropriate ICD therapies	72.3 (61.9-84.5)	72.7 (61.9-85.3)	0.950
Appropriate ATP	88.6 (80.9-96.9)	80.0 (70.3-91.0)	0.179
Any documented VT[a]	71.2 (60.7-83.5)	64.8 (53.6-78.5)	0.470
Hospitalization for VA[a]	92.1 (85.7-99.1)	65.8 (54.4-79.5)	<0.001
Cardiac hospitalization	79.6 (70.2-90.3)	55.9 (44.4-70.2)	0.008
Incessant/undetected VT/ electric storm[a]	95.2 (90.0-100)	75.5 (65.3-87.4)	0.002
VT storm[a]	96.6 (92.1-100)	92.3 (85.9-99.1)	0.234
Slow undetected VT[a]	97.1 (93.3-100)	82.8 (73.5-93.3)	0.014
Inappropriate ICD therapies	96.7 (92.3-100)	92.8 (86.2-99.9)	0.350
Inappropriate ICD shocks	96.7 (92.3-100)	92.8 (86.2-99.9)	0.350
Inappropriate ATP	96.7 (92.3-100)	98.0 (94.2-100)	0.613

[a]Post hoc analyses.
KM = Kaplan-Meier; other abbreviations as in Tables 1, 2, and 3.

outcome was driven by a trend towards fewer hospitalizations for worsening heart failure and a significant reduction in severe treatment-related adverse events/complications (9.9% vs 28.8%; HR: 0.30; 95% CI: 0.13-0.71; $P = 0.006$).

During the trial, there were 3 deaths in the ablation group and 4 in the AAD group; none of them were attributed to the assigned treatment.

Treatment-related complications are detailed in Table 5 and summarized in Supplemental Table 4. In the AAD group, there were 23 events in 21 subjects. Adverse events were so severe that they led to hospitalization in 17 patients and/or discontinuation of amiodarone in 6 (2 patients had both). In 11 of them, ablation had to be performed during hospitalization because of incessant or ICD-undetected slow VT; in 10 patients the undetected VT lasted hours and required hospitalization because of hemodynamic deterioration. In 3 patients with single-chamber ICD, amiodarone caused symptomatic bradycardia that could not be managed with device pacing, necessitating withdrawal of beta-blockers or amiodarone, or upgrade to cardiac resynchronization therapy. In the ablation group, there were 8 severe adverse events in 7 patients. All of them occurred in the first month after the procedure and were resolved completely without sequelae. Two patients experienced a stroke with mild neurological impairment. In both it resolved completely within 48 hours, and prolonged hospitalization by 3 and 5 days, respectively.

Additionally, there were some minor treatment-related complications (not included in the primary outcome). In the ablation group, 1 patient had femoral hematoma not requiring transfusion. In the AAD group, 6 patients had subclinical hypothyroidism and 1 had phototoxicity; all of them received amiodarone, but they did not require discontinuation of treatment (Supplemental Table 4).

