![Cochrane Library logo](Cochrane Library)

Cochrane Database of Systematic Reviews

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

Kakarla J, Benson C, Abbas M, Begg G, Twomey D, Thornley A, Bates M, Ahmad M, Arif H, Banerjee A, Manmathan GPR, Lambiase PD, James S

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

i

[Intervention Protocol]

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease

Jayant Kakarla[1], Chris Benson[1], Mohamed Abbas[1], Gordon Begg[1], Darragh Twomey[1], Andrew Thornley[1], Matthew Bates[1], Mahmood Ahmad[2], Haseeb Arif[3], Amitava Banerjee[4], Gavin Paul Raphael Manmathan[5], Pier D Lambiase[6], Simon James[1]

[1]James Cook University Hospital, Middlesbrough, UK. [2]Department of Cardiology, Royal Free Hospital, Royal Free London NHS Foundation Trust, London, UK. [3]School of Medicine, Queen's University Belfast, Belfast, UK. [4]Institute of Health Informatics Research, University College London, London, UK. [5]Institute of Cardiovascular Sciences, University College London, London, UK. [6]Centre for Cardiology in the Young, The Heart Hospital, University College London Hospitals, London, UK

Contact: Jayant Kakarla, j.kakarla@nhs.net.

A B S T R A C T

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess and compare the effects of catheter ablation for ventricular tachycardia (VT) with escalation of antiarrhythmic drugs (AADs) in patients with ischaemic heart disease (IHD).

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

1

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

BACKGROUND

Description of the condition

Ventricular tachycardia (VT) is an abnormal rhythm arising from the ventricles (the largest chambers of the heart) and can occur in hearts that are either normal or abnormal in structure. It is characterised on an electrocardiogram (ECG) by a tachycardia (i.e. heart rate > 100 beats per minute) with a broad QRS. The QRS is the part of the ECG that represents the depolarisation (or electrical activation) of the ventricles and, in VT, the QRS duration is > 120 milliseconds. VT can cause symptoms of palpitation, chest pain, breathlessness, dizziness (presyncope) or blackout (syncope). VT can result in haemodynamic instability (a significant reduction in blood pressure) or cardiac arrest (sudden failure of the heart's pump function) and is a common cause of sudden cardiac death (Markman 2018).

VT is classified according to morphology (i.e. ECG appearance), duration and clinical effects.

- Non-sustained VT does not cause haemodynamic instability and terminates spontaneously within 30 seconds
- Sustained VT lasts > 30 seconds and/or requires termination through an intervention and/or causes haemodynamic instability or syncope

VT can be further classified by its ECG appearance as monomorphic (each beat is the same) or polymorphic (beats are different from each other). Monomorphic VT is associated with scar tissue caused by ischaemic heart disease (IHD, narrowing of the heart arteries), or non-ischaemic causes such as hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy, right ventricular dysplasia, infiltrative heart disease (e.g. sarcoidosis), or prior cardiac surgery. Polymorphic VT is associated with a generalised abnormality of the myocardium (heart muscle) and has multiple causes including acute myocardial ischaemia (a sudden lack of blood supply) and significant abnormalities of electrolytes (or blood salts) but also occurs in inherited conditions including both short and long QT syndrome, Brugada syndrome and catecholaminergic polymorphic VT. Finally, idiopathic VT is a form of VT in which none of the above causes can be found (Koplan 2009).

IHD is the commonest cause of VT and patients with IHD can present with monomorphic or polymorphic VT. Polymorphic VT in IHD is most commonly associated with acute myocardial ischaemia and is often managed by treatment to reduce ischaemia, including interventions to restore myocardial blood supply (i.e. coronary revascularisation) (Tung 2010).

