

Ablation of Stable VTs Versus Substrate Ablation in Ischemic Cardiomyopathy



The VISTA Randomized Multicenter Trial

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ABSTRACT

BACKGROUND Catheter ablation reduces ventricular tachycardia (VT) recurrence and implantable cardioverter defibrillator shocks in patients with VT and ischemic cardiomyopathy. The most effective catheter ablation technique is unknown.

OBJECTIVES This study determined rates of VT recurrence in patients undergoing ablation limited to clinical VT along with mappable VTs ("clinical ablation") versus substrate-based ablation.

METHODS Subjects with ischemic cardiomyopathy and hemodynamically tolerated VT were randomized to clinical ablation (n = 60) versus substrate-based ablation that targeted all "abnormal" electrograms in the scar (n = 58). Primary endpoint was recurrence of VT. Secondary endpoints included periprocedural complications, 12-month mortality, and rehospitalizations.

RESULTS At 12-month follow-up, 9 (15.5%) and 29 (48.3%) patients had VT recurrence in substrate-based and clinical VT ablation groups, respectively (log-rank p < 0.001). More patients undergoing clinical VT ablation (58%) were on antiarrhythmic drugs after ablation versus substrate-based ablation (12%; p < 0.001). Seven (12%) patients with substrate ablation and 19 (32%) with clinical ablation required rehospitalization (p = 0.014). Overall 12-month mortality was 11.9%; 8.6% in substrate ablation and 15.0% in clinical ablation groups, respectively (log-rank p = 0.21). Combined incidence of rehospitalization and mortality was significantly lower with substrate ablation (p = 0.003). Periprocedural complications were similar in both groups (p = 0.61).

CONCLUSIONS An extensive substrate-based ablation approach is superior to ablation targeting only clinical and stable VTs in patients with ischemic cardiomyopathy presenting with tolerated VT. (Ablation of Clinical Ventricular Tachycardia Versus Addition of Substrate Ablation on the Long Term Success Rate of VT Ablation (VISTA); [NCT01045668](https://clinicaltrials.gov/ct2/show/study/NCT01045668)) (J Am Coll Cardiol 2015;66:2872-82) © 2015 by the American College of Cardiology Foundation.

Ischemic cardiomyopathy (IC) is the most prevalent cause of ventricular arrhythmias leading to sudden cardiac death in Western countries. Ventricular tachycardia (VT) caused by scar-related re-

entry represents the most common mechanism of VTs in these patients (1,2). Implantable cardioverter-defibrillators (ICDs) reduce mortality; however, ICD shocks in primary and secondary prevention settings

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are associated with decreased quality of life and increased mortality (3-6).

Catheter ablation and antiarrhythmic drugs (AADs) are used to reduce ICD shocks and potentially improve survival rates in patients with IC and VT. AADs have shown limited improvement on survival and suboptimal benefits on ICD shock reduction (3). Amiodarone reduced shocks by 70% versus beta-blockade alone in the OPTIC trial, but it is often associated with serious side effects (6).

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Radiofrequency catheter ablation is effective for the treatment of drug-refractory and clinically stable VTs in patients with IC, although recurrence rates remain high (7-10). Three-dimensional (3D) mapping systems, open irrigated catheters, and the advent of percutaneous epicardial ablation have improved overall success rates of these procedures (1,10-12). Nonrandomized studies have suggested that a substrate-based ablation is superior to ablation of clinical and hemodynamically stable VT (13-16).

METHODS

The study enrolled 118 patients who had received an ICD before the ablation and suffered from recurrent stable monomorphic VTs that were symptomatic or required ICD therapies despite AADs. Between April 2009 and July 2013, patients from 7 centers were randomized to substrate-based ablation (n = 58) or to ablation of clinical and mappable VTs only (n = 60) (Figure 1).

Exclusion criteria included VT that presented with syncope, loss of consciousness, or cardiac arrest; age <18 years; severe renal insufficiency (glomerular filtration rate 15 to 29 ml/min/1.73 m² for ≥3 months), left ventricle (LV) thrombus, unstable angina, severe aortic stenosis, end-stage heart failure with limited life expectancy, and prior failed VT ablation.

The study was approved by the institutional review boards of respective participating centers.

ENDPOINTS. Primary endpoint was recurrence of any VT during the 12-month post-ablation period, as demonstrated by device interrogation and clinical evaluation. Secondary endpoints included periprocedural complications, 12-month post-procedure mortality, rehospitalization, and combined incidence of rehospitalization and mortality. Rehospitalization was defined as a hospital admission during the post-index procedure follow-up for arrhythmia-related causes, or symptoms, signs, or complications of heart failure.

DEFINITIONS. Arrhythmia recurrence was defined as any arrhythmia receiving device-based treatments (adenosine triphosphate or shock) or any VT episodes assessed at clinical evaluation. VTs induced at the time of ablation were defined as clinical if there was a match in clinical cycle length, 12-lead electrocardiography (when available), and on the intracardiac tracings from ICD interrogation when available.

ICDs were uniformly programmed in all patients and consisted of a VF zone with a cutoff rate of 220 beats per minute and a VT zone of 180 beats per minute with antitachycardia pacing followed by shock therapy and a monitor zone that detected the slowest inducible VT for each patient. A slow VT window was activated in a monitor-only mode in patients with known slow VT.

