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Safety and Outcomes of Ventricular Tachycardia Substrate Ablation During Sinus Rhythm

A Prospective Multicenter Registry

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ABSTRACT

OBJECTIVES This study sought to analyze safety and outcomes of ventricular tachycardia (VT) substrate ablation during sinus rhythm (SR), without baseline VT induction.

BACKGROUND Safety and outcomes after scar-related VT ablation during SR are not well known. Hemodynamic instability and need for electrical cardioversion can compromise safety of VT ablation procedures.

METHODS Four hundred twelve consecutive patients with structural heart disease undergoing VT ablation were included in a prospective multicenter registry. Substrate ablation during SR, without baseline VT induction, was the first step of the ablation procedure and the standard protocol. Scar dechanneling was the substrate ablation technique used. VT inducibility was tested after substrate ablation.

RESULTS VT induction protocol was negative after substrate ablation in 289 patients (70.1%), completing the procedure in SR. Procedure-related complication rate was 6.5%, including 1 death (0.2%). Thirty-day mortality after first VT ablation procedure was 1.7%. Overall survival was 95.8% and 88.6% at 1 and 3 years of follow-up, respectively. In a multivariable proportional hazards regression model, age ≥70 years (hazard ratio [HR]: 4.95 [2.59 to 9.47]; $p < 0.001$), chronic obstructive pulmonary disease (HR: 2.37 [1.24 to 4.52]; $p = 0.008$), left ventricular ejection fraction <30% (HR: 2.43 [1.37 to 4.33]; $p = 0.002$), and incomplete substrate ablation (HR: 2.37 [1.24 to 4.52]; $p = 0.026$) were independent predictors of overall mortality. At 12 months' follow-up, VT-free survival was 82.5% after 1 procedure and 87.8% after *n* procedures

CONCLUSIONS Substrate ablation during SR avoiding multiple VT induction has low procedure-related complications and low early mortality. Age, chronic obstructive pulmonary disease, and reduced left ventricular ejection fraction, but also incomplete substrate elimination, are predictors of mortality. (J Am Coll Cardiol EP 2020;6:1435–48)

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ABBREVIATIONS AND ACRONYMS

3D = 3-dimensional

ARVC = arrhythmogenic right ventricular cardiomyopathy

CC = conducting channel

ce-MDCT = contrast-enhanced multidetector computed tomography

CMR = cardiac magnetic resonance imaging

COPD = chronic obstructive pulmonary disease

ECG = electrocardiogram

EGM = electrogram

EGM-DC = electrogram with delayed components

HR = hazard ratio

HSC-EGM = hidden slow conduction electrogram

ICD = implantable cardioverter-defibrillator

ICM = ischemic cardiomyopathy

LAVA = local abnormal ventricular activity

LGE = late gadolinium enhancement

LV = left ventricular

LVEF = left ventricular ejection fraction

NICM = nonischemic cardiomyopathy

RF = radiofrequency

RV = right ventricular

SHD = structural heart disease

SR = sinus rhythm

VT = ventricular tachycardia

Catheter ablation has become an essential tool in the treatment of ventricular arrhythmias in patients with structural heart disease (SHD) providing improved outcomes in recurrent tachycardias despite antiarrhythmic drugs (1). Various randomized clinical trials have shown that early indication of catheter ablation reduces the incidence of appropriate implantable cardioverter-defibrillator (ICD) shocks (2,3). However, preventive ablation before ICD implantation has not shown a reduction in mortality (4). Ventricular tachycardia (VT) ablation techniques have evolved during the recent years. Substrate ablation techniques permit to abolish multiple VT circuits irrespective of their inducibility or hemodynamic tolerability improving outcomes with respect to clinical VT ablation (5). These advances have expanded the indications for VT ablation in patients with SHD.

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Diverse ablation targets and approaches have been proposed for VT substrate ablation (6–8). Beyond the differences in the substrate ablation technique, inhomogeneous procedure workflows (i.e., conventional ablation of clinical vs. all inducible VT, use of ventricular support devices) are used for scar-related VT ablation. Substrate ablation has been shown to be superior to clinical and stable VT ablation (5); however, induction, mapping, and ablation during ongoing VT continues being part of the standard ablation protocol. In recent years, the use of ventricular assist devices has been proposed to allow mapping multiple unstable VTs, with mixed results in efficacy and safety (9–11). On the other hand, in a previous single-center randomized trial, we observed that the standard approach of VT induction and mapping before substrate ablation increases the procedure duration and requirements (radiation exposure and the need for electrical cardioversion) without improving the results (12). In addition, the hemodynamic instability and the need for repeated electrical cardioversions could negatively influence the long-term outcomes in the same way that ICD shocks have been proven to be associated with increased mortality in ICD carriers (13).

Limited data are available regarding the safety and long-term prognosis of patients with VT and SHD undergoing substrate ablation (14–18). The aim of this prospective study is to analyze the safety, outcomes, and predictors of mortality in patients with SHD who undergo a VT substrate ablation during stable rhythm.

METHODS

MULTICENTER REGISTRY OF SUBSTRATE ABLATION DURING SINUS RHYTHM. This is a prospective multicenter observational study of substrate-guided VT ablation during sinus rhythm. The aim of this registry is to evaluate the safety and short- and long-term outcomes of VT substrate ablation, by means of scar dechanneling, in patients with SHD following an ablation protocol starting with substrate ablation during stable rhythm (sinus or paced).

PATIENT POPULATION. All consecutive patients (N = 412) undergoing scar-related VT ablation in 6 centers were included. All patients provided written informed consent to participate. The local ethics committees approved the study. Inclusion criteria were having a sustained monomorphic VT documented by electrocardiogram (ECG) or ICD recording and SHD. Patients with etiologies of ischemic cardiomyopathy (ICM), nonischemic cardiomyopathy (NICM), and arrhythmogenic right ventricular (RV) cardiomyopathy (ARVC) were included. Patients with ventricular arrhythmias due to reversible causes were excluded. Patients presenting with an arrhythmic storm were treated with antiarrhythmic drugs, heart failure medication, sedation and mechanical ventilation, and mechanical support if needed until rhythm stabilization before submitting them to VT ablation, which was done whenever possible during sinus rhythm (SR) or ventricular pacing (in the case of bradycardia or atrioventricular block).

PRE-PROCEDURAL EVALUATION. All patients received a complete clinical evaluation. The ECG of the clinical VT or the ICD morphology channel was also analyzed (depending on ECG availability). All the patients were studied with general biochemistry, blood count, and coagulation times, as well as transthoracic and/or transesophageal echocardiogram. Recommended tests at the discretion of the attending physician included late gadolinium enhancement (LGE) cardiac magnetic resonance imaging (CMR) and/or ECG-gated contrast-enhanced multidetector computed tomography (ce-MDCT). Wall thinning at ce-MDCT was used to estimate infarct transmurality. LGE-CMR images were post-processed with ADAS3D imaging (ADAS 3D SL, Barcelona, Spain) platform using a previously described method (19,20). In patients in whom LGE-CMR was acquired, 3-dimensional (3D) pixel signal

intensity maps and 3D border zone corridors were obtained to identify and characterize the scar areas.