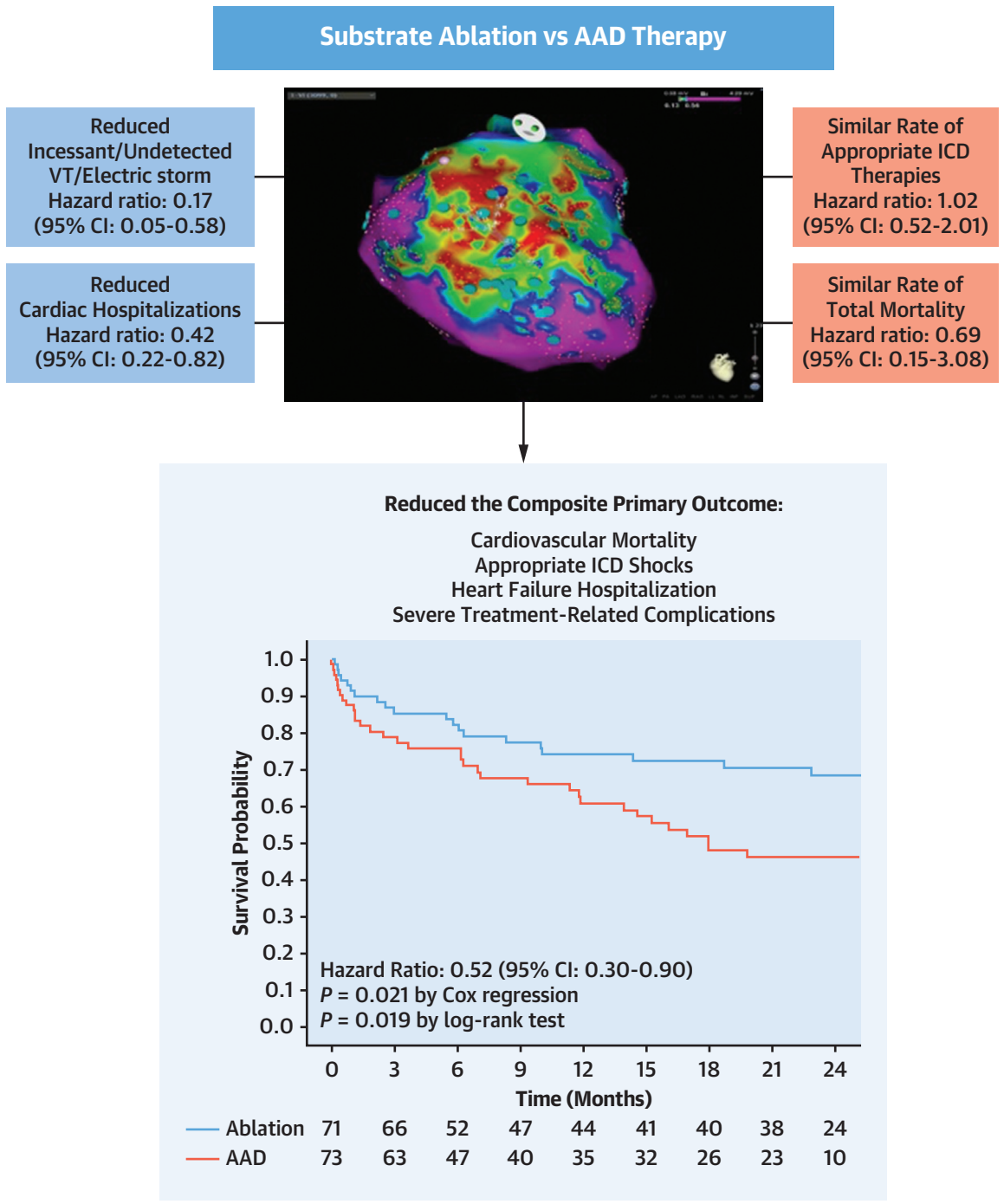
SECONDARY AND POST HOC OUTCOMES AND ANALYSES. Secondary and post hoc additional outcomes are presented in Tables 3 and 4. Recurrence as VT storm, incessant VT, and/or slow undetected VT, as well as hospital admissions for ventricular arrhythmias (HR: 0.21; 95% CI: 0.08-0.57; $P = 0.002$), and any cardiac hospitalization were significantly lower in the ablation group (Supplemental Figure 2). ICD cutoff zones for VT detection were similar between groups (Table 2). There were no changes in LVEF and quality of life during the study nor differences between the groups (Supplemental Figures 3 and 4). Other secondary outcomes are reported in the Supplemental Appendix.

DISCUSSION

In patients with ischemic heart disease and symptomatic VT, this trial has shown that a substrate-based catheter ablation procedure was associated with a significantly lower rate of the composite endpoint of appropriate ICD shocks, cardiovascular death, hospitalization for worsening heart failure, and severe treatment-related severe adverse events in comparison to AAD. We also found that there was a significant benefit in hospitalization for cardiovascular causes.

The SURVIVE-VT trial further supports that both AAD and catheter ablation are highly effective in preventing ICD therapies and ICD shocks as previously reported.[7,9] In the OPTIC (Comparison of Beta-Blockers, Amiodarone plus Beta-Blockers, or Sotalol for Prevention of Shocks from Implantable Cardioverter Defibrillators) trial, 38% of patients receiving beta-blockers have had appropriate ICD shocks at 1 year, while in the present study 77% of patients on AAD and 80% of patients in the ablation group were free of appropriate shocks. The efficacy of ablation was similar to that reported in other studies such as the SMASH VT (Substrate Mapping and

CENTRAL ILLUSTRATION **Ablation vs Antiarrhythmic Drugs for Ventricular Tachycardia in Ischemic Cardiomyopathy**