RANDOMIZATION. A central randomization process with block randomization and 1:1 allocation generated the randomization list. A computer algorithm written in SAS version 9.2 (SAS Institute Inc., Cary, North Carolina) was used for performing block randomization. To maintain allocation concealment, the center-level administrators retained the randomization sequence and investigators were not provided with the upcoming assignment until patient's eligibility was confirmed.

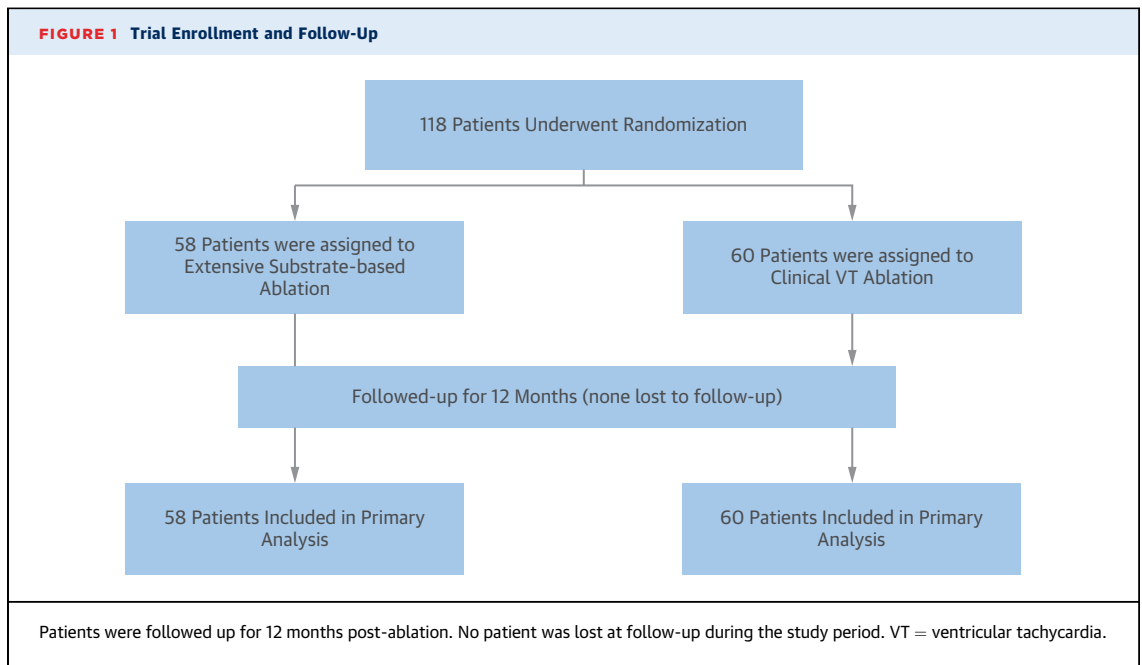
ELECTROPHYSIOLOGY STUDY. With the patients under conscious sedation, transvenous multipolar catheters were placed into the cardiac chambers

ABBREVIATIONS AND ACRONYMS

AADs = antiarrhythmic drugs
HR = hazard ratio
IC = ischemic cardiomyopathy
ICD = implantable cardioverter-defibrillator
LV = left ventricle
LVEF = left ventricular ejection fraction
3D = three-dimensional
VT = ventricular tachycardia

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Manuscript received February 27, 2015; revised manuscript received October 1, 2015; accepted October 6, 2015.



appropriate for the arrhythmia being studied (right ventricle and LV). LV mapping was performed via the retrograde aortic or transseptal approach. When necessary, subxiphoid epicardial access was obtained by fluoroscopic guidance as previously described (11). For areas near the phrenic nerve, high-output pacing was performed from the ablation catheter, and these locations were marked on the 3D mapping system and avoided, or when necessary, an esophageal dilation balloon was used to move the phrenic nerve from the epicardial surface to allow for ablation with reduced potential for phrenic nerve injury (17).

3D electroanatomic maps (CARTO, Biosense Webster, Diamond Bar, California), including voltage and activation, were obtained in sinus rhythm and/or during hemodynamically stable VT using a 3.5-mm open irrigated tip catheter (Thermocool, Biosense Webster) with the fill threshold setting at 15 mm. Intracardiac signals were filtered at 30 to 400 Hz.

All patients underwent bipolar substrate mapping with standard scar settings defined as normal tissue >1.5 mV and dense scar <0.5 mV. Dense scar was defined as areas with amplitudes less than or equal to baseline noise level of the recording system. Maps included higher density points around areas of scar, focusing on the scar border and electrograms within the scar. Normal tissue was less densely mapped. Areas of fractionated or late potentials were tagged with color-coded tags to denote the electrogram's

type. These notations were done irrespective of the voltage obtained.

His bundle electrograms were tagged with separate colored-coded tags. Maps were considered complete when the entire chamber of interest was completely mapped and all scar borders were clearly defined. Intracardiac echocardiography assisted in defining mechanical structures, monitoring for potential complications, and performing transseptal punctures.

Ablation was performed at individual sites for ≥ 60 s at ≤ 50 W with a temperature limit of 40°C . Systemic anticoagulation was achieved with intravenous heparin targeted to a minimum activation clotting time of 300 s. Epicardial access was obtained after anticoagulation reversal with protamine in patients without coronary artery bypass graft or prior sternotomy and when clinical VTs were still inducible after endocardial ablation was concluded. Epicardial 3D electroanatomic mapping was performed in patients undergoing epicardial access.

