Patients with unstable ventricular tachycardia (VT), cardiac arrest or syncope, and a left ventricular ejection fraction ≤40% in the presence of coronary artery disease have a high risk of recurrent ventricular arrhythmias. Intervention with an implantable cardioverter–defibrillator (ICD) is the standard therapy to reduce the risk of sudden cardiac death and improve prognosis in these patients. However, ICD therapy does not prevent tachyarrhythmias. After detection, the arrhythmias are terminated either by shocks or by ventricular pacing. ICD shocks are associated with increased mortality and impairment of the patient’s quality of life. Reduction in the number of shocks or ICD interventions can generally be achieved by...
WHAT IS KNOWN

• Two previous randomized trials (SMASH-VT [Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia] and VTACH [Substrate Modification in Stable Ventricular Tachycardia in Addition to ICD Therapy]) have shown that prophylactic catheter ablation before implantable cardioverter–defibrillator (ICD) implantation reduces ICD therapy for recurrent ventricular tachycardia.

• The prospective randomized SMS (Substrate Modification Study) was also designed to assess whether prophylactic catheter ablation of the arrhythmogenic substrate reduces ventricular arrhythmia recurrence in coronary artery disease patients with unstable ventricular tachyarrhythmias.

WHAT THE STUDY ADDS

• Although prophylactic catheter ablation did not prolong the time to first ventricular arrhythmia recurrence, it was associated with a >50% reduction in the total number of ICD therapies throughout follow-up.

Randomization

Patients were randomized to either substrate ablation with ICD implantation or to ICD implantation only. Randomization was stratified according to the presence or absence of amiodarone and β-blocker therapy.

Procedures

Catheter ablation was to be performed before ICD implantation. Attempts were made to ablate all inducible VTs. Three strategies for mapping and ablation were available: (1) mapping using the CARTO electroanatomic system (Biosense Webster, Inc, Diamond Bar, CA); (2) mapping using the EnSite NavX system (St. Jude Medical, Inc, Minneapolis, MN); and (3) conventional mapping. Mapping criteria for ablation in stable VT and the lesion design for substrate modification in cases of noninducible or unstable VT followed standard criteria. The end point was noninducibility of the clinical tachycardia (success) or lack of adequate endocardial target sites or ineffective lesions despite adequate target sites (failure). The inducibility of the targeted VT was assessed by programmed stimulation using the same protocol as before ablation, stimulation at 2 sites in the right ventricle with ≤3 extrastimuli at 2 drive cycle lengths.

ICDs were implanted according to current standards. Recommended were an R-wave amplitude >5 mV and a pacing threshold ≤2 V at 0.5 ms of the transvenous lead, intraoperative induction of 2 episodes of VF terminated by shocks of 10 J below the maximum output of the device, programming of one VF zone with a cutoff rate of 200 to 220 beats per minute, a detection of 18 out of 24 beats, shock therapy only, and one VT zone with a detection of at least 16 consecutive beats, antitachycardia pacing (ATP), and shock therapy. In cases of VT rates exclusively >220 beats per minute, programming the VT zone with a cutoff rate of 160 to 180 beats per minute was recommended. In cases of VT rates ≤220 beats per minute, programming the VT zone with a cutoff cycle length of 60 ms above the slowest VT was recommended.

All ICD systems were provided by the study sponsor, Medtronic, Inc.

As necessitated by the underlying heart disease, patients were treated with aspirin (250 mg/d) or warfarin. An echocardiographic study was performed after the ablation procedure to rule out a pericardial effusion and to assess cardiac anatomy and valvular physiology.

Patients were followed up at 3-month intervals during the first year (3, 6, 9, and 12 months) and at 3- or 6-month intervals (at the discretion of the investigator) until completion of the study or until 33-month follow-up were reached. Drug management during follow-up was left to the discretion of the investigator.

