Ventricular Tachycardia Ablation Clinical Trials

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KEYWORDS

• Ventricular tachycardia • Clinical trial • Catheter ablation • Outcome

KEY POINTS

- Catheter ablation is an effective treatment option to reduce ICD therapies in patients with ventricular tachycardia.
- To date, there have been limited data from prospective randomized clinical trials comparing efficacy of VT ablation versus antiarrhythmic drugs, and evaluating the effect of VT ablation on long-term mortality.
- There are several barriers to enrollment and completion of randomized clinical trials for ventricular tachycardia ablation.

INTRODUCTION

Ventricular tachycardia (VT) occurs most frequently in patients with structural heart disease, and implantable cardioverter defibrillators (ICDs) have been clearly shown to improve mortality in these patients by preventing death due to recurrent ventricular arrhythmias. However, ICDs do not prevent recurrent VT episodes, which may result in ICD shocks. Antiarrhythmic drugs (AADs) can be effective in preventing recurrent VT and reducing appropriate ICD shocks, but may be associated with significant long-term side effects and organ toxicities.

Radiofrequency (RF) catheter ablation of VT is an effective method to reduce VT recurrences and appropriate ICD therapies (both shocks and antitachycardia pacing [ATP]). Although the number of VT ablations performed on a yearly basis has gradually risen over the past decade,[1] patients with structural heart disease are still frequently referred fairly late in their disease course—particularly at institutions that do not routinely perform VT ablations. Data from a limited number of prospective randomized controlled trials (RCTs) have demonstrated the effectiveness of VT ablation in reducing recurrent VT, but these trials have not shown a clear improvement in patient-based hard clinical outcomes, including overall survival, health care utilization costs, and quality of life after ablation.[2] A recent meta-analysis examining the efficacy of catheter ablation versus AADs to prevent VT in patients with ICDs demonstrated that both treatment strategies are similarly effective in preventing recurrent VT, but neither strategy was associated with decreased mortality.[3] Interestingly, a reduction in recurrent VT with AADs was seen only among those treated with amiodarone, and amiodarone was also independently associated with increased mortality (odds ratio 3.36, 95% confidence interval [CI], 1.36–8.3; $P = .009$).

Standardization of Reporting Outcomes of Clinical Trials for Ventricular Tachycardia Ablation

There is a significant amount of diversity in the methodology and reporting of outcomes in studies

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Card Electrophysiol Clin ■ (2016) ■–■
http://dx.doi.org/10.1016/j.ccep.2016.10.012

for VT ablation, particularly among observational studies. Several variables may exist that can profoundly affect interpretability of results between studies, including heterogeneity of patient selection, arrhythmia severity (number of VT episodes, hemodynamic stability of VTs,), ablation strategies (ie, mapping strategies, extensive substrate vs limited ablation approaches, endocardial vs endocardial/epicardial approach, and so forth), and outcome reporting. In particular, there tends to be a wide variation in substrate-based ablation approaches between different operators and institutions. The 2009 VT ablation guidelines have proposed standards in an attempt to minimize heterogeneity of reporting results of clinical trials for VT ablation (**Box 1**).[4]

Systematic Review of Ventricular Tachycardia Ablation Clinical Trials

Using the search term "Ventricular tachycardia," the authors identified 270 clinical trials in the National Institutes of Health (NIH) database (clinicaltrials.gov) and 25 clinical trials in "circulatory domain" in the International Standard Randomised Controlled Trial Number (ISRCTN) registry. Upon review of these 295 studies, 18 of these were identified to be RCTs comparing ablation or catheter/surgical denervation procedure with placebo or medications (17 from NIH database, 1 from ISRCTN registry). Fifteen of the studies were for catheter ablation (an additional 4 were for catheter/surgical denervation procedures). Among the 15 catheter ablation trials, 4 have been completed, 3 are ongoing, 6 were prematurely terminated before completion, and 2 have unknown status. All 4 of the denervation trials are currently ongoing. **Table 1** lists the completed, ongoing, terminated clinical trials on catheter ablation or denervation for treatment of VT as well as those with unknown status.

Completed Randomized Control Trials

There have been 4 major prospective RCTs comparing catheter ablation with no ablation for VT in patients with ischemic cardiomyopathy (ICM), which are summarized in later discussion.

Substrate mapping and ablation in sinus rhythm to halt ventricular tachycardia

Published in 2007, the Substrate Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia (SMASH-VT) study was the first large-scale RCT comparing catheter ablation with medical therapy.[5] It was a multicenter prospective RCT that initially enrolled patients with prior myocardial infarction (MI) who underwent recent (within 6 months) ICD implantation for secondary prevention and later included those who received ICD for primary prevention but received an appropriate ICD therapy for a single episode of VT or ventricular fibrillation (VF). Importantly, patients who had been treated with class I or III AADs were excluded from this trial. Patients were randomized 1:1 to either ablation plus ICD or ICD plus standard medical therapy. Those in the ablation group were treated with primarily substrate-based endocardial ablation, although entrainment mapping was performed when VT was hemodynamically stable. The primary endpoint was survival from any appropriate ICD therapy (ATP or shock), and secondary endpoints were freedom from inappropriate ICD shock, death, and ICD storm ($\geq$3 shocks within a 24-hour period). A total of 128 patients were included (64 in the ablation group and 64 in the control group), and after 2 years of follow-up, patients randomized to VT ablation were significantly more likely than those in the control group to achieve freedom from any appropriate ICD therapy (shock or ATP) (88 vs 67%; hazard ratio [HR] 0.35, 95% CI, 0.15–0.78; $P = .007$). However, there was no significant difference in overall survival between groups ($P = .29$).

SMASH-VT enrolled relatively low-risk patients who had experienced a single episode of VT/VF and had not been previously treated with AADs and demonstrated that "prophylactic" substrate modification with catheter ablation in these patients can effectively decrease the likelihood of developing recurrent VT/VF requiring appropriate ICD therapy. Although the study was underpowered to show differences in mortality between groups, there did appear to be a trend toward mortality benefit in the ablation group (9 vs 17%; $P = .29$). One major limitation of the study was the omission of data on ICD programming, which could have influenced outcomes between groups. Importantly, the fact that the control group in SMASH-VT was not treated with AADs limits the relevance of the study results because no comparisons could be made on efficacy and safety between VT ablation versus AADs, including amiodarone.

Ventricular tachycardia ablation in coronary heart disease

The Ventricular Tachycardia Ablation in Coronary Heart Disease (VTACH) study was a prospective multicenter European RCT published in 2010 that compared ICD plus VT ablation with ICD alone.[6] Eligible patients were those with prior MI, with reduced left ventricular ejection fraction (<50%), and had stable VT, who qualified for