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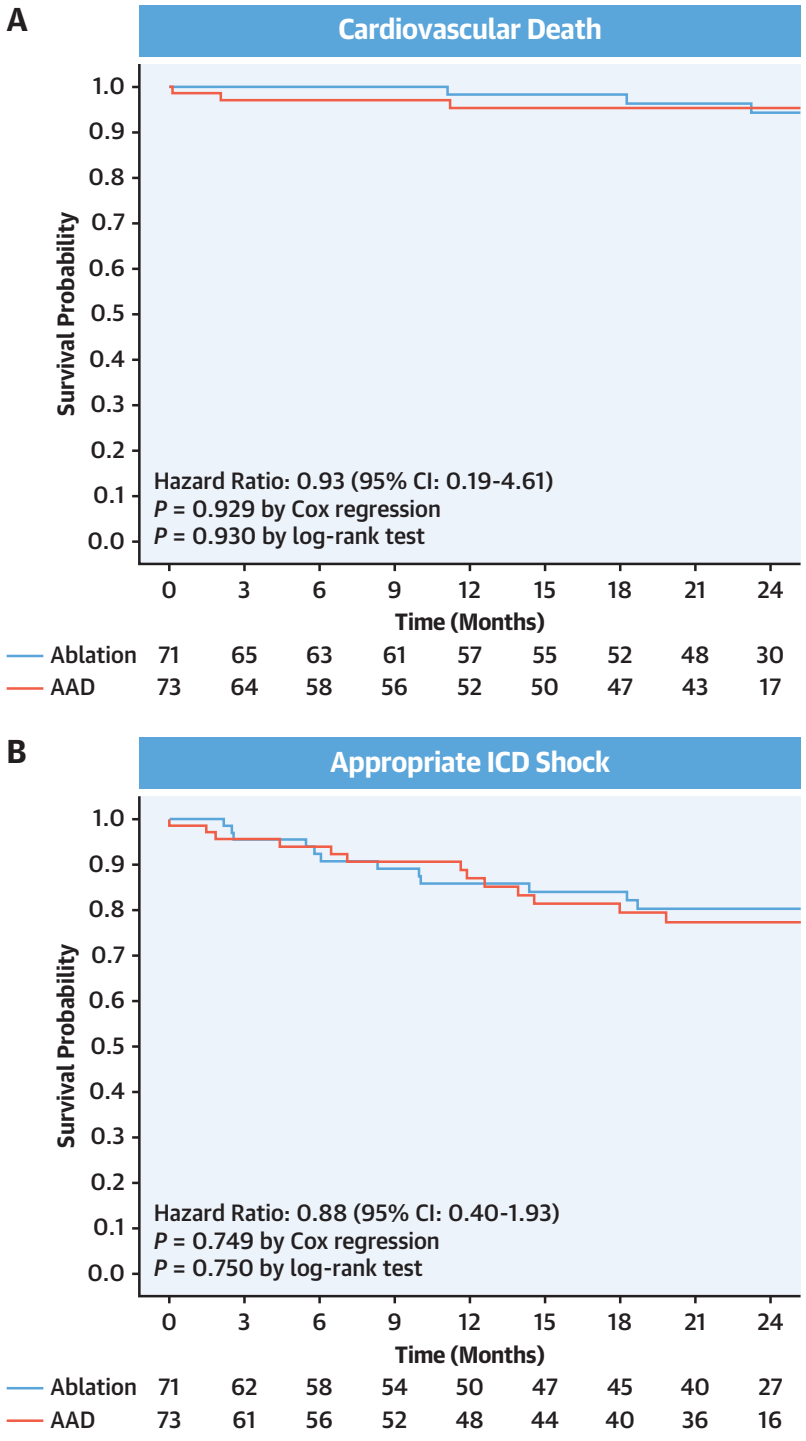
Kaplan-Meier curves comparing the primary outcome-free survival in the 2 trial groups. Day 0 is the time of randomization. The curves compare the cumulative probability of having the combined endpoint between ablation of endocardial VT substrate (all intrascar channels and late potential recorded in the scar area, shown center) and antiarrhythmic drugs. After 24 months of follow-up, Kaplan-Meier event-free survival estimates were 68.5% in the ablation group and 46.2% in the antiarrhythmic drug (AAD) group. Additionally, there was a reduction in cardiac hospitalizations and incessant/undetected ventricular tachycardia (VT) or electric storm. There were no differences in appropriate implantable cardioverter-defibrillator (ICD) therapies or mortality.