PROCEDURE TECHNIQUES. The procedure was performed under conscious sedation or general anesthesia. An invasive radial arterial line was obtained for blood pressure control. Transseptal approach was preferred for left ventricular (LV) endocardial mapping (BRK needle, Medtronic, Minneapolis, Minnesota). After left chamber access, heparin was administered intravenously to maintain an activated clotting time >300 s. The CARTO 3 system (Biosense Webster, Diamond Bar, California) was the navigation system most used in this registry (95.9%). A 3.5-mm-tip open-irrigated ablation catheter (ThermoCool NaviStar or SmartTouch, Biosense Webster) and/or multipolar catheter (PentaRay, Biosense Webster) were used for mapping. A 40 to 50 W power limit with 26 to 30 ml/min irrigation rate (17 ml/min at the epicardium) was recommended for ablation. Each radiofrequency application lasted 30 to 60 s, depending on the local electrogram (EGM) response/abolition. Epicardial mapping criteria were as follows: 1) underlying disease with a high probability of having epicardial substrate (ARVC or Chagas disease); 2) epicardial hyperenhancement on LGE-CMR; 3) endocardial mapping not identifying endocardial scar; 4) ECG of clinical or induced VT, suggesting an epicardial origin; and 5) after previous endocardial ablation failure. First-line endoepicardial mapping in patients with ICM and transmural infarction was decided at the discretion of the attending physician.

PROCEDURAL PROTOCOL. The ablation procedure was focused on the identification and elimination of the arrhythmogenic substrate during SR. Scar dechanneling was the technique used in all patients. The mapping and ablation protocol is detailed in a previous publication (21). Briefly, the first step of the procedure was a high-density endocardial (and epicardial when it was appropriate) electroanatomic mapping acquisition during SR or RV apex pacing.

In patients in whom LGE-CMR was acquired, 3D maps were included in the navigation system to improve substrate definition. Anatomic reconstructions of the ascending aorta or the RV with landmarks such as the ostium of the left coronary artery were used for the coregistration between magnetic resonance imaging and/or CT scan and electroanatomic mapping.

EGMs with delayed components (EGM-DCs) were tagged and dichotomously classified as entrance or inner conducting channel (CC) points, depending on delayed-component precocity during SR (21,22). EGM-DC was defined as any abnormal electrogram (<3 mV, >70 ms, fractionated or with delayed components) with double or multiple components distinguishable from the far-field electrogram without requiring the presence of an isoelectric line between the far-field and the local component. CCs were considered as ≥2 consecutive EGM-DCs within the scar area, connecting with healthy tissue and showing an activation sequence of the delayed component, although the individual delineation of the CCs was not required for mapping. No absolute delay was required with respect to the QRS but only the identification of at least 2 components, 1 far-field (usually of higher voltage and lower frequency) and another delayed local component (usually low voltage and high frequency) without needing an isoelectric line among them. CC entrances were defined as EGM-DC in which fusion between the local potential and the far-field was observed.

During the inclusion period of the study, the double-extrastimuli technique was implemented in the substrate identification protocol (23). EGMs with >3 deflections not meeting criteria for fractionated EGM (duration <133 ms) identified within the scar area or in the myocardium surrounding the scar area were considered potential hidden slow conduction EGM (HSC-EGM). At sites where HSC-EGM was suspected, a double extrastimuli from RV was delivered at a ventricular effective refractory period of +60 ms and +40 to +20 ms, respectively (23). Response was considered positive when the local potential delayed and split from the far-field signal.

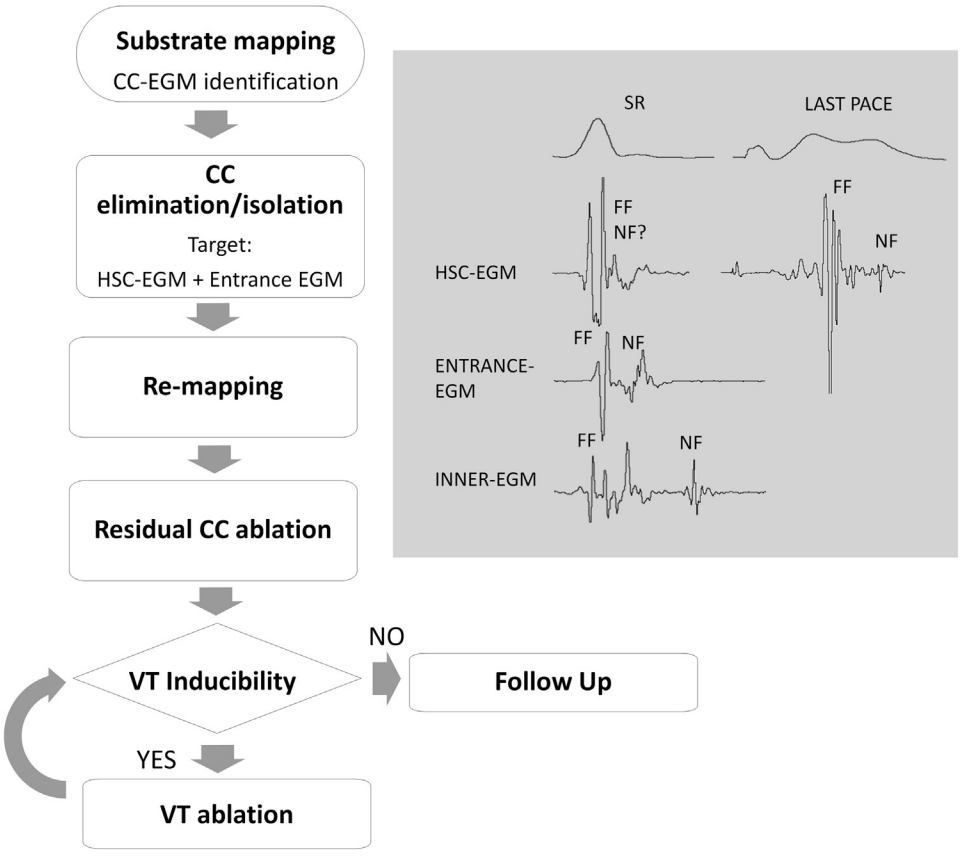
All CC entrances (mostly located at the periphery of the scar) and HSC-EGM identified during substrate mapping were targeted for ablation. Backup radiofrequency (RF) applications were delivered inside the scar area when RF lesions at the CC entrance did not eliminate internal EGM-DCs.

A remapping was used to target residual EGM-DCs with the same approach used previously. The absence/persistence of EGM-DCs that could not be eliminated was reported.