Study End Points

The primary study end point was the time to first recurrence of VT/VF. Secondary end points were appropriate ICD therapies, quality of life according to the Medical Outcome Study Short Form-36 score (version 1.0, scored using 1990 General Population norms, ranging from 0 [maximum disability] to 100 [no disability]), number of hospital readmissions because of a cardiac indication, and severe clinical events (death, number of syncopes, and number of electrical storm episodes, defined as >3 VT episodes within 24 hours). Episodes of any VT were documented by the ICD memory and classified by an independent experienced board of cardiologists. Episodes were classified after detection and before therapies were initiated and after the last therapy as induced, oversensing or spontaneous rhythm, atrial rhythm/arrhythmia, or ventricular arrhythmia.

Statistics

The sample size calculation for the primary end point was based on the assumption of a 20% recurrence rate in the ablation-plus-ICD arm and a 50% recurrence rate in the ICD-only arm, compared with a 2-sided log-rank statistic with 85% power and an α of 5%. With corrections for a 15% dropout rate, the study was set up for 110 patients with a minimum follow-up of 24 months.
The primary end point was assessed by survival analysis methods. The study arms were compared with the log-rank test. Primary and secondary end points were analyzed using a Cox proportional hazards model analyzing the time to first event and, in addition to the prespecified analysis, the times to multiple events to address multiple end point recurrences. For multiple occurrences of the primary end point, the Andersen–Gill model was fitted to use the times to recurring end points. The analyses were made in modified intention-to-treat cohorts, including all randomized patients with available follow-up data who had received an ICD.

Continuous variables are presented as mean and SD or median plus quartiles (Q1–Q3) where appropriate. They were compared using Student test or, if not normally distributed, Mann–Whitney test. Categorical variables are presented by absolute and relative frequencies and compared with the \( \chi^2 \) test or Fisher exact test. A 2-sided \( P \) value <0.05 was considered statistically significant.

Each of the Short Form-36 scores was analyzed with a repeated-measures mixed linear regression model, with the baseline value and randomized arm as fixed covariates and a random intercept for patient.

Statistical analysis was done using SAS version 9.1.3 or higher.

**Results**

**Patients**

A total of 117 patients were enrolled during 7 years at 10 European sites (8 in Germany and 1 each in the Czech Republic and Denmark). Randomization assigned 60 patients to VT ablation plus ICD implantation (ablation group) and 57 patients to ICD-only therapy. Six patients randomized into the ablation group did not undergo ablation and were excluded from further analysis because of missing ICD data crucial for the main analysis; 5 of them did not receive an ICD, 1 had an ICD implanted, but important implantation data were missing, and the patient was not followed up at all. Thus, 111 patients remained for modified intention-to-treat analysis, 54 in the ablation group and 57 in the ICD-only group (Figure 1). Baseline characteristics of these patients are given in Table 1.

Single- and dual-chamber ICDs were implanted in 61 patients (55%; ablation 28 patients [52%] and ICD-only 33 patients [58%]) and 39 patients (35%; ablation 21 patients [39%] and ICD-only 18 patients [32%]) respectively, and 11 patients (10%; ablation 5 patients [9%] and ICD-only 6 patients [11%]) received an ICD with cardiac resynchronization modality (Figure 2). There was no statistically significant difference in the distribution of ICD types between the 2 study arms.

**Procedural Outcomes**

At the baseline electrophysiological study, a VT was induced in 89 of the 111 patients. The induced VT matched the documented clinical VT in 48 of 68 patients (71%) in whom VT was documented at enrollment (28/37 in the ablation group and 20/31 in the ICD-only group).

Of the 54 modified intention-to-treat patients randomized to catheter ablation, 48 actually underwent the procedure; the reasons for not performing ablation in 6 patients were the inability to locate a VT substrate (n=3), no vascular access (n=1), pericardial tamponade (n=1), and hemodynamic instability during the procedure (n=1). Mapping during ablation used the CARTO system in 36 patients (75%), the EnSite NavX system in 10 patients (21%), and neither system (conventional mapping) in 2 patients (4%).