CLINICAL VT ABLATION. Conventional mapping techniques (pace-mapping, activation mapping, and entrainment mapping) were used to define the mechanism of the arrhythmias and identify potential sites for ablation. After complete substrate mapping, pacing protocols were used to induce clinical VT. Programmed ventricular stimulation was performed using ≤ 3 extrastimuli to refractoriness from 2 different right

ventricle sites. Burst pacing and medications for provocation, such as intravenous isoproterenol (up to 5 µg/min), were used as necessary.

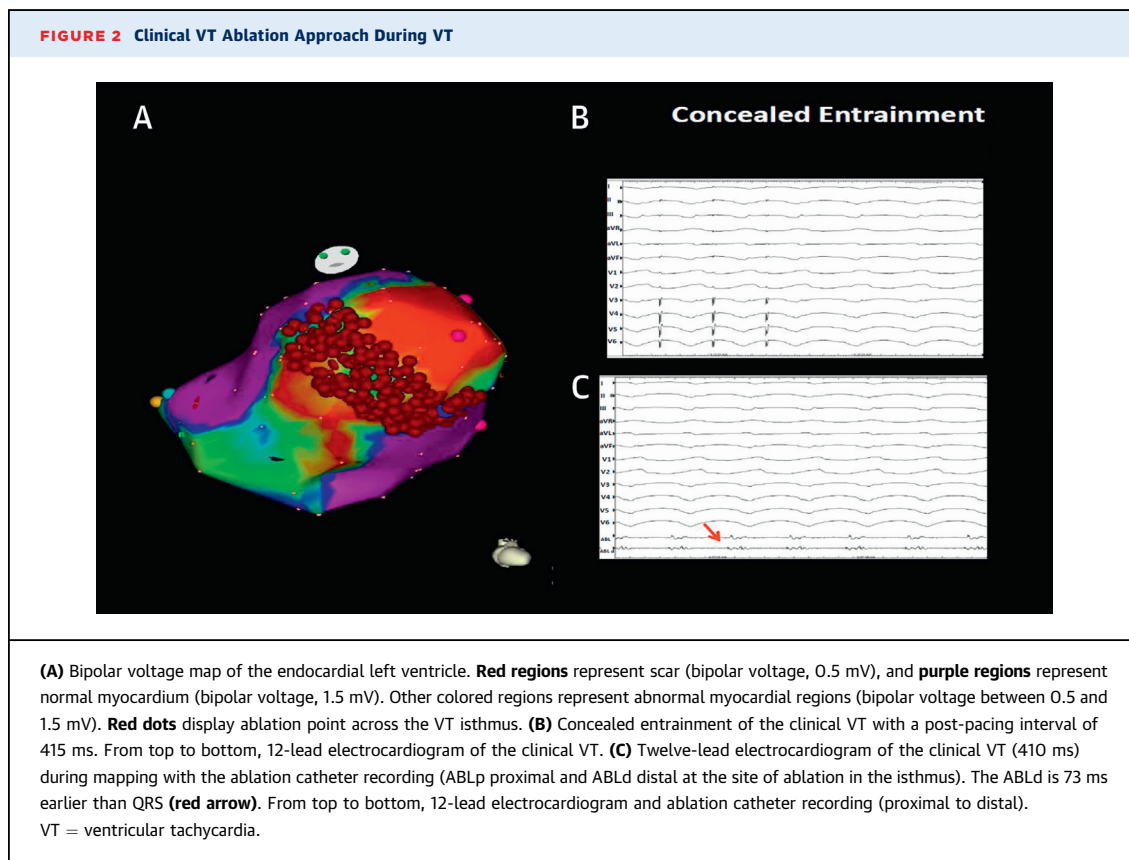
If clinical tachycardias were not inducible, pacing was performed from within the scar. After induction of clinical VT, a complete activation map was performed if the VT was hemodynamically tolerated. The earliest activation was defined in reference to a surface electrocardiogram lead. Entrainment mapping and pace mapping confirmed appropriate ablation sites within the critical isthmus. In patients who did not tolerate clinical VT, activation mapping was limited to the area near the scar, and pace-mapping was used to determine appropriate exit sites. Entrainment mapping was also used if possible. Clinical VT and hemodynamically stable, mappable VTs were targeted for ablation. Nonclinical VTs were targeted for ablation if stable or if they had morphology similar to the clinical one. Unstable nonclinical tachycardias were not targeted for ablation.

Ablation was performed at the optimal ablation sites based on the previously mentioned criteria, preferentially in tachycardia to observe cycle length slowing and termination. Potential channels within

the scar were identified by substrate mapping and targeted only when confirmed to be involved in the VT circuits by entrainment mapping (Figures 2A to 2C). Linear ablation lesions were placed to transect the VT isthmus and terminate inducible VTs. If clinical VT was not tolerated, hemodynamic support with percutaneous LV-assist device was used at the discretion of the physician. At the end of the ablation, programmed stimulation with and without isoproterenol was performed in all cases to test the inducibility of VAs. If clinical VTs remained inducible after endocardial ablation, epicardial mapping and ablation were considered.

SUBSTRATE-BASED ABLATION. Voltage and activation mapping were as previously described. Careful identification of fractionated, delayed, or abnormal electrograms was performed. VT induction was not required in this group. Ablation was never performed in VT, and induction was only used as the post-ablation endpoint.