Programmed RV apex stimulation with 3 basal cycle lengths (600, 500, and 430 ms); up to 3 ventricular extrastimuli decremented until refractoriness or 200 ms was used for VT induction after substrate ablation. In the case of residual sustained monomorphic VT induction, it was targeted for ablation. Inducibility was retested after each residual VT ablation. **Figure 1** shows the procedural protocol flowchart.

PROCEDURAL ENDPOINT. Procedural endpoint was double: 1) complete eliminating EGM-DCs (substrate ablation endpoint); and 2) achieving noninducibility

FIGURE 1 Scar-Related VT Ablation Procedure Workflow



The ablation procedure was focused on substrate ablation during sinus rhythm (SR) without baseline VT induction. Electrograms (EGMs) with delayed components (EGM-DC) are classified as entrance or inner conducting channel (CC) points depending on delayed-component (near-field [NF]) precocity during SR. At sites where hidden slow conduction (HSC-EGM) was suspected, a double ventricular extrastimuli was delivered. Programmed ventricular stimulation was used for VT induction after remapping and residual EGM-DC ablation. Induced VT was targeted. FF = far-field electrogram; VT = ventricular tachycardia.

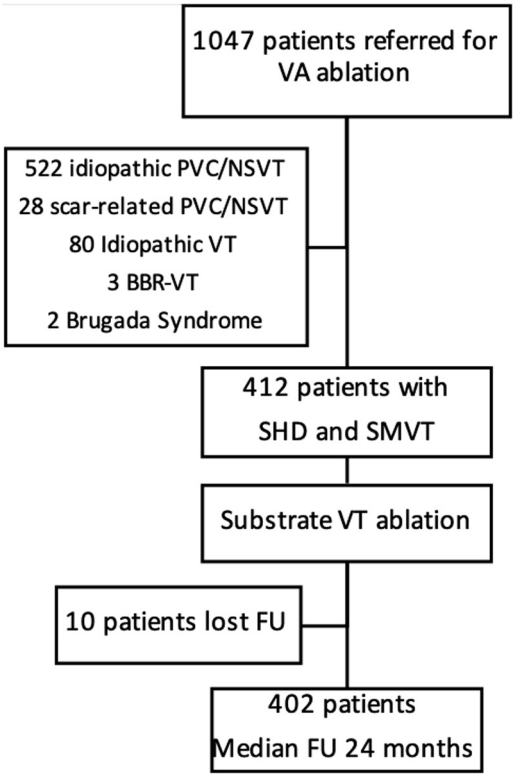
of any VT. Acute procedural success was considered when no sustained monomorphic VT was inducible. Incomplete substrate ablation was considered in 3 scenarios: 1) persistence of residual EGM-DCs or HSC-EGMs after ablation; 2) mid-myocardial septal scar considered nonreachable; and 3) epicardial non-accessibility in patients with evidence of epicardial substrate according to cardiac imaging.

FOLLOW-UP. The patients included in the study were followed every 6 months. Device programming was performed at the discretion of the treating physician. At each visit, the ICD was interrogated and the clinical status evaluated. Noninducible patients after ablation did not receive antiarrhythmic treatment during the follow-up, excluding beta-blockers in case of clinical indication or in order to maintain sinus rhythm in nonpermanent atrial fibrillation patients. Otherwise, the recommended antiarrhythmic drugs were sotalol or amiodarone.

Ventricular arrhythmia-free survival was the primary endpoint. Any episode of sustained VT (>30 s) or appropriate ICD therapy was considered VT recurrence. Data on total mortality, cardiac mortality, and sudden death were also collected. Early and late mortality were defined as death occurring within 30 days or later from the index procedure, respectively. Procedure-related complications and admissions for cardiovascular causes were collected.

STATISTICAL ANALYSIS. Values are expressed as percentage, mean ± SD, or median (interquartile range) when appropriate. The PAINESD mortality risk score after VT ablation was analyzed in this population (17). The Student's *t*-test was used to compare continuous data and Wilcoxon signed rank

FIGURE 2 Patient Flow Diagram



During the registry period, 1,047 patients were referred for ventricular arrhythmia ablation in the participating centers. A total of 412 patients with sustained monomorphic VT or appropriate implantable cardioverter-defibrillator therapies and SHD were included. BBR-VT = bundle branch re-entrant ventricular tachycardia; FU = follow-up; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular contraction; SHD = structural heart disease; SMVT = sustained monomorphic ventricular tachycardia; VA = ventricular arrhythmia; VT = ventricular tachycardia.

TABLE 1 Baseline Characteristics of the Patient Population (N = 412)

Age, yrs	64 ± 14
Men	376 (91.3)
Hypertension	265 (64.3)
Diabetes	104 (25.2)
LVEF, %	38 ± 13
ICM, %	271 (65.8)
ICD	250 (60.7)
AAD	359 (87.1)
β-Blockers	293 (71.1)
Class I	18 (4.4)
Class III	230 (55.8)
VT storm	133 (32.3)
Clinical VT CL, ms	356 ± 110

Values are mean ± SD or n (%).
AAD = antiarrhythmic drugs; CL = cycle length; ICD = implantable cardiac defibrillator; ICM = ischemic cardiomyopathy; VT = ventricular tachycardia.

test and Mann-Whitney *U* test for nonnormally distributed data. Competing risks analysis was used to estimate the cumulative incidence of VT recurrence. Aalen-Johansen estimators of cumulative incidence functions were used to estimate the incidence of VT recurrence and death. Gray's test was used for between-groups comparisons. Variables selected from the univariate analyses ($p \leq 0.10$) were entered into multivariable Cox proportional hazards regression models to estimate predictors of mortality and VT recurrence. Procedural endpoint variables were included separately in the multivariable analysis because they were correlated and therefore different multivariate models were needed. Due to relative low number of events, particularly cardiac death, we have added a regression model with only pre-operative characteristics. A value of $p < 0.05$ was considered significant. Statistical analysis was performed using SPSS Statistics 23 software (IBM, Chicago, Illinois). Analysis of competing risks has been carried out with software R (R Core Team, 2019, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PATIENT CHARACTERISTICS. During the registry period 412 consecutive patients with SHD undergoing a first ablation of scar-related VT were included in 6 centers. Figure 2 shows the flow diagram of patients who underwent ventricular arrhythmia ablation during the registry period. Forty-one patients (9.9%) had a second procedure, and 3 patients (0.7%) a third procedure. Clinical baseline characteristics are summarized in Table 1. A total of 271 patients (65.8%) had ICM, 56 (13.6%) had ARVC, and 85 (20.6%) had NICM. In the subgroup of NICM patients, 48 (56.4%) had dilated cardiomyopathy, 9 (10.6%) had hypertrophic cardiomyopathy, 6 (7.1%) had left dominant arrhythmogenic cardiomyopathy, 6 (7.1%) had hypertensive cardiomyopathy, 2 (2.4%) had Chagas disease, 2 (2.4%) had post-myocarditis, and 12 (14.1%) had other. Patients had a median of 4 VT episodes within 6 months before ablation, and 32.3% had arrhythmic storm or incessant VT.

