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Making ventricular tachycardia VANISH: timing of catheter ablation in secondary prevention

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Take Home Messages

- Guidelines recommend catheter ablation in patients with ventricular tachycardia (VT) and structural heart disease as secondary prevention although the optimal timing remains unclear.
- The VANISH trial was a randomised controlled trial (RCT) comparing catheter ablation of VT versus escalated anti-arrhythmic drug (AAD) therapy in ischaemic cardiomyopathy patients with an implantable cardioverter defibrillator (ICD) and recurrent VT whilst receiving regular AAD therapy.
- In the VANISH trial, VT ablation was superior to escalated AAD therapy in reducing the composite endpoint (death, VT storm or appropriate ICD shock).
- The BERLIN VT trial was a RCT comparing 'preventive' VT ablation and ICD versus ICD and 'deferred' VT ablation in patients with ischaemic heart disease and a secondary prevention indication for ICD.
- In the BERLIN VT trial, preventive VT ablation before ICD implant did not reduce the composite endpoint (all-cause death and unplanned hospitalisation for symptomatic ventricular arrhythmia or worsening heart failure).
- The VANISH and BERLIN VT trials support the use of VT ablation in patients who have received an ICD shock and in those with recurrent VT despite AADs (i.e. Amiodarone or Sotalol).

Introduction

Ventricular tachycardia (VT) is a potentially life-threatening arrhythmia associated with increased mortality risk in patients with structural heart disease, of which ischaemic heart disease is the commonest cause. Implantable cardioverter defibrillator (ICD) therapy prevents sudden cardiac death and reduces mortality risk in patients with ischaemic VT.[1] ICDs can terminate VT by anti-tachycardia pacing (ATP) or by delivering a direct current shock, however they cannot prevent VT recurrence. Furthermore ICD shocks are associated with increased patient mortality and morbidity (e.g. psychological distress and physical trauma).[2,3] The main treatment options to prevent VT recurrence include anti-arrhythmic drugs (AADs) or catheter ablation. For the purposes of this article the term AADs refers to medications with anti-arrhythmic properties excluding conventional betablockers; in the United Kingdom (UK) Amiodarone is typically first line followed by Mexiletine or Sotalol. Prior to the publication of the VANISH (Ventricular Tachycardia Ablation versus Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease) trial in 2016,[2] ischaemic cardiomyopathy patients who received recurrent ICD shocks while on AAD therapy would typically have their drugs (e.g. Amiodarone, Sotalol) escalated in the first instance as it was shown to be more effective than placebo or beta-blockers in randomised controlled trials (RCTs).[4–6] Although consensus statements and guidelines recommended the use of catheter ablation when AAD therapy failed to prevent recurrent VT, they were largely based on expert opinion and case series.[7,8]

About the author

Dr Ven Gee Lim is a Cardiology Registrar subspecialising in Electrophysiology and Devices in the West Midlands Deanery. He graduated with an MBChB (Hons) from the University of Edinburgh in 2009 and obtained his Masters in Internal Medicine (Distinction) from his alma mater in 2014. In 2015, he pursued a PhD at University College London where the focus of his research was the role of SGLT2 inhibitors in cardioprotection.

Prior randomised studies have demonstrated benefit of VT ablation in patients with ischaemic heart disease undergoing an ICD for a primary prevention indication.[9,10] However, it was unclear as to whether VT ablation was superior to AAD escalation in patients with ischaemic heart disease and recurrent VT despite AAD therapy. Furthermore, the optimal timing of catheter ablation in secondary prevention of VT remained unclear. In this article I will describe two recent RCTs addressing the role of VT ablation in secondary prevention: the VANISH trial[2] and the Preventive Ablation of Ventricular Tachycardia in Patients with Myocardial Infarction (BERLIN VT) trial.[11]

The VANISH trial

How does catheter ablation of VT compare with escalated anti-arrhythmic drug therapy?