Ablation lesions were empirically extended throughout the entire scar based on the substrate map defined by 3D mapping and targeting any abnormal potentials in normal sinus rhythm. Electrograms were monitored during ablation to ensure reduction in



amplitude to the noise level except for the border region. Ablation was continued until abnormal and late potentials were extinguished. The endpoint in the substrate-based ablation group was elimination of all abnormal potentials. This was documented by the absence or significant modification of these potentials as assessed by visual inspection and by non-inducibility after elimination or modification of all abnormal potentials. Abnormal potentials were usually defined as fractionated electrograms and/or late potentials. At the end of the ablation session, programmed stimulation with and/or without isoproterenol (up to 5 $\mu\text{g}/\text{min}$) was performed in all cases to test the inducibility of any VAs following extensive substrate ablation. The areas of abnormal potentials were remapped after ablation to ensure that they were modified (Figure 3).

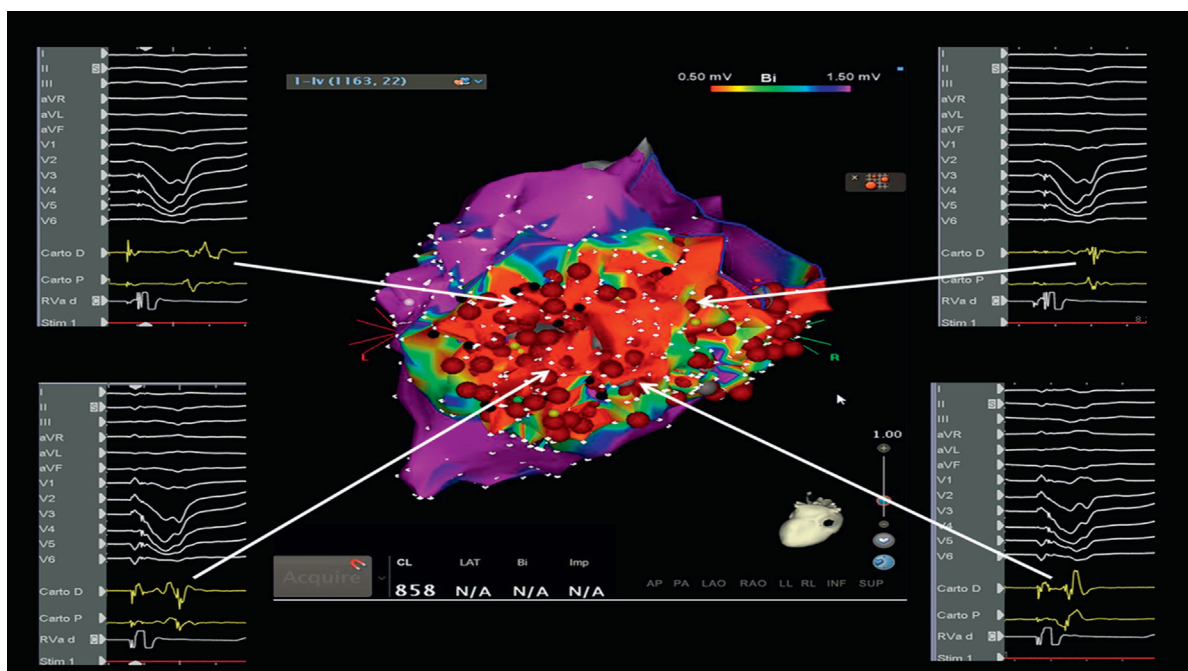
In cases where clinical VTs were inducible after endocardial ablation, epicardial mapping and ablation were considered. After substrate ablation, high output pacing at 20 mA from within the scar was performed to confirm that no tissue could be captured.

FOLLOW-UP. All patients were followed at 3-month intervals with remote monitoring or office visits where implantable devices were interrogated and during any symptomatic event. One expert electrophysiologist per center, who was blinded to the intervention group, reviewed the stored ICD electrograms and adjudicated the arrhythmic events. Arrhythmia recurrence was defined as any symptomatic arrhythmia or arrhythmia receiving device-based treatments (adenosine triphosphate or shock). Following ablation, all AADs were discontinued and reinitiated for recurrent VT when applicable.

STATISTICAL ANALYSIS. Using log-rank test, the study was designed to detect at least 25% reduction in recurrence rate (50% to 25%) at 12-month follow-up (hazard ratio [HR]: 0.415; null hazard 0.057) at 2-sided type I error (α) of 0.05, and 80% power. A total of 116 patients (58 per group) were required to provide the power.

Continuous data were described as mean \pm standard deviation (median and interquartile range

FIGURE 3 Substrate-Based Ablation Approach in Sinus Rhythm



Endocardial bipolar voltage map of the left ventricle. **Red regions** represent scar (bipolar voltage, 0.5 mV), and **purple regions** represent normal myocardium (bipolar voltage, 1.5 mV). Other colored regions represent abnormal myocardial regions (bipolar voltage between 0.5 and 1.5 mV). The entire scar underwent extensive substrate-based ablation (**red dots**). Electrograms of representative endocardial mapping sites are shown with **white arrows**. In each electrogram recording, 12-lead electrocardiogram leads and electrogram on proximal (**Carto P**) and distal (**Carto D**) ablation catheter are shown. Each **red dot** represents RF application in the area of the scar with abnormal electrograms as explained in the Methods section.

for non-normal data) and as counts and percent if categorical. Student *t* test and chi-square tests were used to compare groups.