CARDIAC IMAGING BEFORE ABLATION. Pre-procedural LGE-CMR was available in 199 patients (48.3%). In 110 of them (55.3%), 3D DE-CMR–derived images of

TABLE 2 Procedural Data (N = 412)

Procedure time, min	212 ± 72
Fluoroscopy time, min	20 ± 12
Epicardial mapping	126 (30.6)
Number of endo map points	
Multipolar catheter	1471 ± 1,635
Ablation catheter	465 ± 298
Number of inner CC EGMs/patient	34 ± 34
Number of CC entrance EGMs/patient	11 ± 12
Radiofrequency ablation time, min	21 ± 14
Complication	28 (6.8)
Heart block	6
Puncture hematoma	5
Cardiac tamponade	6
Stroke/TIA	3
Phrenic nerve palsy	3
Hemodynamic decompensation	3
Transient ST-segment elevation	1
Death	1
Procedural endpoint	
Complete substrate elimination	319 (77)
Partial acute procedural success*	3,381 (92.3)
Acute procedural success†	310 (75.2)

Values are mean ± SD or n (%). *Clinical VT noninducible. †Noninducibility of any VT.

CC = conducting channel; EGM = electrogram; TIA = transient ischemic attack; VT = ventricular tachycardia.

the ventricles and myocardial scars were integrated into the navigation system to guide VT substrate ablation. A total of 167 patients (40.5%) underwent ce-MDCT before the procedure for integration purposes. Both imaging modalities were used in 57 patients (13.9%). Neither ce-MDCT nor LGE-CMR was obtained in 125 patients (30.3%).

PROCEDURAL DATA. The procedural characteristics are shown in Table 2. Transseptal puncture was the preferred approach for LV endocardial mapping (62.3%). Combined retroaortic and transseptal LV access was used in 47 patients (11.4%).

Percutaneous pericardial access for epicardial mapping during the first procedure was attempted in 133 patients and performed in 126 patients (30.6%). Pericardial access was obtained in 75% of ARVC (n = 42), 40% of NICM (n = 34), and 18.45% of ICM patients (n = 50).

Multipolar mapping was performed with multipolar catheter in 100 of patients (24%): 5 radiating spines with a 2-6-2-mm interelectrode distance (PentaRay) in 86 patients and 64-pole mini-basket catheter (IntellaMap Orion, Boston Scientific, Marlborough, Massachusetts) in 14 patients. No LV assist devices were used in any patient during the procedure.

SUBSTRATE MAPPING AND ABLATION. Mechanically induced or spontaneous VT during substrate mapping occurred in 64 patients (15.5%). These VTs were terminated per protocol (with burst or cardioversion), but in 22 patients (5.3%) with good hemodynamic tolerance, activation mapping was performed for ablation.

A median of 834 ± 1,592 points were collected in each electroanatomic map. The data on abnormal EGMs are presented in Table 2. Double-extrastimulus technique was used in 218 patients (53%), identifying a mean of 8.12 ± 11 HSC-EGMs per patient. In the remap obtained after the first ablation round, a mean of 4 ± 8 residual EGM-DCs were identified. The mean RF time, including the time needed for substrate ablation and for residual inducible VT ablation, was 21 ± 14 min.

VT INDUCTION, MAPPING, AND ABLATION. The VT induction protocol was negative after substrate ablation in 289 patients (70.1%); therefore, the procedure was finished. A mean of 1.28 ± 0.7 residual VTs were induced in the remaining patients. VT induction was not performed in 1 patient due to hemodynamic instability. Pace mapping or activation/entrainment mapping was used for residual VT ablation depending on hemodynamic tolerance. After residual VT ablation, the ventricular induction protocol was repeated (a median of 2 [interquartile range: 1 to 2] inductions in patients with residual VT). Acute procedure success was obtained in 310 patients (75.2%). VT was inducible at the end of the procedure in 9 ARVC (16.1%), 64 ICM (23.6%), and 29 NICM (34.1%) patients (p = 0.042).

PROCEDURE-RELATED COMPLICATIONS. Procedure-related complications occurred in 28 patients (6.8%). Three patients had severe acute hemodynamic decompensation that was resolved with standard support measures and required procedure termination. One patient died 2 h after the procedure due to pulseless electrical activity not responding to advanced resuscitation maneuvers. Mechanical complications were ruled out with echocardiography in this patient. All complications are shown in Table 2.

OUTCOMES: EARLY AND LATE MORTALITY. Thirty-day mortality after the first VT ablation procedure was 1.7% (n = 7). Of these, 3 patients died before hospital discharge: 1 patient due to refractory cardiogenic shock, another patient with advanced heart failure and recurrent VT storm died due to voluntary withdrawal of life support, and 1 procedure-related death described in the preceding text. Early VT-related death occurred in 1 patient

TABLE 3 Univariate and Multivariate Analysis of Risk Factors Associated With Overall Mortality

	Univariate HR (95% CI)	p Value	Multivariable I HR (95% CI)	p Value	Multivariable II HR (95% CI)	p Value	Multivariable III HR (95% CI)	p Value
Age ≥70 yrs	4.42 (2.55–7.66)	<0.001	4.64 (2.43–8.84)	<0.001	4.95 (2.59–9.47)	<0.001	4.63 (2.43–8.83)	<0.001
ICM	2.29 (1.23–4.26)	0.012	0.895 (0.42–1.87)	0.768	0.98 (0.46–2.06)	0.960	0.93 (0.44–1.93)	0.846
CKD	3.25 (1.80–5.87)	<0.001	1.60 (0.845–3.05)	0.148	1.58 (0.83–3.02)	0.164	1.67 (0.87–3.19)	0.119
COPD	3.48 (1.87–6.49)	<0.001	2.18 (1.15–4.10)	0.016	2.37 (1.24–4.52)	0.008	2.17 (1.15–4.10)	0.016
Diabetes	1.98 (1.15–3.4)	0.013	1.42 (0.72–2.79)	0.307	1.45 (0.73–2.87)	0.289	1.39 (0.70–2.75)	0.337
HBP	1.93 (1.08–3.46)	0.026	0.85 (0.417–1.74)	0.662	0.75 (0.36–1.56)	0.445	0.86 (0.42–1.76)	0.696
LVEF <30%	2.25 (1.35–3.75)	0.002	2.23 (1.26–3.92)	0.005	2.43 (1.37–4.33)	0.002	2.23 (1.26–3.92)	0.005
NYHA functional class III–IV	2.32 (1.29–4.15)	0.005	1.31 (0.65–2.66)	0.443	1.40 (0.69–2.82)	0.347	1.31 (0.65–2.66)	0.444
Acute procedural success*	0.56 (0.34–0.94)	0.023					0.68 (0.36–1.30)	0.251
Incomplete substrate ablation	1.87 (1.04–3.34)	0.035			2.37 (1.24–4.52)	0.026		

*Noninducibility of any VT.

CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; HBP = high blood pressure; HR = hazard ratio; ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; VT = ventricular tachycardia.

(0.24%). The PAINESD risk score was not significantly different between patients with early or late mortality (14.57 ± 6 vs. 12.3 ± 5; p = 0.41).

During a median follow up of 24 months (interquartile range: 7 to 39 months), 63 patients (15.3%) died (49 of these patients had ICM and 14 NICM). Overall survival was 95.8% and 88.6% at 1 and 3 years' follow-up, respectively. In an univariate analysis, age, chronic obstructive pulmonary disease (COPD), hypertension, chronic kidney disease, left ventricular ejection fraction (LVEF) <30%, diabetes, New York Heart Association (NYHA) functional class III to IV, ICM, unsuccessful procedure, and incomplete substrate ablation were associated with global mortality (Table 3). In a multivariable proportional hazards regression model, age ≥70 years (hazard ratio [HR]: 4.95; 95% confidence interval (CI): 2.59 to 9.47; p < 0.001), COPD (HR: 2.37; 95% CI: 1.24 to 4.52; p = 0.008), LVEF <30% (HR: 2.43; 95% CI: 1.37 to 4.33; p = 0.002), and incomplete substrate ablation (HR: 2.37; 95% CI: 1.24 to 4.52; p = 0.026) were independent predictors of global mortality. Survival curves according to complete or incomplete substrate elimination are shown in Figure 3.

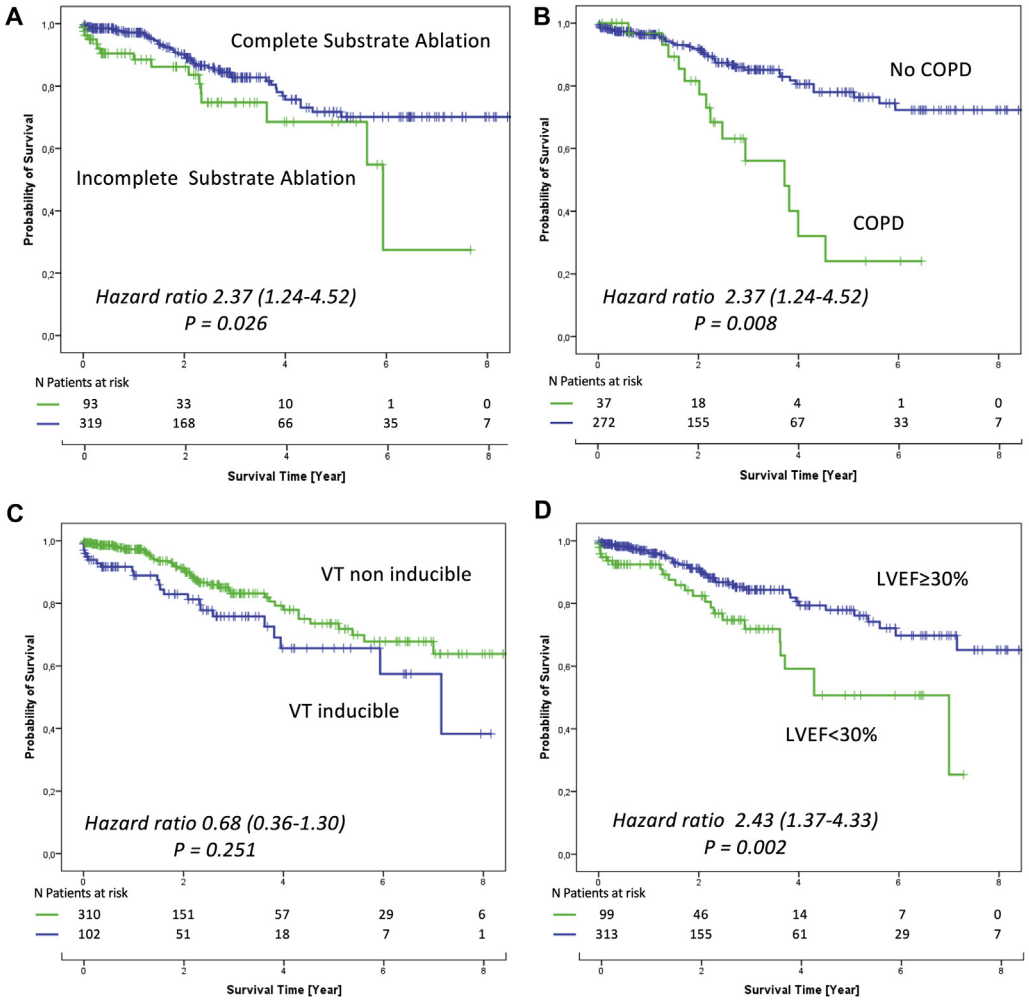
Cardiac mortality occurred in 24 patients. In a univariate analysis (Table 4), age, incomplete substrate ablation, chronic kidney disease, diabetes, LVEF <30%, NYHA functional class III to IV, electrical cardioversion during procedure, and successful procedure were related to cardiac mortality. In a multivariate analysis, age ≥70 years (HR: 4.18; 95% CI: 1.63 to 10.72; p = 0.003), LVEF <30% (HR: 3.83; 95% CI: 1.61 to 9.11; p = 0.002), short-term procedure success (HR: 0.29; 95% CI: 0.13 to 0.67; p = 0.003), and incomplete substrate ablation (HR: 3.44; 95% CI: 1.36 to 8.65; p = 0.009) were associated with cardiac mortality.

OUTCOMES: VT RECURRENCE. At the end of the follow-up period, cumulative VT-free survival was 72.2%. One-year VT-free survival was 82.5% after 1 procedure and 87.8% after *n* procedures. At the end of follow-up, 32% of patients were taking amiodarone, 14% sotalol, and the rest (55%) were free of antiarrhythmic drugs. In a multivariate analysis (Table 5), VT inducibility at the end of the procedure, incomplete substrate elimination, LVEF, and arrhythmic storm or incessant VT were predictors of VT recurrence after the first procedure. The cumulative VT-free survival curves according to the procedural endpoints (noninducibility and substrate elimination) are shown in Figure 4. There were no differences in VT recurrence rate between centers (log rank p = 0.445). VT recurrence rate was 25.5% in survivors and 38.7% in patients who died during follow-up. VT recurrence was not associated with global mortality in univariate analysis (HR: 1.38; 95% CI: 0.83 to 2.29; p = 0.212). VT recurrence rate was not significantly different among patients with ICM, NICM, or ARVC (p = 0.130), although there is a trend toward a higher VT recurrence in nonischemic patients. Cumulative VT-free survival curves depending on the etiology of the SHD are shown in Figure 5.