In the VANISH trial, Sapp *et al* performed the first RCT to compare catheter ablation of VT with escalated AAD therapy in patients with ischaemic cardiomyopathy and an ICD who had VT despite first-line AAD therapy.[2] This was a multicentre collaboration involving 22 tertiary centres in Canada, Europe, the United States and Australia. Patients were included if they had a myocardial infarction (MI) (but not an acute coronary syndrome or a recent ST elevation MI <1month), an ICD implant and an episode of VT while on Amiodarone or another class I or class III AAD within the previous 6 months. Any one of the following were defined as VT episodes: ≥3 VT episodes treated with ATP (≥1 episode was symptomatic); ≥1 appropriate ICD shocks; ≥3 VT episodes within 24 hours; sustained VT below the programmed detection rate of the ICD. The VT episodes had to also be monomorphic with rates of <250bpm.

Patients allocated to the ablation group underwent the procedure within 14 days of randomisation either under conscious sedation or general anaesthesia. Patients in the escalated AAD group were treated with either oral Amiodarone or Amiodarone plus Mexiletine (200mg three times daily) depending on the drug and dose taken at the time of the index arrhythmia.

The AAD escalation protocol was as follows:

1. **For patients already on Amiodarone<300mg once daily (OD):** Amiodarone dose was increaseed (loading dose 400mg twice daily (BD) for 2 weeks then 400mg OD for 1 week then maintenance dose of 300mg OD);
2. **For patients on Amiodarone>300mg OD:** Mexiletine 200mg three times daily was added;
3. **For patients on another AAD:** Amiodarone was initiated (loading dose of 400mg BD for 2 weeks, then 400mg OD for 4 weeks then maintenance dose of 200mg OD).

The primary outcome measure was a composite of death or VT storm (≥3 VT within 24 hours) or appropriate ICD shock after 30-days of treatment. The pre-specified secondary outcomes included each of the primary outcome parameters and adverse effects.

The VANISH trial: Outcomes

In the VANISH trial, 259 patients were randomised with 132 patients allocated to the ablation arm and 127 patients allocated to the escalated AAD arm. No patients were lost to follow-up but 5 patients withdrew from the ablation arm and 4 patients withdrew from the escalated AAD arm. The average age was 67-70 years, predominantly male (93%) with an average of 16 years since last MI. Almost all patients were taking betablockers (~95%), and AADs at baseline predominantly included Amiodarone (~65 %) or Sotalol (~35 %).

During a mean follow up of 28 months, the primary outcome occurred in 59.1% of patients in the ablation group and 68.5% in the escalated AAD group (hazard ratio (HR) 0.72, 95% confidence interval (CI), 0.53-0.98; p=0.04). The significantly lower primary outcome rate in the ablation group was driven mainly by reduction in the rates of appropriate ICD shocks (HR 0.77, 95% CI 0.53-1.14; p=0.19) and VT storm (HR 0.66, 95% CI 0.42-1.05; p=0.08).

Interestingly, if patients were already on Amiodarone at baseline, the benefit in terms of the primary outcome was seen in the catheter ablation group (HR 0.0.55, 95% CI 0.38-0.80; p=0.001). However, if patients were on a non-Amiodarone AAD, then the benefit of catheter ablation was not

observed. There was no difference in mortality between the two groups (HR 0.96, 95% CI 0.60-1.53; p=0.86).

In terms of adverse events, the procedural complications in the ablation group included cardiac perforation (n=2, 1.5%), major bleeding (n=3, 2.3%) and vascular injury (n=3, 2.3%) but there were no procedure-related deaths. However, in the escalated AAD group treatment-related adverse events occurred in more patients (39 vs 20, p=0.003) and were more frequent (51 vs 22, p=0.002). The adverse events in the escalated AAD group included: death (2.4%) from pulmonary toxicity (n=2) and liver dysfunction (n=1), pulmonary infiltration (n=2; 1.6%), thyroid dysfunction (n=10, 7.8%), liver dysfunction n=6, 4.7%) and tremor/ataxia (n=6, 4.7%).

The VANISH trial: Discussion

In summary, in ischaemic cardiomyopathy patients with an ICD who experienced VT despite being on AAD, catheter ablation of VT led to a significantly lower rate of the composite primary outcome of death, VT storm or appropriate ICD shock compared to escalated AAD therapy. Such benefits were only observed in patients who were already on amiodarone when the index arrhythmia occurred. Importantly, the VANISH trial demonstrated that catheter ablation of VT was relatively safe (1.5-2.3% procedural complications with no mortality) compared to escalated AAD therapy (1.6% death with up to 7.8% treatment-related complications).