Kaplan-Meier methodology was used to assess survival time and compare recurrence rate between groups. Time-to-event was defined as time from procedure to occurrence of outcome event. For patients event-free at end of the 12-month study period, duration of survival was censored. Death from any cause within the 12-month period was considered for mortality analysis and was censored at date of death for VT recurrence endpoint. Univariate and multivariate Cox proportional hazards models were used to identify significant predictors of VT recurrence and death. Proportional hazards assumption for the covariates was tested by Schoenfeld residual analysis. Likelihood ratio tests were performed to test nonlinear relation. HR and 95% confidence intervals (CI) from the Cox model were reported.

All randomized patients underwent the ablation procedure and were included in the efficacy analysis. All tests were 2-sided, and a *p* value < 0.05 was considered statistically significant. Analyses were performed using SAS 9.2 (SAS Institute Inc.).

RESULTS

Baseline clinical characteristics and electrophysiologic features were not significantly different between the substrate ablation and clinical ablation groups; mean LV ejection fraction (LVEF) was 32.0 ± 9.9% and 32.6 ± 14.1% (*p* = 0.8), and patients failed an average of 1.4 ± 0.7 and 1.5 ± 0.7 AADs, respectively (*p* = 0.86) (Table 1).

PROCEDURAL DATA. Mean cycle length of induced clinical VTs was 399 ± 86 ms in the substrate-based ablation group and 410 ± 90 ms in clinical VT ablation group (*p* = 0.49). Although pre-ablation induction was not required in the substrate-based ablation arm, 22 (38%) patients in this group had clinically stable VT induction. In the clinical ablation group, the median number of induced clinical stable VTs was 2. Nonclinical VTs were inducible in 47 (78%) of clinical ablation patients, with an average of 2.7 ± 1.2 VTs per patient. These VTs had an average cycle length of 376 ± 100 ms. Sustained clinical VT was inducible in 59 (98%) patients in this group. Hemodynamic support was used for 8 patients during catheter ablation because of circulatory instability and/or for intolerance to anesthesia, and was discontinued at the conclusion of the procedure.

TABLE 1 Baseline and Procedural Characteristics of Study Population

	Extensive Substrate-Based Ablation (n = 58)	Clinically Stable VT Ablation (n = 60)	p Value
Age, yrs	67 ± 9	65 ± 12	0.13
Male	54 (93.1)	56 (93.3)	0.96
Hypertension	44 (75.9)	43 (71.7)	0.60
Diabetes	24 (41.7)	19 (31.7)	0.27
BMI	26.4 ± 6.1	24.9 ± 7.2	0.22
NYHA III/IV	31 (53.4)	37 (61.7)	0.37
LVEF	32.0 ± 9.9	32.6 ± 14	0.80
Hyperlipidemia	44 (75.9)	43 (71.7)	0.60
Prior CABG	19 (32.8)	21 (35.0)	0.79
Failed AADs	1.4 ± 0.7	1.5 ± 0.7	0.86
Medications			
Sotalol	4 (6.9)	5 (8.3)	1.00
Beta-blocker	46 (79.3)	50 (83.3)	0.57
Mexiletine	5 (8.6)	6 (10.0)	0.68
Nonsustained VT cycle length	352 ± 86	376 ± 100	0.20
Sustained VT cycle length	399 ± 86	410 ± 90	0.49
Procedure time, h	4.2 ± 1.3	4.6 ± 1.6	0.14
Fluoroscopy time, min	35 ± 32	28 ± 16	0.13
RF time, min	68 ± 21	35 ± 27	<0.001