Acute ablation success was achieved in 45 of the 48 patients (94%) who underwent the procedure. Of the 31 patients with VT inducible at baseline (Table 1), 28 became noninducible, 2 were still inducible, and the result remained undefined in 1 patient. In the remaining 17 patients, substrate modification was successfully performed as intended. Recurrence of the clinical VT necessitated a repeat ablation 5 days after the index procedure in 1 patient. Repeat ablation later than 10 days after randomization was performed in 5 patients at a median of 78 days (range, 21–875 days) after randomization. One patient from the ICD-only group, having

---

**Figure 1.** Patient flow chart. FU indicates follow-up; mITT, modified intention to treat; R, randomization; and VT, ventricular tachycardia.
met the primary end point, crossed over to the ablation group 76 days after randomization.

ICDs were implanted at a median of 2 days (range, 1–5 days) after ablation. Six patients received the ICD at a median of 6 days (range, 2–21 days) before the ablation procedure. Of note, these patients had no VT events between randomization and ablation.

There were no deaths during the ablation procedure or during ICD implantation. However, 1 ablation-group patient died suddenly without documentation of a ventricular arrhythmia 21 days after ICD implantation, and 1 ICD-only patient died 7 days after ICD implantation of noncardiac reasons. In the first 30 days, periprocedural complications other than death occurred in 10 patients (9.0%). They comprised third-degree atrioventricular conduction block during the ablation procedure (managed by early ICD implantation) and tamponade requiring pericardiocentesis in 2 ablation-group patients, pneumothorax in 1 ICD-only patient, and lead dislodgement requiring repositioning in a total of 5 patients (Table 2).

### Primary End Point
Overall, 111 patients were followed up for 2.3±1.1 years (Table 3). Mean follow-up as documented by the device memory was 1.9±1.1 years. The underlying drug treatment was similar in both groups throughout follow-up, with 30 patients (27%) on amiodarone therapy at the time of enrollment (Table 4).

A total of 1449 episodes were detected by the ICDs, excluding nonsustained episodes without electrogram information. Electrogram information was available for 912 episodes (63%). Missing electrogram information was because of lack of ICD memory in patients experiencing many episodes. Of the 912 episodes, 612 (152 [25%] in the ablation group) were classified as spontaneous VT/VF episodes—the primary end point—in a total of 51 patients; the primary end point was reached by the 25 ablation-group patients and 26 ICD-only patients. Kaplan–Meier analysis of time to first verified VT/VF episode in 51 patients revealed no significant difference in the primary end point

<table>
<thead>
<tr>
<th>Baseline Patient Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
</tr>
<tr>
<td>Diagnosis at enrollment, n (%)</td>
</tr>
<tr>
<td>Spontaneous unstable VT</td>
</tr>
<tr>
<td>Syncope with unstable VT inducible</td>
</tr>
<tr>
<td>Cardiac arrest with unstable VT inducible</td>
</tr>
<tr>
<td>Cardiac arrest and syncope with unstable VT inducible</td>
</tr>
<tr>
<td>Mean LVEF</td>
</tr>
<tr>
<td>LVEF ≤30%</td>
</tr>
<tr>
<td>LVEF ≤20%</td>
</tr>
<tr>
<td>LVEDD, mm</td>
</tr>
<tr>
<td>Previous percutaneous revascularization, n (%)</td>
</tr>
<tr>
<td>Previous surgical revascularization, n (%)</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
</tr>
<tr>
<td>Years between MI and randomization, n (%)</td>
</tr>
<tr>
<td>Rate of documented VT, beats per min</td>
</tr>
<tr>
<td>Amiodarone at enrollment, n (%)</td>
</tr>
<tr>
<td>β-Blockers at enrollment, n (%)</td>
</tr>
</tbody>
</table>

ICD indicates implantable cardioverter–defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and VT, ventricular tachycardia.
was found in the primary end point (log-rank \(P=0.85\)).

When the 60 patients (30 in either group) with moderately impaired left ventricular ejection fraction (>30%) were analyzed separately—as done in VTACH10—also no significant difference was found in the primary end point (log-rank \(P=0.85\)).