Monomorphic VT in ischaemic heart disease (but in the absence of acute ischaemia) is associated with scar tissue in the myocardium caused by prior myocardial infarction (MI; heart attack). After an infarct, a remodelling process occurs and necrotic (dead) myocardium is replaced with fibrous tissue that surrounds surviving myocytes within the scar. These surviving myocytes conduct energy abnormally due to a variety of cellular and extracellular factors, exhibiting exaggerated anisotropy (different speeds of electrical conduction), slowed conduction velocities, and conduction block. With remodelling, channels of these surviving, abnormal myocytes can connect areas of healthy myocardium around an infarct. This creates the substrate for re-entry – a self-perpetuating 'loop' of electrical activation that conducts slowly through the scar to an exit site and then rapidly through the normal myocardium back to an entry site into the scar, leading to sustained monomorphic VT (Cronin 2019; Stevenson 1993; Stevenson 1998; Wilber 1995). The electrical substrate for re-entry, within an infarct scar, can be detected in many patients with assessment of electrical conduction in normal (sinus) rhythm. Endocardial recordings (i.e. from the inner surface of heart muscle) in areas of myocardial scar that can support VT, consistently demonstrate low amplitude (low intensity of the electrical charge), prolonged duration, and multicomponent potentials (electrical charges which are complex) frequently occurring after the end of the QRS complex when assessed during sinus rhythm. These signals are often termed "late potentials" (Cronin 2019; Stevenson 1993; Stevenson 1998; Wilber 1995).

The overall incidence of VT (of any cause) globally is difficult to determine, as individuals must have cardiac monitoring in place for it to be detected (e.g. non-sustained VT) and such monitoring has not been commonly used in large populations of asymptomatic people. The paucity of data in developing countries creates further challenges in estimates of global VT incidence. A 2018 study of half a million UK biobank members found that 0.16% of patients aged < 55 years, 0.37% of those aged 55 to 65 years and 0.59% of those aged > 65 years had any ventricular arrhythmia, including VT (Khurshid 2018). An indirect but useful method of looking at incidence of VT is through the incidence of sudden cardiac death, as the majority of sudden cardiac death is caused by VT or ventricular fibrillation (VF; another abnormal rhythm that causes cardiac arrest), and data on sudden cardiac death is often more widely available internationally. The annual incidence of sudden cardiac death is 50 to 100 per 100,000 in the USA and Europe (Fishman 2010). A study in Cameroon showed an annual incidence of sudden cardiac death of 31.3 per 100,000 (Bonny 2017), and in China the incidence was 41.8 per 100,000 (Hua 2009).

Regarding the specific focus of this review, the incidence of sustained monomorphic VT after ST-elevation MI (STEMI) has reduced due to smaller infarct sizes (i.e. smaller areas of scar) following the widespread availability of primary percutaneous coronary intervention (PCI). This has enabled emergency reopening of blocked arteries in patients with STEMI and similar early invasive management with PCI in patients with acute coronary syndromes, including non-STEMI (Anter 2014). This reduction, however, has occurred in the context of increased prevalence (proportion of the overall population) of IHD, owing to an ageing population and better survival following MI. The time interval from infarct to first episode of VT is highly variable, frequently occurring after many years (De Bakker 2000; Roy 1986). In some longitudinal cohorts (a large group of patients followed up for a period of time), only a minority of patients, about 10%, will develop scar-related VT following a MI over the course of their life (Tran 2019). Approximately 30% of those who develop VT will experience the first episode of sustained monomorphic VT within the first year of MI, with a predictable incidence (rate of occurrence of a disease) of 2% to 5% per year thereafter (De Bakker 2000; Roy 1986; Anter 2014).

Description of the intervention

Catheter ablation is an established treatment option for recurrent VT in patients with IHD (Josephson 2016; Anter 2014). This

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

2

minimally-invasive procedure is carried out in a cardiac catheter laboratory, under general anaesthetic or conscious sedation. The aim of ablation is to identify the causative areas of abnormal myocardium (i.e. scar) and render them electrically inert, and therefore unable to sustain further VT. Catheters are introduced to the endocardial surface of the heart usually via the femoral blood vessels under fluoroscopic (x-ray) guidance. The epicardium (outside surface of the heart) can also be accessed if required via a percutaneous route. The catheters are equipped with tip electrodes that allow recording of cardiac electrical activity at precise locations – both the amplitude (voltage) and timing of electrical activation, with reference to a stable electrode elsewhere in the heart or the surface ECG. Three-dimensional electroanatomical mapping systems are able to localise these catheters using magnetic fields and/or electrical impedance, and thus be used to create a geometrical model of the heart, incorporating electrical information of the tissue. Substrate mapping is commonly used to identify areas that can support re-entrant VT. Abnormal channels of tissue within the scar (or isthmuses) can be heated using radiofrequency energy emitted from an ablation catheter, and thereby rendered electrically inactive (Cronin 2019). Catheter ablation of scar-related VT requires an advanced level of experience by the operator and laboratory staff, availability of specialised technology, and commonly support from both anaesthetic and cardiothoracic surgical staff. As such, it is resource-intensive and generally only available in specialist (tertiary) centres. From a global perspective, access to VT ablation as a treatment option may be currently limited.