FIGURE 2 Primary Outcome Components



Kaplan-Meier curves comparing primary outcome components-free survival in the 2 trial groups. There were similar rates of cardiovascular death **(A)** and appropriate implantable cardioverter-defibrillator (ICD) shocks **(B),** lower unplanned hospitalizations for worsening heart failure **(C),** and a significantly lower rate of treatment-related severe adverse events **(D).** Other abbreviation as in Figure 1.

Continued on the next page

FIGURE 2 Continued

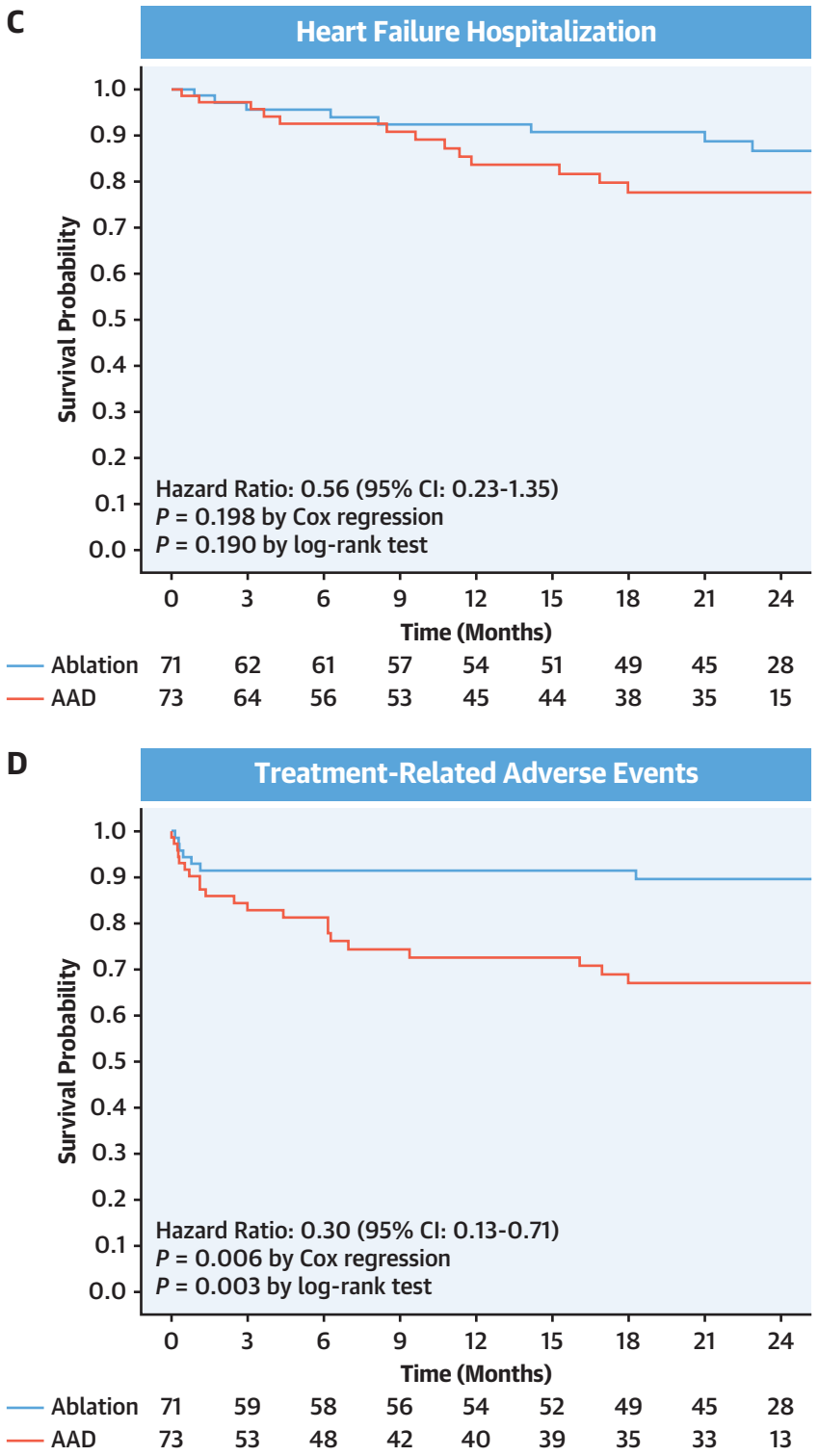


TABLE 5 Detailed Treatment-Related Adverse Events

AAD Strategy No vs Ablation	Patient No	Adverse Event	Time After Randomization, mo	Action, Comments
AAD				
3	24	Sinus bradycardia	1	Hospitalization, beta-blocker withdrawal
3	25	Sinus bradycardia and renal failure	<1	Hospitalization, upgrade CRT
3	30	Dyspnea	1	Amiodarone discontinuation
1	35	Slow VT (VTCL: 410 ms)	5	Hospitalization, ablation
1	36	Slow VT (VTCL: 380 ms)	7	Hospitalization, ablation
1	40	Bradycardia/intolerance	3	Amiodarone discontinuation
		Slow VT (VTCL: 370 ms)	4	Hospitalization, ablation
3	43	Hypothyroidism	7	Amiodarone discontinuation
1	58	Slow VT (VTCL: 400 ms)	17	Hospitalization, ablation
1	68	Hyperthyroidism	2	Amiodarone discontinuation
2	75	Slow VT (470)	9	Hospitalization, ablation
2	76	Slow VT (VTCL: 380 ms)	1	Hospitalization
3	80	Pulmonary toxicity	2	Amiodarone discontinuation, resolution
3	87	Incessant VT (VTCL: 400 ms)	1	Hospitalization, ablation
1	93	Incessant VT	1	Hospitalization
1	101	Slow VT (VTCL: 440 ms)	1	Hospitalization, ablation
		Pulmonary toxicity	7	Amiodarone discontinuation
3	104	Slow VT (VTCL: 370 ms)	5	Hospitalization, ablation
3	106	Slow VT (VTCL: 390 ms)	17	Hospitalization, ablation
2	128	Incessant VT	2	Hospitalization, ablation
3	133	Slow VT (VTCL: 470 ms)	1	Hospitalization, ablation
3	134	Incessant VT (VTCL: 420 ms)	7	Hospitalization
1	140	Incessant VT (VTCL: 380 ms)	1	Hospitalization
Ablation				
	21	Stroke	<1	Prolonged hospitalization, resolution
		Pseudoaneurysm	<1	Surgery, resolution
	44	Stroke	1	Hospitalization, resolution
	63	Cardiogenic shock	1	Hospitalization, resolution
	96	Incessant VT	1	Hospitalization/ablation
	97	Pericardial effusion	1	Pericardial drainage, resolution
	102	Incessant VT	1	Hospitalization, resolution