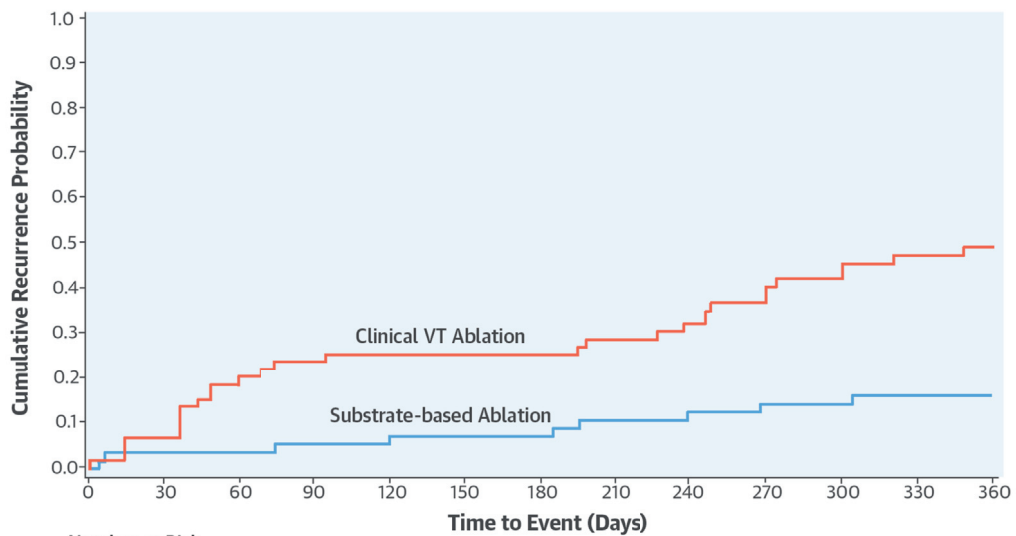
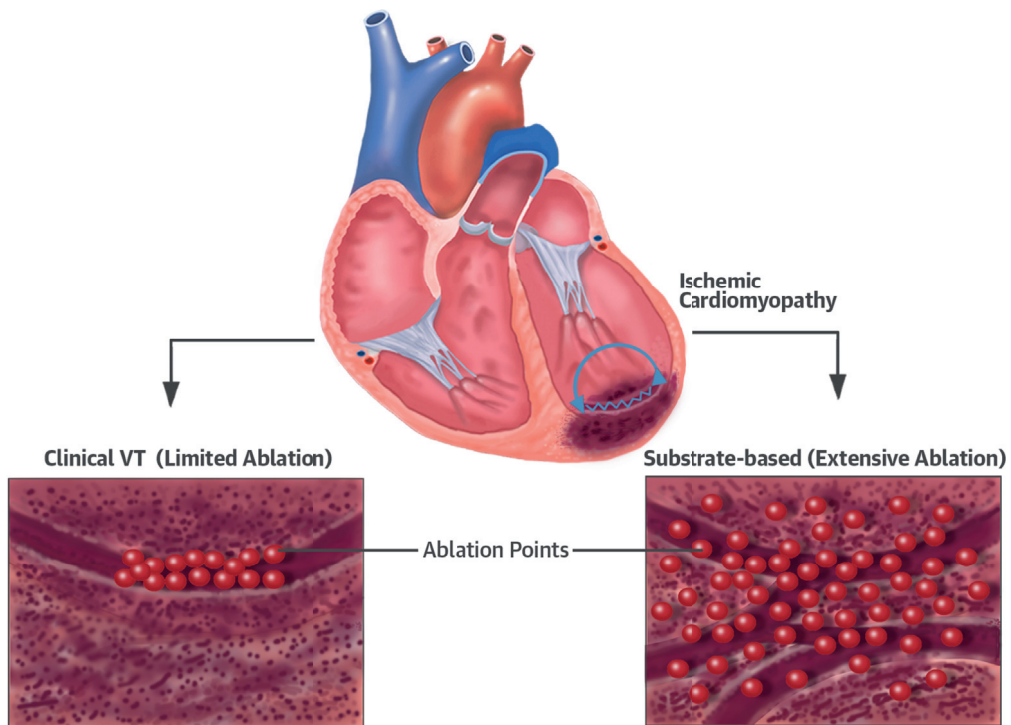
Values are mean ± SD or n (%).
AAD = antiarrhythmic drug; AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RF = radiofrequency; VT = ventricular tachycardia.

The procedural (4.2 ± 1.3 h and 4.6 ± 1.6 h; *p* = 0.14) and fluoroscopy times (35 ± 32 and 28 ± 16 min; *p* = 0.13) were not statistically different between substrate-based ablation and clinical ablation groups, although a trend of longer procedural time was observed during clinical ablation. However, after removing substrate-based ablation patients in whom induction of VT was performed (22 cases), procedural time decreased to 3.4 ± 1.7 h, which was significantly shorter than in clinical ablation (4.2 ± 1.3 vs. 3.4 ± 1.7; *p* = 0.018). Procedural and fluoroscopy times for these 22 patients were 4.7 ± 0.9 h and 36 ± 18 min, respectively. Radiofrequency time was substantially longer in substrate-based ablation (68 ± 21 vs. 35 ± 27 min; *p* < 0.001) (Table 1).

Elimination of all abnormal potentials within the scar tissue during substrate-based ablation was not achieved in 9 (16%) of the cases. In 8 of the cases, epicardial ablation was not possible because of coronary artery bypass graft.

In the clinical ablation group, epicardial ablation was performed in 7 (11.7%) patients, whereas it was performed in 6 of the substrate-based ablation

CENTRAL ILLUSTRATION VT Ablation in Patients With Ischemia



Ablation Strategy	Number at Risk												
Substrate-based	58	56	56	55	55	54	54	52	51	50	50	49	49
Clinical Stable VT	60	56	48	46	45	45	45	43	41	38	35	32	31

Di Biase, L. et al. J Am Coll Cardiol. 2015; 66(25):2872-82.

The curve compares the cumulative probability of VT recurrence (on or off antiarrhythmic drug) between patients undergoing substrate-based ablation and stable clinical ablation. Patients with substrate-based ablation exhibited significantly lower recurrence rate at 12-month follow-up: 9 of 58 (15.5%) compared with 29 of 60 (48.3%) patients in clinical VT ablation (log-rank $p < 0.001$). Median time to recurrence was 7.0 months (interquartile range: 6.3 to 7.8 months) and 2.5 months (interquartile range: 1.2 to 8.6 months), respectively (unadjusted hazard ratio: 0.26 [95% confidence interval: 0.11 to 0.61]). VT = ventricular tachycardia.