### Secondary End Points

The secondary end points of appropriate ICD therapies, hospital readmissions because of a cardiac indication, serious adverse events, and overall mortality, as well as the additionally investigated end points of spontaneous episodes with ATP or shock therapy, VT/VF episodes with ATP or shock therapy, spontaneous episodes with shock, VT/VF episodes with therapy, or VT/VF episodes without therapy and lasting longer than 30 seconds, showed no significant differences between groups when comparing time to first event by calculating the hazard ratio using a Cox proportional hazards model (Table 5).

However, using an Andersen–Gill proportional hazards model that incorporated the times to multiple end point occurrences13 revealed significant differences between the study arms in favor of catheter ablation for the primary end point and all subgroups of detected arrhythmias except for VT/VF episodes with shocks; the latter finding could be because of the low number of such episodes (Table 5). Hazard ratios ranged between 0.33 and 0.44 for all types of reported arrhythmias, implying that the number of arrhythmia episodes was more than halved by the ablation therapy.

Short Form-36 scores were assessed at baseline and at every scheduled follow-up visit. Analyses were done only in patients in whom quality of life was assessed at baseline and at least one follow-up visit. Results were available in 24 ablation-group patients, with a final follow-up visit at 722 days (median; Q1–Q3, 370–943 days), and 20 ICD-only patients, with a final follow-up visit at 666 days (median; Q1–Q3, 347–1080 days). No significant improvement in ablation-group patients was found (Table 6).

### Adverse Events Out of Hospital (Later Than 30 Days)

Eighteen of the 111 patients (16%) analyzed died later than 30 days after the index intervention, 8 patients (15%) in the ablation group and 10 patients (18%) in the ICD-only group (Table 7). In the 108 patients with a follow-up >30 days, Kaplan–Meier estimates of survival at 2 years were 90.2% (95% confidence interval, 80.0%–95.8%) in the ablation arm and 80.7% (95% confidence interval, 67.9%–88.8%) in the ICD-only arm (\(P=0.54\)). No death was related to implantation, follow-up procedure, ICD, or ICD lead performance. The causes of death are given in Table 7.

After hospital discharge, a total of 16 patients (14.4%; 9 in the ablation group) experienced adverse events other than death. In both groups, these events were predominantly related to the ICD and comprised exchange of the device (3 patients) or reprogramming (1 patient), lead dislodgement or dysfunction in a total of 7 patients, and surgical intervention for imminent lead perforation in 1 patient. The other 4 patients experienced serious clinical adverse events, namely, stroke and heart transplantation (Table 7).

### Discussion

#### Main Findings

SMS is the third randomized trial after SMASH-VT9 and VTACH10 to investigate the impact of prophylactic catheter ablation followed by ICD implantation on VT recurrences in patients with sustained ventricular arrhythmias. However, it is the first of these 3 trials that did not show a benefit of prophylactic catheter ablation with respect to the primary end point of time to recurrence of any VT. This end point was not different between patients undergoing prophylactic VT ablation before ICD implantation and patients receiving only ICD implantation, regardless of the patients’ left ventricular ejection fraction. Furthermore, none of the secondary end points showed significant differences between groups when comparing time to first event.
However, when using an Andersen–Gill model with repeat events for the primary end point and to almost all secondary end points, prophylactic VT ablation was associated with significant reductions in the numbers of spontaneous VT/VF episodes, spontaneous episodes with ATP or shocks, episodes with adequate ATP or shocks, VT/VF episodes with ATP or shocks, episodes with shocks, and VT/VF episodes with ATP or shocks or VT/VF >30 seconds during the entire study period. Only VT/VF episodes with shocks were not significantly reduced. In this respect, SMS supports the strategy of prophylactic catheter ablation as shown in the 2 previous randomized trials.