	143	Acute pulmonary edema	<1	Prolonged hospitalization, resolution

VTCL = ventricular tachycardia cycle length; other abbreviations as in Tables 1 and 2.

Ablation in Sinus Rhythm to Halt Ventricular Tachycardia), in which 90% of patients were shock-free.[7]

Substrate-based catheter ablation significantly reduced the primary endpoint by avoiding severe AAD-related complications. In the ablation group, electrical storms occurred in only 2.8% of patients during the follow-up, which is much lower than the rate of electrical storm reported (up to 30%) in secondary prevention patients.[15] Besides, substrate-based ablation proved to be safe as serious complications related to the procedure occurred in only 6 patients (8%), all of them resolved completely and there were no deaths in the first 30 days after ablation. These figures are reassuring and in agreement with previous randomized trials evaluating substrate-based prophylactic ablation where complication rates ranged between 2.8% and 8.7%.[7,8,10,16,17] In these trials, including ours, only 1 death occurred in more than 500 patients in the first 30 days of the ablation procedure. These data are in contrast with those reported in more complex clinical scenarios where early mortality can be up to 5%.[12] Two factors may contribute to the lower rate of complications: 1) prophylactic ablation is performed in patients in stable condition; and 2) the substrate-based strategy does not require the tachycardia to be induced multiple times. The conventional ablation strategy requires induction and mapping of VT that are generally poorly tolerated. Patients who underwent this strategy have more complications and recurrences in comparison with the strict substrate-based ablation.[14] The conventional approach could make procedures

longer, which has been related to increased hospital admissions for heart failure.[17] Importantly, no study or meta-analysis has shown better outcomes with the conventional strategy compared to the substrate-based ablation.[18,19] In our study, the ablation strategy based on substrate mapping and ablation, followed occasionally by programmed stimulation and ablation of the tachycardias that remained inducible, is very effective and has few complications as previously reported.[7,14]