There were several important limitations of the trial. Firstly, the treatment allocation was unblinded due to the different nature of both interventions. However subjecting patients to a sham procedure comes with its own ethical challenges and may expose patients to significant procedural risks. Secondly, the trial was inadequately powered to assess the effect of the intervention on a hard end point – mortality. Thirdly, this was a multicentre trial with variations in the procedural experience and outcomes. It may be possible that undergoing VT ablation in a more specialised referral centre may have led to better outcomes. Nevertheless, the inclusion of multiple centres makes the findings more generalisable. Lastly, patients enrolled into the VANISH trial had a high disease burden with advanced disease progression where VT ablation was second-line therapy.

Nevertheless this was a high impact clinical trial which demonstrated important and relevant findings that paved the way for the international guideline recommendation for the use of catheter ablation of VT in ischaemic cardiomyopathy patients with an ICD who present with recurrent monomorphic VT/VT storm/ICD shocks despite AAD therapy.[12]

The first VT ablation trial published in the new decade: the BERLIN VT trial

Does the timing of VT ablation pre/post-ICD implantation matter?

This was the question addressed by the latest trial on catheter ablation of VT which was published in January 2020 by the BERLIN VT investigators.[11] The BERLIN VT trial sought to examine if a preventive VT ablation strategy before a secondary prevention ICD implantation can improve outcomes compared to the routine practice of deferred ablation strategy after multiple ICD therapies. The hypothesis was that VT ablation before ICD implantation would be more effective at preventing subsequent ICD therapies, compared to a deferred ablation strategy. It is worth remembering that this study was different to the VTACH trial which compared a preventive VT ablation strategy against no ablation.[10] The SMASH-VT trial was also different as it compared VT ablation post-ICD implantation against no ablation.[9] Furthermore, other previous studies had only compared VT ablation with non-ablative therapies.[2,13]

The BERLIN VT study was a multicentre RCT which included 26 clinical centres in Europe. Patients were included if they had a prior MI (older than 4 weeks), a moderately reduced left ventricular ejection fraction (30-50%), and any stable or life-threatening ventricular arrhythmias requiring an ICD implantation.

Patients were randomly assigned (1:1) to receive catheter ablation for VT either before ICD implantation (‘preventive ablation strategy’) or after ICD shock for VT (‘deferred ablation strategy’). Patients allocated to the ‘preventive ablation strategy’ group had to undergo the procedure within 2 weeks of enrolment and then receive an ICD. In contrast, patients in the ‘deferred ablation strategy’ group underwent the procedure only after the third appropriate ICD shock for VT. It is worth noting

that the patients and investigators were not blinded to the treatment assignment.

The primary outcome measure was a composite of all-cause mortality and unplanned hospitalisation (at least one overnight stay) for either symptomatic VT or worsening heart failure. The secondary outcome measures were: Sustained VT or ventricular fibrillation, appropriate and inappropriate ICD therapy, all-cause mortality, cardiovascular mortality, unplanned hospitalisation for any cause and cardiac reasons, change in quality of life from enrolment to the 12-month follow-up.

The BERLIN VT trial: Outcomes

Using the prespecified criteria for interim analyses, the trial was terminated early due to futility. 163 patients were randomised with 77 patients allocated to the preventive ablation arm and 86 patients allocated to the deferred ablation arm. 4 patients (1 in preventive group, 3 in deferred group) dropped out before any study procedure or follow-up and were excluded from the analysis. In the preventive ablation group, 7/76 (9.2%) patients did not undergo ablation; reasons included non-inducible VT (n=3), ablation refusal (n=2), lack of scarred substrate (n=1) and redirection to cardiac surgery (n=1). As for the 90.8% who underwent ablation, the acute ablation success was 76.8% according to non-inducibility of VT. In the deferred ablation group, 10/83 (12%) underwent VT ablation at a median of 46 days after enrolment with an acute ablation success of 80% according to non-inducibility of VT.

During a mean follow up of 418 days in the prevention ablation group and 376 days in the deferred ablation group, there was no difference in the primary outcome (HR 1.09, 95% CI 0.62-1.92; p=0.77). Among the secondary outcomes, the proportion of patients with sustained ventricular tachyarrhythmia (39.7% vs 48.2% p=0.050) and appropriate ICD therapy (34.2% vs 47.0% p=0.030) were numerically reduced in the preventive ablation group (no P-value adjustment for multiple testing). The large standard deviations and small patient numbers made it difficult to draw any further conclusions from the other secondary outcome measures.