Comparison With Other Randomized Controlled Trials

Patients

The reason why SMS, in contrast to SMASH-VT and VTACH, failed to reach the primary end point is multifactorial. SMS patients did not differ from SMASH-VT patients except for the fact that the latter included 15% of patients with a primary ICD indication who had experienced an appropriate ICD shock in the ensuing 6 months. SMASH-VT also included patients with a primary manifestation of syncope with inducible VT, which is not necessarily unstable VT, and they had no hemodynamic definition of unstable VT. Furthermore, no antiarrhythmic treatment was given in SMASH-VT, but in SMS, 30 patients (27%) received amiodarone. Nevertheless, the recurrence rate, as detected in the ICD storage, at 2 years in the SMS control group (47.6%) was markedly higher than that in the SMASH-VT control group (33%).

In both SMASH-VT and SMS, only VT/VF recurrences documented in the ICD were counted. Therefore, differences in ICD programming may have accounted for potential differences in recurrence rates between the studies. In SMS, the ICD was programmed to a VF and a VT zone, with a VT zone cutoff cycle length 60 ms above the longest cycle length of the clinical VT when the VT rate was <220 per minute. In SMASH-VT, at least one VT zone was programmed, which was, however, not further specified. Consequently, for future ICD trials, predefined ICD programming criteria would be important.

In VTACH, only patients with the first episode of a stable VT after myocardial infarction were enrolled; in that study, all VT recurrences were counted, including slow, only clinically documented VTs with a rate below the VT detection rate of the ICD. This fact likely explains why the VT recurrence rate

![Table 4. Patient Medication](image)

Values are given as n (%). AA indicates antiarrhythmic agent; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and ICD, implantable cardioverter–defibrillator.

![Figure 3. Primary end point: time to first ventricular tachycardia (VT)/ventricular fibrillation (VF) recurrence. Log-rank P=0.84. Note that 2 implantable cardioverter–defibrillator (ICD)–only patients were not included in the Kaplan–Meier analysis because ICD information on VT/VF recurrence during follow-up was not available.](image)
(71.2%) in the control group of VTACH was significantly higher than that in the control groups of both SMASH-VT and SMS.

**Ablation Strategies**

Differences in ablation strategy between the 3 studies may have played a major role in the different reported clinical outcomes. SMASH-VT was a 3-center study, whereas SMS was a 10-center study. The latter, therefore, involved many more investigators with individual differences in performing catheter ablation. Apart from these individual differences, the overall ablation strategies were different in SMASH-VT and SMS. Whereas in SMASH-VT ablation was only done in sinus rhythm, ablation was allowed in SMS in sinus rhythm and during VT. Moreover, the end point in SMS was noninducibility of the clinical VT with or without additional substrate modification, whereas in SMASH-VT substrate modification was the only end point. Therefore, catheter ablation, in particular the elimination of late potentials, was probably more extensive in SMASH-VT than in SMS, which may have contributed to less VT recurrences after ablation in SMASH-VT.

Epicardial ablation was not performed in SMS and VTACH and may have been performed but was not evaluated in SMASH-VT. Epicardial ablation may be necessary in ≤15% of post–myocardial infarction patients. Moreover, for various reasons, 6 patients (10%) randomized to VT ablation never underwent actual ablation yet remained part of the intention-to-treat analysis.

Thus, differences in patient and treatment center selection and in ablation strategies may have underestimated in SMS the potential benefit of VT ablation with respect to time to first VT/VF event. However, despite all limitations, the benefit of prophylactic ablation could be demonstrated, with a >50% reduction in the number of almost all types of arrhythmia episodes, when the times to multiple VT/VF events were analyzed. This is concordant with the 2 previous randomized trials and of clinical relevance for a VT patient population.