Practically, the immediate priority in the acute treatment of a patient with ongoing VT is restoration of sinus rhythm. This is usually accomplished using antiarrhythmic drugs (AADs; drugs that work on the electrical system of the heart) and/or electrical direct current cardioversion with correction of any underlying precipitant of VT (e.g. acute ischaemia, electrolyte disturbance, anaemia). The priority then becomes prevention of further VT, and drug therapy will usually be continued to reduce this risk (Priori 2015). Commonly used AADs are disopyramide, quinidine, mexiletine, propafenone, amiodarone, procainamide, sotalol, dofetilide, dronedarone and ranolazine. These are often divided using the Vaughan-Williams Classification into class I (sodium channel blockers), class II (beta-adrenergic receptor blockers), class III (potassium channel blockers) and class IV agents (calcium channel blockers) (Darbar 2014). There are significant trials in this area using a variety of AADs to prevent VT, including beta blockers, amiodarone and sotalol (in the OPTIC study) (Chen 2005; Connolly 2006).

After a patient survives an episode of VT without a reversible cause, an implantable cardioverter-defibrillator (ICD) will often be considered to reduce the risk of future sudden cardiac death (Priori 2015). ICDs can provide immediate treatments to terminate VT or VF, but they cannot prevent the occurrence of VT/VF. ICDs are also considered for primary prevention (i.e. in the absence of previously documented VT) in patients who have severely reduced left ventricular ejection fraction (Priori 2015), as the risk of sudden cardiac death is significantly elevated in this group.

Essentially, there are two treatment options in patients presenting with recurrent VT, either catheter ablation and/or a change in their pharmacological therapy, referred to as escalation of antiarrhythmic therapy. In practical terms, escalation involves commencing a new antiarrhythmic agent in addition to or to replace the agent they were taking at the time of their recurrent VT. Escalating pharmacological therapy may be limited by side effects, adverse drug interactions and/or further recurrent VT. In these scenarios, further escalation of therapy with an alternative AAD regime or VT ablation should be considered. In patients with an ICD, recurrent VT may also result in multiple therapies (including shocks) which can have significant adverse psychological effects (Manzoni 2015). Sapp et al carried out a multicentre trial showing that in patients with poor left ventricular function with ICDs and recurrent VT, those undergoing invasive catheter VT ablation had a better combined composite outcome (mortality, shocks and VT storm) than patients with escalated medical therapy alone (Sapp 2016). A meta-analysis within this population reported those undergoing invasive VT ablation had lower rates of shocks, VT storm or hospitalisation compared with AAD alone. Adverse effects were, however, only reported in a single publication, which suggested it was more common in the AAD arm (Martinez 2020).

How the intervention might work

Catheter ablation for VT is a minimally-invasive procedure involving passing long catheters through the veins, typically from the groin, to the bottom chambers of the heart to localise critical areas of myocardium necessary to sustain VT. These areas are exposed to a localised burst of radiofrequency energy to create a small lesion 4 mm to 5 mm in diameter. The number of lesions required to render the tissue electrically inert, and therefore break the VT circuit, is variable. To access the left ventricle from the right heart, where the veins typically enter, a needle may be used to puncture the intra-atrial septum (the wall separating the two top chambers of the heart) and a sheath used to access the left ventricle via the mitral valve. Alternatively, a catheter can be passed from an artery in the groin to access the left ventricle retrogradely via the aorta. A three-dimensional electroanatomical map is created by moving the catheter within the heart chambers using a computer mapping system. The catheter position is determined using the mapping system and x-ray (flouroscopy) (Tung 2010).

If the VT originates from the outside surface of the heart, then a puncture may be performed beneath the breast bone to access the pericardium (an external covering of the heart separated from it by a fluid layer). The ablation catheter is then manipulated within the pericardial sac. The ablation procedure is usually performed under deep sedation or general anaesthesia. The procedure is complex and usually performed at specialist (tertiary) centres (Tung 2010).