TABLE 2 Summary of Outcomes by Study Groups

	Substrate-Based Ablation (%)	Clinical Ablation (%)	p Value	HR (95% CI)
VT recurrence rate	15.5 (8.4-27.7)	48.3 (36.6-61.2)	<0.001	0.26 (0.11-0.61)
All-cause mortality rate	8.6 (1.4-14.2)	15.0 (5.9-24.2)	0.21	0.54 (0.17-1.82)
Arrhythmia-related rehospitalization	12.1 (3.8-19.7)	31.7 (22.1-41.6)	0.014	0.31 (0.13-0.78)
Composite: rehospitalization and mortality	20.7 (10.3-30.1)	46.7 (34.0-59.3)	0.003	0.32 (0.17-0.61)
Composite: VT recurrence and mortality	24.1 (13.2-35.1)	63.3 (51.1-75.5)	<0.001	0.20 (0.09-0.43)

The summary table presents the event rates (95% confidence interval), p values from log-rank test, and unadjusted hazard ratio for the outcome measures.
 CI = confidence interval; HR = hazard ratio; VT = ventricular tachycardia.

patients (10.3%) because of persistent clinical VT inducibility after endocardial ablation (p = 1.00).

POST-ABLATION INDUCIBILITY AND ICD PROGRAMMING.

After ablation, all patients from the substrate-based ablation group underwent the same pre-ablation induction protocol as for the clinical ablation group. Noninducibility of the clinical VTs was achieved in all patients in both groups. In the clinical ablation group, the average number of post-ablation unstable nonclinical VTs induced was lower than what observed at the beginning (2.0 ± 1.4 vs. 2.7 ± 1.2; p = 0.011).

Only 3 (5%) patients undergoing clinical VT ablation and 2 (3%) undergoing substrate-based ablation had the device programmed in a manner that differed from the protocol-required device programming, but this was considered appropriate by the implanting physician (p = 1.00).

FOLLOW-UP. All patients in the study were included in the survival analysis and none was lost to follow-up during the study period. At the time of analysis, all recurrence-free patients had completed 12-month follow-up in both groups.

We observed a nonsignificant trend toward improvement in LVEF and New York Heart Association functional class at 1 year in substrate-based ablation patients. LVEF change was 2.4 ± 6.6% in the substrate-based ablation group versus 2.1 ± 5.8% in the clinical ablation group (p = 0.13). The number of patients with New York Heart Association III/IV decreased from 53.4% to 46.6% in the substrate-based ablation, and from 61.7% to 53.3% in the clinical ablation group (p = 0.26).

VT RECURRENCE. Substrate-based ablation was associated with significantly lower VT recurrence rates at 12-month follow-up compared with clinical ablation (15.5% vs. 48.3%; log-rank p < 0.001). Unadjusted HR for recurrence was 0.26 (0.11 to 0.61). Median time to recurrence was 7.0 months (interquartile range, 6.3 to 7.8) and 2.5 months

(interquartile range, 1.2 to 8.6), respectively. Kaplan-Meier curves comparing cumulative recurrence rate on or off AADs are presented in the **Central Illustration**. More patients receiving clinical ablation were on AADs after ablation compared with substrate-based ablation 58% versus 12%, respectively (p < 0.001).

REHOSPITALIZATION. Seven (12.1%) in the substrate-based ablation group and 19 (32%) in the clinical ablation group required rehospitalization (p = 0.014). Median time to rehospitalization was 6.5 months and 3.4 months, respectively. Two rehospitalizations in the substrate-ablation group and 7 readmissions in the clinical group were VT- and heart-failure related (p = 0.16).

MORTALITY. Overall mortality during 12-month follow-up was 11.9%; 5 (8.6%) in the substrate-based ablation group and 9 (15.0%) in the clinical ablation group (log-rank p = 0.21). Three patients in the substrate-based ablation group and 5 in the clinical VT ablation group died from nonarrhythmic cardiovascular causes, mostly from refractory heart failure. Death from noncardiac causes, including sepsis from device infection and cancer, occurred in 2 patients undergoing substrate-based ablation and 4 patients undergoing clinical VT ablation.

COMBINED REHOSPITALIZATION AND MORTALITY.

The combined incidence of rehospitalization and mortality was significantly lower in substrate-based ablation (20.7% [95% CI: 10.3% to 30.1%] vs. 46.7% [95% CI: 34.0% to 59.3%]; p = 0.003). Event rates for all outcomes and unadjusted HR are summarized in **Table 2**.

PROCEDURAL COMPLICATIONS. One arteriovenous fistula and 5 pericardial effusions occurred in the overall study population. The arteriovenous fistula occurred in the clinical ablation group. Three effusions (5.17%) were reported in the substrate-based ablation group and 2 (3.33%) in the clinical ablation group (p = 0.61). All effusions were treated conservatively.

TABLE 3 Univariate and Multivariate Cox Regression Analyses of Potential Risk Factors for VT Recurrence

Factors	Univariate Model		Multivariate Model	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, per 5 yrs	1.11 (1.07-1.53)	0.016	1.09 (0.87-1.63)	0.271
Male	3.23 (1.13-6.28)	0.029	2.53 (0.59-10.75)	0.210
LVEF	0.77 (0.48-0.92)	0.035	1.05 (0.80-1.39)	0.716
Diabetes	3.11 (1.19-8.12)	0.020	2.75 (1.01-7.46)	0.042
Hypertension	1.34 (0.61-2.93)	0.460	1.14 (0.89-1.45)	0.303
No. of VT morphologies	1.01 (0.75-1.37)	0.952	1.04 (0.76-1.42)	0.817
Electrical storm	1.86 (1.06-2.81)	0.043	1.29 (0.95-1.83)	0.102
ICD shocks	2.53 (0.59-7.80)	0.209	2.24 (0.47-10.77)	0.314
Substrate-based ablation	0.26 (0.11-0.61)	0.001	0.33 (0.13-0.18)	0.014

ICD = implantable cardioverter-defibrillator; other abbreviations as in Tables 1 and 2.