**Safety of Prophylactic Catheter Ablation**

Prophylactic VT ablation turned out to be safe in SMS, with no patient death attributed to the ablation procedure. Two

### Table 5. End Points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Ablation (n=54)</th>
<th>ICD Only (n=57)</th>
<th>Hazard Ratio (95% CI)*</th>
<th>Hazard Ratio (95% CI)†</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous VT/VF episodes</td>
<td>2.8±6.0</td>
<td>8.1±19.1</td>
<td>0.43 (0.22–0.85)</td>
<td>...</td>
<td>0.015</td>
</tr>
<tr>
<td>Patients with spontaneous VT/VF (primary end point)</td>
<td>25</td>
<td>26</td>
<td>...</td>
<td>0.95 (0.55–1.64)</td>
<td>0.84</td>
</tr>
<tr>
<td>Spontaneous episodes with ATP or shock</td>
<td>2.8±6.4</td>
<td>12.9±34.6</td>
<td>0.34 (0.18–0.65)</td>
<td>...</td>
<td>0.001</td>
</tr>
<tr>
<td>Patients with ATP or shock</td>
<td>27</td>
<td>30</td>
<td>...</td>
<td>0.91 (0.54–1.53)</td>
<td>0.71</td>
</tr>
<tr>
<td>VT/VF episode with ATP or shock</td>
<td>1.8±4.8</td>
<td>7.6±18.6</td>
<td>0.33 (0.15–0.69)</td>
<td>...</td>
<td>0.004</td>
</tr>
<tr>
<td>Patients with VT/VF episode and ATP or shock</td>
<td>20</td>
<td>24</td>
<td>...</td>
<td>0.81 (0.45–1.47)</td>
<td>0.49</td>
</tr>
<tr>
<td>Spontaneous episodes with shock</td>
<td>0.7±2.8</td>
<td>2.1±6.1</td>
<td>0.36 (0.15–0.90)</td>
<td>...</td>
<td>0.028</td>
</tr>
<tr>
<td>Patients with shock</td>
<td>13</td>
<td>20</td>
<td>...</td>
<td>0.62 (0.31–1.25)</td>
<td>0.18</td>
</tr>
<tr>
<td>VT/VF episodes with shock</td>
<td>0.6±2.8</td>
<td>1.2±4.1</td>
<td>0.44 (0.14–1.34)</td>
<td>...</td>
<td>0.15</td>
</tr>
<tr>
<td>Patients with VT/VF episode and shock</td>
<td>8</td>
<td>14</td>
<td>...</td>
<td>0.55 (0.23–1.32)</td>
<td>0.18</td>
</tr>
<tr>
<td>VT/VF episodes with ATP or shock or &gt;30 s</td>
<td>2.0±5.0</td>
<td>7.6±18.6</td>
<td>0.35 (0.17–0.74)</td>
<td>...</td>
<td>0.006</td>
</tr>
<tr>
<td>Patients with VT/VF episode and ATP or shock or &gt;30 s</td>
<td>21</td>
<td>24</td>
<td>...</td>
<td>0.87 (0.48–1.56)</td>
<td>0.64</td>
</tr>
<tr>
<td>Death</td>
<td>9</td>
<td>11</td>
<td>...</td>
<td>0.82 (0.34–1.97)</td>
<td>0.65</td>
</tr>
<tr>
<td>Hospital readmission</td>
<td>0.6±1.1</td>
<td>0.7±1.1</td>
<td>0.97 (0.73–1.29)</td>
<td>...</td>
<td>0.82</td>
</tr>
<tr>
<td>Patients with hospital readmission</td>
<td>21</td>
<td>25</td>
<td>...</td>
<td>0.83 (0.46–1.50)</td>
<td>0.54</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1.0±1.2</td>
<td>1.1±1.4</td>
<td>0.95 (0.75–1.20)</td>
<td>...</td>
<td>0.67</td>
</tr>
<tr>
<td>Patients with serious adverse events</td>
<td>34</td>
<td>33</td>
<td>...</td>
<td>1.10 (0.67–1.78)</td>
<td>0.71</td>
</tr>
<tr>
<td>Electrical storm</td>
<td>0.1±0.4</td>
<td>0.3±1.0</td>
<td>0.69 (0.24–1.97)</td>
<td>...</td>
<td>0.49</td>
</tr>
<tr>
<td>Patients with electrical storm</td>
<td>4</td>
<td>7</td>
<td>...</td>
<td>0.60 (0.18–2.06)</td>
<td>0.42</td>
</tr>
<tr>
<td>Syncope</td>
<td>0.1±0.3</td>
<td>0.1±0.3</td>
<td>1.00 (0.29–3.40)</td>
<td>...</td>
<td>0.99</td>
</tr>
<tr>
<td>Patients with syncope</td>
<td>4</td>
<td>4</td>
<td>...</td>
<td>1.08 (0.27–4.33)</td>
<td>0.91</td>
</tr>
<tr>
<td>Death, syncope, or electrical storm</td>
<td>0.3±0.6</td>
<td>0.5±1.2</td>
<td>0.79 (0.47–1.30)</td>
<td>...</td>
<td>0.35</td>
</tr>
<tr>
<td>Patients with death, syncope, or electrical storm</td>
<td>12</td>
<td>17</td>
<td>...</td>
<td>0.73 (0.35–1.52)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