DISCUSSION

The main findings of the study are: 1) VT ablation based on substrate elimination during stable rhythm is safe and effective, and has reproducible results; 2) with this approach, hemodynamic decompensation

FIGURE 3 Predictors of All-Cause Mortality



Overall survival after **(A)** complete and incomplete substrate ablation, **(B)** presence of chronic obstructive pulmonary disease (COPD), **(C)** inducibility of any VT after the procedure, and **(D)** severe left ventricular dysfunction. LVEF = left ventricular ejection fraction; VT = ventricular tachycardia.

was uncommon (none of the patients required a ventricular assist device), and early mortality was low; 3) complete substrate elimination is associated with improved survival; and 4) both procedural endpoints (complete substrate ablation and non-inducibility) are predictors of VT recurrence.

PATIENT AND PROCEDURAL FEATURES. In this prospective registry of consecutive patients with SHD undergoing VT ablation, the characteristics of the patient population are comparable to those published in previous retrospective registries. The majority of patients were men (mean age 64 years) with ICM and a LVEF <30% in one-quarter of the population (excluding ARVC patients) (24). Imaging techniques, particularly LGE-CMR, were frequently used to plan and/or guide VT ablation (61% of patients underwent LGE-CMR and/or ce-MDCT before the procedure). Epicardial access was performed in 31% of patients, a higher proportion than in previous series (i.e., 6% to 7% of patients) (17,24). Although increased risk is expected if an epicardial ablation in addition to an endocardial one is performed, the complication rate (6.8%) was inferior to the rates reported in the

TABLE 4 Univariate and Multivariable Analysis of Risk Factors Associated With Cardiac Mortality

	Univariate HR (95% CI)	p Value	Multivariable I HR (95% CI)	p Value	Multivariable II HR (95% CI)	p Value	Multivariable III HR (95% CI)	p Value
Age ≥70 yrs	3.53 (1.52–8.22)	0.003	2.58 (0.82–8.15)	0.105	4.18 (1.63–10.72)	0.003	4.33 (1.77–10.61)	0.001
CKD	4.25 (1.60–11.32)	0.004	2.15 (0.75–6.16)	0.151	2.16 (0.76–6.17)	0.149	2.54 (0.86–7.50)	0.092
Diabetes	2.51 (1.11–5.64)	0.026	1.62 (0.54–4.87)	0.384	1.58 (0.52–4.83)	0.417	1.53 (0.49–4.75)	0.461
LVEF <30%	2.79(1.25–6.19)	0.011	2.72(1.00–7.41)	0.049	3.83 (1.61–9.11)	0.002	3.33 (1.47–7.56)	0.004
NYHA functional class III–IV	3.88 (1.71–8.80)	0.001	2.84 (0.99–8.18)	0.052	2.14 (0.71–6.50)	0.177	2.02 (0.65–6.24)	0.222
Electrical cardioversion during procedure	2.69 (1.20–6.03)	0.016			1.15 (0.42–3.10)	0.784	0.88 (0.29–2.70)	0.829
Acute procedure success*	0.29 (0.13–0.65)	0.003					0.29 (0.13–0.67)	0.003
Incomplete substrate ablation	2.70 (1.11–6.59)	0.028			3.44 (1.36–8.65)	0.009		

*Noninducibility of any VT.
Abbreviations as in Table 3.

published reports (8% to 10%) (25). The protocol was homogeneous among centers and focused on substrate-guided ablation (scar dechanneling technique) during stable SR or ventricular pacing, avoiding prolonged mapping during VT to minimize the risk of hemodynamic decompensation and the need for electrical cardioversion. As a result, 74% of patients had no VT inducible after substrate ablation, completing the entire procedure in stable rhythm. Only 4 patients (0.97%) had complications related to hemodynamic decompensation.

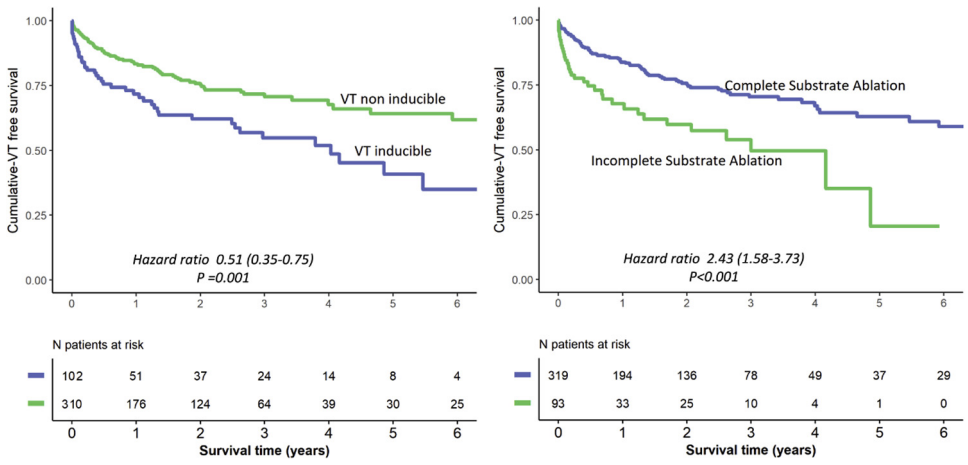
ROLE OF VT MAPPING IN SUBSTRATE-GUIDED ABLATION PROCEDURES. Substrate ablation techniques emerged to permit ablation of hemodynamically nontolerated or nonsustained VTs. Gradually, substrate modification has been getting a more prominent role in VT ablation procedures. In the VISTA (Ablation of Clinical Ventricular Tachycardia Versus Addition of Substrate Ablation on the Long Term Success Rate of VT Ablation) randomized trial, extensive substrate ablation proved to be superior to clinical and stable VTs ablation by obtaining a lower VT recurrence rate at 12 months (15.5% vs. 48.3%) (5). Although the relevance of the substrate elimination or modification in VT ablation procedures is already recognized, the exact place given to the substrate modification during the procedure is not yet well-defined. Unlike the more extended practice, in this registry, the induction protocol was performed only after substrate ablation aiming to acutely evaluate the effect of substrate modification and, when positive, to help unmask undetected substrate or help decide whether to access unmapped areas (i.e., epicardium). The strategy of initial mapping and ablation of clinical VT and all hemodynamically tolerated VTs is commonly used. In a recent series of patients undergoing scar-related VT ablation following this strategy, 11% had acute hemodynamic decompensation that was associated with increased mortality (26). In the present series in which the substrate ablation was done without VT induction at the beginning of the procedure, hemodynamic decompensation occurred only in 0.97% of patients. In a previous

TABLE 5 Univariate and Multivariable Analysis of Variables Associated With VT Recurrence