PREDICTORS OF VT RECURRENCE. Univariate and multivariate association of clinical and procedural variables are displayed in Table 3. Age (5-year increments), male sex, electrical storm, LVEF, diabetes, and substrate-based ablation showed significant unadjusted association with VT recurrence.

After adjusting for covariates in Cox multivariate model, substrate-based ablation was associated with 67% lower risk of recurrence compared with clinical ablation (HR: 0.33 [95% CI: 0.13 to 0.81]; $p = 0.014$). Age and LVEF were not associated with recurrence, whereas history of diabetes (HR: 2.75 [95% confidence interval: 1.01 to 7.46]; $p = 0.042$) was an independent predictor of VT recurrence.

DISCUSSION

This is the first randomized multicenter study showing that substrate-based ablation reduces recurrence of any VT at follow-up when compared with ablation limited to clinical and mappable VTs in patients with IC. Furthermore, combined reduction of rehospitalization and mortality was observed in the substrate ablation group. Our study suggests that a larger area of scar tissue must be ablated to reduce recurrence from any VTs in patients with IC and stable clinical VTs. A larger percentage of patients was able to discontinue AADs after substrate ablation, an important finding because AADs can have significant long-term side effects.

Clinical studies have demonstrated the superiority of radiofrequency catheter ablation compared with medical therapy in controlling recurrent post-myocardial infarction VT (18-21). However, long-term freedom from VT remains an issue, with

reported long-term success rates of $\leq 55\%$ to 60% (8-10,22).

Noninducibility of clinical VT by programmed electrical stimulation represents the endpoint endorsed by current guidelines. However, a direct association between VT noninducibility and long-term freedom from any VT has not been uniformly reported (22-24). Furthermore, the definition of noninducibility has been heterogeneous among studies (22-24).

The site of programmed electrical stimulation might also play a role; some studies have highlighted the limitation of right ventricular versus LV stimulation for induction of the clinical VT and the importance of stimulation from areas inside the scar tissue (23,24).

In the clinical ablation group, the number of induced post-ablation nonclinical VTs was lower. This may be because some nonclinical VTs may also be eliminated, due to shared areas of the critical isthmus.

Surviving cardiac fibers within and around the scar tissue create areas of slow conduction that generate the arrhythmogenic substrate of ischemic VT (25). Identification of these areas by low-voltage electrograms on the mapping catheter is possible in sinus rhythm and in VT. Mapping during VT may be difficult because of hemodynamic instability (10,13-16). Identification of abnormal electrograms during sinus rhythm has been linked to critical sites of VT. Ablation of the isthmus responsible for clinical VT is the technique of choice in this setting (10) despite unsatisfactory outcomes at long-term follow-up (8-10).

Nonrandomized series have proposed substrate-based ablation techniques, which target abnormal electrograms indexing slow conduction (i.e., abnormal, split, and late electrograms) in sinus rhythm as reasonable surrogates of the VT isthmus (13-16).

Experience in cardiac arrhythmia surgery (18) showed worse results with incomplete elimination of the scar area by either aneurysmectomy or endocardial resection (19-21). A possible reason for the failure of aneurysmectomy is that it did not include all critical areas of diseased myocardium responsible for the arrhythmia. Josephson et al. (18) postulated that the subendocardial Purkinje fibers that survive myocardial infarction represent a component of the re-entrant circuit and suggested subendocardial resection in the area of the earliest activity as a method of removing the source of the arrhythmia. In their work, subendocardial resection was extended to the normal-appearing tissue (26-28).

Other important findings of our study were that a higher number of patients discontinued AADs in the substrate-based ablation group, and substrate

ablation could be performed during sinus rhythm, with shorter overall procedural times.

STUDY LIMITATIONS. Complete elimination of abnormal potentials within the scar tissue in the substrate ablation group was not possible in 16% of the population. We believe this is in part because epicardial access could not be obtained in patients with previous coronary artery bypass graft. However, we still noted an incremental benefit in terms of arrhythmia-free survival in patients in whom complete elimination of abnormal signals within the scar could not be achieved. Determination of whether an induced VT is “clinical” is sometimes difficult because similarity in cycle lengths and intracardiac ICD morphologies are imperfect predictors, another potential limitation.

CONCLUSIONS

This is the first randomized trial showing that substrate-based ablation approach is superior to ablation targeting only clinical and stable VTs in

patients with IC presenting with tolerated VT and is associated with a significant reduction in the combined endpoint of rehospitalization and mortality.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with ischemic cardiomyopathy and scar-related, sustained, re-entrant VT, substrate-based ablation in sinus rhythm is associated with greater freedom from VT without antiarrhythmic drug therapy than induction and ablation of clinical VT.

TRANSLATIONAL OUTLOOK: Further studies are needed to compare the efficacy of various methods of substrate-based ablation in patients with ischemic cardiomyopathy.

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KEY WORDS amiodarone, catheter ablation, ischemic cardiomyopathy, myocardial infarction, outcomes, ventricular tachycardia