*Values are given as medians (interquartile range) or n (%). ATP indicates antitachycardia pacing; CI, confidence interval; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Time to all events.
†Time to first event.
‡For hazard ratio.
pericardial tamponades occurred in the 54 patients randomized to catheter ablation. Although prophylactic catheter ablation was not associated with a prolongation in time to first event and patient-related electric events were not different between groups, all other end points regarding the overall number of electric events were significantly reduced in the ablation arm (except for VT/VF episodes with shocks). Therefore, prophylactic catheter ablation may still be considered the treatment of choice in such a patient population. It has the potential advantage of ablation being performed under stable hemodynamic conditions, rather than in an emergency situation when patients undergo ablation rather late, that is, only after multiple ICD shocks often associated with either incessant VT or electrical storm. In that situation, adverse events of catheter ablation are more frequent (3.6% to 10%), and the intervention is associated with some mortality (0% to 3%).7,8,17 In contrast, SMASH-VT and VTACH reported major complications during ablation in 3.8 to 4.7% of patients, with no mortality.9,10

### Patient Enrollment

SMS addresses another fundamental problem of many, if not all, multicenter VT ablation studies performed in recent years, namely, that patient enrollment in these trials is rather slow (enrollment of 117 patients in SMS took 7 years). It almost always exceeds the projected time of enrollment significantly. This is particularly true for the randomized VT ablation trials. Slow patient recruitment does not necessarily imply low ablation volume or inexperience. Recruitment depends on protocol, inclusion and exclusion criteria, on management of the study by a contract research organization, reimbursement, and other factors. Moreover, cardiac and general medical treatment changes over time as does the specific treatment tested in a trial, such as the catheter ablation strategy in SMS.

### Limitations

SMS is limited by the small number of patients randomized. However, even this number was difficult to obtain. Furthermore, patients had multiple types of ventricular arrhythmia, with the common denominator of hemodynamic instability. The ablation procedure was not prespecified in detail, which would have led to a more homogeneous approach among individual investigators and participating centers. Finally, proper randomization was affected by 6 patients (10%) from the ablation arm excluded from the analysis because of missing data.

### Conclusions

In conclusion, SMS was a prophylactic VT ablation trial that failed to demonstrate a difference in time to first VT/VF recurrence between the 2 study groups. However, catheter ablation did achieve a >50% reduction in the total number of ICD interventions during the duration of follow-up.

The slow enrollment into the study calls for a better coordination of future VT ablation studies by an international VT study consortium.

### Acknowledgments

We would like to thank the participating centers for patient enrollment into the Substrate Modification Study: University Heart Center, Department of Cardiology - Electrophysiology, Hamburg (Dr Thomas Meinertz, Dr Philipp Willems, and Dr Rodolfo Ventura; 29 patients); University Hospital Bergmannsheil, Bochum (Dr Thomas Deneke and Dr Leif Bösche; 26 patients); Asklepios Hospital St. Georg, Hamburg (Dr Karl-Heinz Kuck, Dr Feifan Ouyang, and Dr Roland Tilz; 15 patients); Aarhus University Hospital, Skejby, Aarhus, Denmark (Dr Peter Steen Hansen and Dr Henrik K. Jensen; 11 patients); Mährsische Kliniken GmbH, Lüdenscheid (Dr Markus Zarse; 11 patients); University Hospital Frankfurt, Frankfurt (Dr Stefan Hohnloser; 10 patients); Institute for Clinical and Experimental Medicine,
Sources of Funding

The Substrate Modification Study was funded by Medtronic GmbH.