	Univariate HR (95% CI)	p Value	Multivariable I HR (95% CI)	p Value	Multivariable II HR (95% CI)	p Value	Multivariable III HR (95% CI)	p Value
LVEF	0.97 (0.96–0.99)	0.002	0.97 (0.96–0.99)	0.007	0.97 (0.96–0.99)	0.006	0.97 (0.96–0.99)	0.008
NYHA functional class III–IV	1.67 (1.05–2.67)	0.039	1.34 (0.82–2.19)	0.229	1.20 (0.70–2.05)	0.506	1.28 (0.77–2.12)	0.329
VT storm	1.63(1.10–2.40)	0.013	1.53(1.03–2.27)	0.036	1.52 (0.99–2.33)	0.053	1.52 (1.02–2.27)	0.038
Electrical cardioversion	1.50 (1.02–2.19)	0.037			1.22 (0.80–1.87)	0.344	0.95 (0.60–1.51)	0.854
Acute procedure success*	0.49 (0.33–0.73)	<0.001					0.51 (0.35–0.75)	0.001
Incomplete substrate ablation	2.69 (1.77–4.10)	<0.001			2.43 (1.58–3.73)	<0.001		

*Noninducibility of any VT.
Abbreviations as in Table 3.

FIGURE 4 Predictors of VT Recurrence



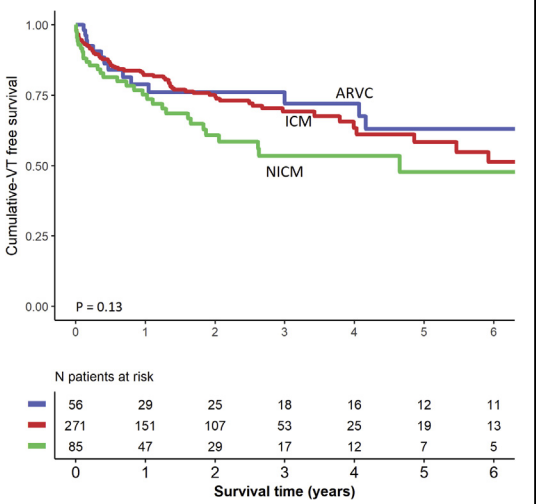
Event-free survival curves estimated with competing risk analysis compare the cumulative probability of VT recurrence according to procedural endpoints: VT inducibility and complete substrate elimination. Incomplete substrate ablation and VT inducibility after ablation were independent predictors of VT recurrence. VT = ventricular tachycardia.

randomized study, VT induction and mapping before substrate ablation proved to prolong the procedure and fluoroscopy time, and the need of electrical cardioversion without improving ablation results (12). The use of LV assist devices has been proposed to facilitate mapping of multiple unstable VTs, although probably at higher cost and complication risk (10). The rate of major complications ranged from 11% to 32% in studies in which VT ablation was performed using a percutaneous LV assist device (9,11,27). A recent meta-analysis has found no benefit in terms of mortality, short-term procedural success, or VT recurrence by using percutaneous LV assist devices during VT ablation (10).

COMPARISON WITH OTHER SUBSTRATE MODIFICATION TECHNIQUES. Targeting the EGMs that qualify to be considered the CC entrances into the scar aims to optimize the procedure by minimizing the RF ablation time. The RF ablation time was 21 min, less than that reported with local abnormal ventricular activity (LAVA) ablation (36 min) or scar homogenization (68 min) with comparable results: 1-year VT-free survival after a single procedure of 82.7% with scar dechanneling in the present multicenter study, 73% with LAVA ablation, and 84.5% with scar homogenization (5,15). Recently, Aziz et al. (28) have shown good ablation results minimizing RF time by targeting deceleration zones identified as isochronal crowding during baseline rhythm. The functional mapping of the substrate to be complete may require the use of extrastimuli with a short coupling interval to reveal areas with hidden slow conduction (23).

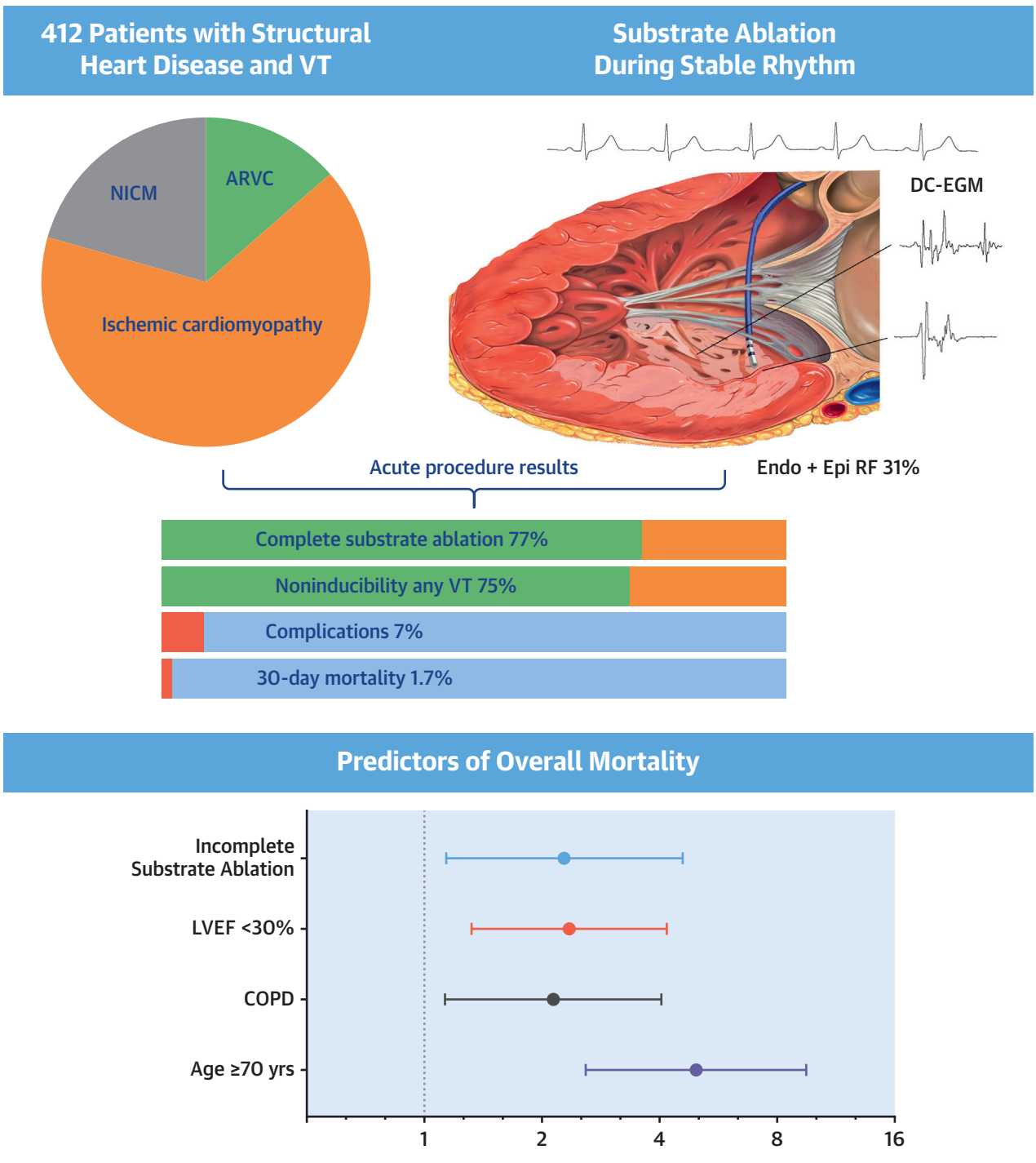
PREDICTORS OF OUTCOMES AFTER SUBSTRATE-GUIDED ABLATION. Most of the published reports