The BERLIN VT trial: Discussion

In summary, the BERLIN VT study found that preventive VT ablation before ICD implantation did not reduce the primary composite endpoint of all-cause mortality and hospitalisation for symptomatic ventricular arrhythmia or worsening heart failure at 1 year follow-up. However, the patients in the preventive VT ablation group had fewer ventricular arrhythmias and ICD therapies compared to that of the deferred VT ablation group.

There were several important limitations of the trial. Firstly, like most VT ablation trials the patients and investigators were not blinded to the treatment allocation. Secondly, the small number of patients in both arms was secondary to the slow patient enrolment (similar to SMASH-VT and VTACH) as well as the high crossover rates (9.2% of patients in the preventive ablation group did not receive ablation while only 12% in the deferred group received ablation). In addition, not all the BERLIN VT investigators adhered to the protocol-defined timing of catheter ablation in the deferred ablation group for various reasons (only 2 patients underwent ablation after 3 ICD shocks as per protocol).

Therefore, the findings of BERLIN VT trial suggest that ischaemic VT ablation should be utilised only upon the recurrence of VT post-ICD implantation. This has the added benefit of avoiding exposure of patients to the risks of invasive catheter ablation.

Table 1 highlights the key findings of the VANISH and BERLIN VT trials.

Table 1. Summary of the VANISH and BERLIN VT trials

Study	VANISH[2]	BERLIN VT[11]
Research question	Is catheter ablation of VT better than escalated AAD therapy in treating VT in ischaemic cardiomyopathy patients who already have an ICD?	When is the optimal time to perform VT ablation in ischaemic cardiomyopathy patients who are suitable for an ICD? 2 weeks before a planned ICD or wait until VT recurs?
Description	RCT comparing **catheter ablation of VT** vs **escalated AAD therapy** in ischaemic cardiomyopathy patients with ICD who had VT despite established AADs.	RCT comparing a **'preventive' VT ablation** strategy at 2 weeks pre-ICD implantation vs '**deferred' VT ablation** strategy after 3 ICD therapies in patients with stable ischaemic cardiomyopathy and VT.
Patient numbers	N=259. Ablation arm (N=132) vs escalated AAD arm (N=127)	N=159. Preventive ablation arm (N=76, 90.8% received ablation) vs Deferred ablation arm (N=83, 12% received ablation)
Primary outcome	**VT ablation led to reduction in the composite primary endpoint of death, VT storm or appropriate ICD shock** compared to escalation of AAD. Driven by a reduction in VT storm and appropriate ICD shock.	**No difference in the composite primary endpoint** of all-cause mortality and hospitalisation for heart failure or arrhythmia.
Other significant findings	If patients were already on amiodarone at baseline, the benefit in terms of the primary outcome was seen in the catheter ablation group. However, if patients were on a non-amiodarone AAD, then the benefit of catheter ablation was not observed. No difference in mortality between the two groups	Reduction in sustained VT and appropriate ICD therapy in the preventive ablation group. The large standard deviations and small patient numbers made it difficult to draw any further conclusions from the other secondary outcome measures.

AAD antiarrhythmic drug, BERLIN VT Preventive Ablation of Ventricular Tachycardia in Patients with Myocardial Infarction, ICD implantable cardioverter defibrillator, MI myocardial infarction, RCT randomised controlled trial, VANISH Ventricular Tachycardia Ablation versus Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease, VF ventricular fibrillation, VT ventricular tachycardia.

Conclusion

The VANISH trial and the recently published BERLIN VT trial have helped shed light on the optimal timing of VT ablation as a secondary prevention treatment of VT in patients with ischaemic cardiomyopathy (see **Figure 1**). The positive findings from the VANISH trial have led to catheter ablation of VT recommended as the treatment of choice in ischaemic cardiomyopathy patients with an ICD who present with recurrent VT/ICD shocks despite AAD therapy (i.e. already taking Amiodarone or Sotalol).[12] The BERLIN VT trial suggests that following index presentation, VT ablation provides no added benefit to ICD implantation but can be safely deferred until recurrence of VT/ICD therapies. Excitingly, more VT ablation trials are being conducted in this new decade and their findings will hopefully help refine patient selection and optimal timing of intervention as well as improve the efficacy and safety of ablation techniques.