Disclosures

Dr Kuck reports having received consulting fees/honoraria from Biosense Webster, Medtronic, Boston Scientific, and St. Jude Medical. Dr Tilz reports having received research grants from St. Jude Medical and speaker’s honoraria from Biosense Webster, Biotronik, Pfizer, Topera, Bristol-Myers Squibb, Bayer, and Sanofi Aventis. Dr Hoffmann reports having received speaker’s honoraria from Boehringer Ingelheim and St. Jude Medical. Dr Hansen reports having received consulting fees/honoraria from Biosense Webster. Dr Zarse reports having received consulting fees/honoraria from AstraZeneca, Boehringer Ingelheim, Bayer, Servier, and St. Jude Medical. Dr Hohnloser reports having received consulting fees from Bayer Healthcare, BI, BMS, Boston Scientific, Cardiome, Daiichi Sankyo, Gilead, Johnson & Johnson, Medtronic, Pfizer, Portola, Sanofi Aventis, Servier, SJM, Zoll; research grants from Sanofi Aventis and St. Jude Medical; and lecture fees from Bayer Healthcare, BI, BMS, Daiichi Sankyo, Pfizer, Sanofi Aventis, St. Jude Medical, and Medtronic. Dr Kautzner reports having received consulting fees/lecture honoraria from Biosense Webster, Biotronik, Boston Scientific, Medtronic, Sorin, and St. Jude Medical. Dr Willems reports having received consulting fees/honoraria from Biosense Webster, Boston Scientific, and St. Jude Medical. The other authors report no conflicts.

References

Impact of Substrate Modification by Catheter Ablation on Implantable Cardioverter–Defibrillator Interventions in Patients With Unstable Ventricular Arrhythmias and Coronary Artery Disease: Results From the Multicenter Randomized Controlled SMS (Substrate Modification Study)

Karl-Heinz Kuck, Roland Richard Tilz, Thomas Deneke, Boris A. Hoffmann, Rodolfo Ventura, Peter Steen Hansen, Markus Zarse, Stefan H. Hohnloser, Josef Kautzner and Stephan Willems for the SMS Investigators

*Circ Arrhythm Electrophysiol.* 2017;10:
doi: 10.1161/CIRCEP.116.004422

*Circulation: Arrhythmia and Electrophysiology* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2017 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:

http://circep.ahajournals.org/content/10/3/e004422

Data Supplement (unedited) at:

http://circep.ahajournals.org/content/suppl/2017/03/14/CIRCEP.116.004422.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation: Arrhythmia and Electrophysiology* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:

http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation: Arrhythmia and Electrophysiology* is online at:

http://circep.ahajournals.org//subscriptions/
Supplemental Figure 1

Product-Limit Survival Estimates
With Number of Subjects at Risk

p = 0.34

Time to first VT/VF recurrence in patients with an enrollment diagnosis of syncope and inducible unstable VT.
Supplemental Figure 2

Product-Limit Survival Estimates
With Number of Subjects at Risk

Time to first VT/VF recurrence in patients with an enrollment diagnosis of spontaneous unstable VT.

Patients with spontaneous unstable VT at enrollment

<table>
<thead>
<tr>
<th>Time since Ablation / ICD Implantation [Years]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
</tr>
<tr>
<td>37</td>
</tr>
<tr>
<td>34</td>
</tr>
</tbody>
</table>

p = 0.87

randITT

1: Ablation as randomized
2: ICD Only as randomized
Time to first VT/VF recurrence in 45 Ablation group patients who were successfully treated and a total of 60 ICD patients comprising 54 mITT ICD-only patients with follow-up (excluding the patient who eventually underwent ablation) and 6 Ablation-group patients who did not undergo ablation.