FIGURE 5 VT Recurrence and Underlying Heart Disease



VT recurrence–free survival curves estimated with competing risk analysis after substrate ablation according to underlying cause of cardiomyopathy shows no statistically significant differences, although there is a trend towards a higher VT recurrence in NICM patients. ARVC = arrhythmogenic right ventricular cardiomyopathy; ICM = ischemic cardiomyopathy; NICM = nonischemic cardiomyopathy; VT = ventricular tachycardia.

CENTRAL ILLUSTRATION **Prospective Multicenter Registry of Substrate Ablation During Stable Rhythm Without Baseline Ventricular Tachycardia Induction**



Fernandez-Armenta, J. et al. J Am Coll Cardiol EP. 2020;6(11):1435–48.

Information on the underlying heart disease is shown in the **top left**. **(Middle)** Complete substrate ablation and noninducibility of any VT was achieved in 77% and 75% of patients, respectively, with 7% of procedure related complications. 30-day mortality was 1.7%. **(Bottom)** Incomplete substrate ablation, LVEF, COPD, and age were predictors of overall mortality. ARVC = arrhythmogenic right ventricular cardiomyopathy; COPD = chronic obstructive pulmonary disease; DC-EGM = electrogram with delayed components; ICM = ischemic cardiomyopathy; LVEF = left ventricular ejection fraction; NICM = nonischemic cardiomyopathy; RV = right ventricular; VT = ventricular tachycardia.

regarding outcomes after VT ablation have been focused on VT recurrences (5,29). Several clinical predictors of early mortality have been identified in a large retrospective registry of patients who underwent VT ablation, substrate-based in the majority (17). Low LVEF, chronic kidney disease, VT storm, unmappable VTs, and post-procedural VT recurrence were predictors of early mortality (17). The PAINESD score has been proposed to identify patients at risk of early mortality that would likely benefit from substrate ablation, avoiding multiple VT induction or prophylactic use of mechanical hemodynamic support (17,26). In this multicenter registry, we have not found significant differences in the PAINESD score between patients with early or late mortality (14.57 ± 6 vs. 12.3 ± 5; p = 0.41). This result could be explained by the low rate of early mortality and by the systematic use of ablation during stable rhythm avoiding the VT induction and mapping in 70% of the patient population, which in turn is related to a low incidence of acute hemodynamic decompensation.

The mortality rate over long-term follow-up was lower than reported in previous studies and registries. The 3-year mortality rate in the present registry was 11.4%. Excluding patients with ARVC, who are not represented in other series, the 3-year mortality rate was 14%. In a German registry, the estimated 2-year mortality after VT ablation in SHD was 19% (24). Overall survival at 3 years after LAVA ablation in a population of post-MI patients was 84%, similar to the 85.5% in ICM patients in the present registry (15). Age, COPD, LVEF, and incomplete substrate ablation were independent predictors of mortality during follow-up (**Central Illustration**). Incomplete elimination of abnormal EGMs identified during substrate mapping has been linked to arrhythmic recurrence with various substrate modification techniques (LAVA ablation, late potentials, or scar dechanneling) (6,21,30). In this sense, the endpoint of the substrate ablation procedure has been proposed to be double: to achieve the noninducibility of any VT and the elimination of all the target abnormal EGMs identified in stable rhythm (21,30). Wolf et al. (15) showed that complete LAVA elimination resulted in less recurrence of VT storm (5% vs. 17%). Complete late potential abolition and VT noninducibility has been associated with reduction in cardiac mortality in post-MI patients (30).

The criteria used to define incomplete substrate ablation was not restricted to the persistence of abnormal EGMs, but included imaging-identified epicardial or mid-myocardial unreachable septal scars. A recent meta-analysis suggests that endoepicardial ablation is associated with less VT recurrence and subsequent lower mortality than endocardial VT ablation, but with a higher complication rate (31). In the present study, an increase in mortality was observed when scars identified by imaging techniques were not targeted, emphasizing the relevance of pre-procedural assessment of substrate extension and accessibility (32). This report shows a reduction in overall mortality associated with the success in substrate elimination. This improvement in survival could be due to the reduction of VT recurrences and ICD shocks, which have a known adverse prognostic effect (13). On the other hand, patients in whom a complete scar dechanneling is achieved may have a more accessible and less extensive substrate, which may reflect less severe heart disease.

STUDY LIMITATIONS. The registry lacks a comparison group using another ablation strategy (i.e., multiple VT induction and mapping, use of LV assist devices). Multicenter randomized studies will be required to compare this strategy with other approaches for scar-related VT ablation. ICD programming heterogeneity may have influenced the detection of VT recurrences. Due to the relatively low number of patients with NICM, and the usual clinical heterogeneity of these patients, the application of the current strategy needs further study. Data on the type of anesthesia/sedation used in the procedure were not fully collected. Multielectrode mapping, which allows for a more precise electroanatomic characterization of the substrate, was performed in only 24% of patients. Not all patients could be examined with LGE-CMR, and the interpretation of the inaccessibility of the substrate was established by the operator, which implies a bias in the designation of incomplete substrate ablation in some cases. In this sense, it would be desirable to carry out more studies to confirm the predictive value for mortality of incomplete substrate ablation. The substrate ablation strategy was the same in all the patient population (scar dechanneling), and therefore, the outcomes cannot be extrapolated with certainty to other substrate ablation techniques. However, the endpoint of complete substrate elimination is similar to others such as LAVA ablation or scar homogenization; therefore, similar clinical outcomes would be expected if ablation would be done during SR.

CONCLUSIONS

Substrate ablation during SR avoiding multiple VT induction has low procedure-related complications and low early mortality. Age, COPD, and reduced LVEF, but also incomplete substrate elimination, are predictors of mortality.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with structural heart disease and VT, arrhythmogenic substrate ablation during stable rhythm, avoiding multiple VT induction, has low procedure complications and low early mortality.

TRANSLATIONAL OUTLOOK: Additional randomized studies are needed to assess the safety and the possible early mortality benefit of performing substrate ablation during stable rhythm, without ventricular tachycardia induction.

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