Significant side effects are the main drawback of AAD. In the AAD group, 21 patients had severe complications attributed to the treatment (n = 18 were using amiodarone) leading to discontinuation of AAD, including 15 incessant and/or slow ICD undetected VT. Ten patients had a sustained VT below the detection rate of the ICD that lasted hours and required hospitalization because of hemodynamic deterioration. Slow and incessant VTs are well-known proarrhythmic complications consequence of slow conduction caused by AAD. Underdetection of ventricular arrhythmias occurred despite programming a cycle length cutoff 60 ms above the clinical VT cycle length as in the ablation group (**Table 2**). This AAD severe adverse event has been reported in the VANISH (Ventricular Tachycardia Ablation versus Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease) trial.[10] Probably 60 ms is not enough in patients receiving amiodarone to avoid this adverse event as suggested by a previous study.[20] Although it can be speculated that a simple lengthening of the cycle length cutoff in patients on AADs would have avoided this complication, this programming modification could bring about many inappropriate therapies. Additional tests such as measuring the induced tachycardia cycle length by noninvasive programmed stimulation or measuring the drug-induced change in the paced QRS duration may help to program a safer cutoff in patients receiving AADs.[21] In the ablation group only 2 patients presented with slow incessant VT soon after ablation, likely caused by modification without complete elimination of the arrhythmogenic substrate during the procedure. Differences in the incidence of slow VT not detected by the ICD could explain the differences in the estimated 2-year primary endpoint-free survival between the 2 study groups in relation to the index VT cycle length (Supplemental Figure 1).

Current international guidelines do not provide clear recommendations for preventing VT recurrences. Whereas the 2015 European Society of Cardiology guidelines propose either catheter ablation or AAD after a first episode (Class of Recommendation: Class IIa; Level of Evidence: B), the 2017 American College of Cardiology/American Heart Association guidelines do not specifically advocate initiating treatment after a single VT and propose a stepwise approach in patients with recurrent episodes, starting with antiarrhythmic medications as first choice (Class I, Level of Evidence: B) and catheter ablation if failure or intolerance (Class I, Level of Evidence: B), while considering its potential use as first-line therapy with a Class IIb (Level of Evidence: C) recommendation.[22,23] Based on these results, catheter ablation should be strongly considered before AAD as a first-line strategy for patients with ischemic cardiomyopathy and ventricular arrhythmias. The net beneficial effect of ablation is likely to grow over time, considering that the incidence of expected AAD side effects would tend to increase with longer follow-up.

STUDY LIMITATIONS. As in many VT ablation trials, enrollment was slower than expected and the population size was inferior to the estimation. Screening data were not collected, so we cannot provide insights into specific reasons for difficulties in enrollment. In our experience, as previously reported, the main limitation for recruitment was that a large number of patients had already started on AADs.[24] The steering committee decided to stop recruitment with no information regarding the results of the trial. Despite being a multicenter trial, only a few specialized centers participated, which may limit the generalization of our findings. Our study circumscribes to patients with ischemic cardiomyopathy and cannot be extrapolated to other substrates. Catheter ablation technologies have evolved over the course of the trial, and the recent multielectrode and contact force sensing catheters that could facilitate ablation were not routinely used. Some analyses were performed post hoc and should be considered only exploratory. Finally this study does not provide data on the appropriate time to treat patients with ICD therapies, but suggests that substrate ablation has less adverse events.

CONCLUSIONS

Substrate-based catheter ablation, performed in sinus rhythm and avoiding repeated VT induction, reduced the composite efficacy and safety endpoint of cardiovascular death, ICD shocks, heart failure hospitalization, and severe treatment-related adverse events in patients with ischemic heart disease and ICD shock or symptomatic VT compared to AAD.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with ischemic cardiomyopathy and either ICD shocks or symptomatic VT, substrate-based catheter ablation during sinus rhythm is associated with similar incidences of ICD therapies and mortality compared to AAD therapy, but fewer treatment-related adverse events and cardiac hospitalizations.

TRANSLATIONAL OUTLOOK: Further studies are needed to evaluate the efficacy of combining substrate-based ablation with AAD therapy in patients with ischemic cardiomyopathy.

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KEY WORDS antiarrhythmic drugs, substrate ablation, ventricular tachycardia

APPENDIX For supplemental text, tables, figures, and references, please see the online version of this paper.