Disclosures

None.

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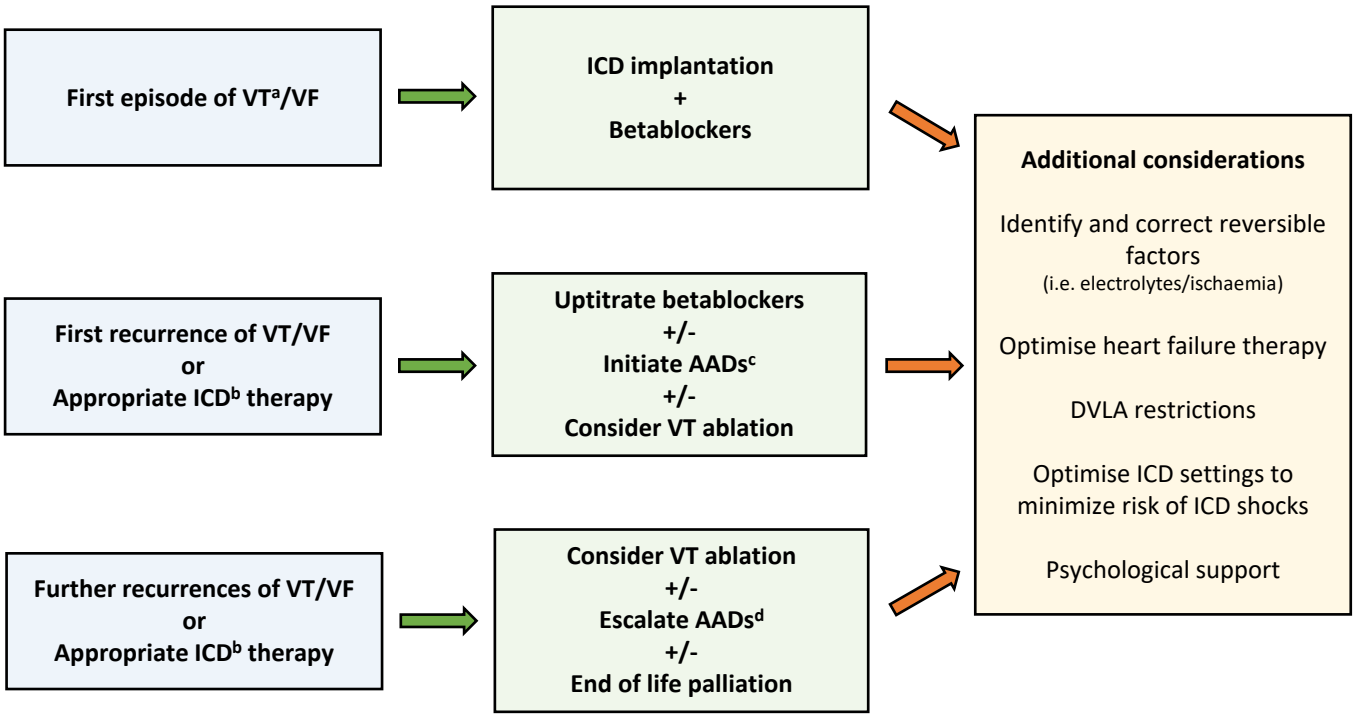

Figure 1. Suggested algorithm for the management of ischaemic ventricular tachycardia

[a] Sustained VT with haemodynamic compromise, [b] including anti-tachycardia pacing, ICD shocks or VT storm, [c] AADs defined as antiarrhythmic drugs excluding betablockers (e.g. in the UK typically Amiodarone is used first line, Sotalol or Mexiletine as second line), [d] Escalation protocol in the VANISH trial: if patient is already on Amiodarone <300mg OD then increase dose (loading dose 400mg BD for 2 weeks then 400mg OD for 1 week then 300mg OD as maintenance); if already on Amiodarone >300mg OD add Mexiletine (200mg three times daily); if patient on another AAD, then start Amiodarone (loading dose 400mg BD for 2 weeks, then 400mg OD for 4 weeks then 200mg OD as maintenance). AAD antiarrhythmic drugs, DVLA driver and vehicle licensing agency, ICD implantable cardioverter defibrillator, VT ventricular tachycardia, VF ventricular fibrillation.

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