Patients with VT generally undergo ICD implantation alongside AADs. An ICD does not stop a patient from going into VT but can provide antitachycardia pacing (ATP) therapy (i.e. pacing the heart at a fast rate to break the VT circuit) or deliver electrical shocks to terminate VT. However, some patients may undergo VT ablation as an additional therapy due to multiple ICD shocks or intolerance of AADs. Success rates for VT ablation vary and are highest in patients with IHD. Due to the length (3 to 6 hours) and complexity of the procedure, an experienced operator is needed with a success rate of 70% for > 90% reduction in VT burden at 12 months (Tung 2010). In comparison, radiofrequency ablation of accessory pathways in Wolff-Parkinson-White syndrome has a success rate of > 95% (Sacher 2010). VT ablation complications include vascular complications (3.6%), cardiac tamponade (0.45%) and thromboembolic (i.e. leg vein clots or clots in the pulmonary

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

3

(lung) arteries) events (0.7%) (Peichl 2014). VT ablation has an in-hospital mortality of 2.7% and a complication rate of 11.5% with a 30-day readmission rate of 19.2%. VT recurrence accounts for 41% of readmissions within 30 days (Cheung 2018).

The macro re-entrant circuits (circuitous electrical loops that cover a large area) in VT involve both structural and functional barriers to conduction. In fact, it is scar tissue separating viable myocytes that forms many of the circuitous and critical pathways in the re-entrant circuits of VT. The ablation strategy relies on targeting channels of residual myocardium within the scar that cause slow conduction and allow re-entry. In the case of VT caused by a previous MI, the anatomical substrate is usually on the subendocardial (inner) layer of the ventricular myocardium. Broadly, two methods are employed during catheter ablation. The first is to map electrical activation of the heart while the patient is in VT, and perform pacing manoeuvres known as 'entrainment', to identify the critical part of the circuit by which the VT is sustained and target it with ablation (Cronin 2019; Josephson 2016; Anter 2014).

However, haemodynamic intolerance often limits electroanatomical mapping during VT. In such cases, target areas are identified with 'substrate mapping' while the patient is in sinus rhythm or a rhythm controlled by pacing. Using this approach, the mapping can identify areas of scar (manifested by low-voltage signals) and the channels of abnormal myocytes that run through the scar, to target for ablation, without the need for ongoing VT (Al-Khatib 2015; Cronin 2019; Josephson 2016).

The comparator to ablation for the purposes of this review is pharmacological therapy with AADs. Multiple medications can be used. Cardioselective beta blockers are first line and were shown in the CIBIS II trial to reduce sudden cardiac death by 44% in patients with heart failure (Chen 2005). Amiodarone is also well established (despite its significant side effect profile) but in the era of ICD use for primary prevention, did not show a mortality benefit (Brady 2005). Amiodarone and beta-blockers together, were shown to be superior to monotherapy with sotalol or beta blockers in the OPTIC trial for secondary prevention ICD recipients, and its use was also associated with a reduction in ICD shocks (Connolly 2006). Sotalol has also been shown to reduce shocks and sudden death in secondary prevention ICD patients, however the OPTIC trial showed significant discontinuation rates (Pacifico 1999). Flecainide is no longer used, as the CAST trial showed it increased mortality in patients with previous MI (Echt 1991). Class I agents overall are inferior to sotalol and amiodarone, but mexiletine is still used occasionally (Exner 2001). Quinidine, procainamide, and disopyramide, which are class Ia antiarrhythmic agents, can also be used as third line for VT, but suffer from a significant risk of torsade de pointes and poor tolerability (Gillis 2004). Combination therapy with class I and III agents may be better than therapy with one agent alone (Van Herendael 2010). Dofetilide has also been used and shown to reduce VT, and may have a role to play in patients who are intolerant of sotalol and amiodarone (Boriani 2001). Ranolozine has also been shown to reduce VT post non-STEMI (Scirica 2007). Finally two drugs that have been used in small trials of VT are azimilide and celivarone (Dorian 2004; Kowey 2011).

Why it is important to do this review

VT is a common and potentially life-threatening cardiac rhythm problem that is frequently challenging to manage. Scar-related re-entry is the most common cause of sustained monomorphic VT in the presence of structural heart disease. Prior MI is the most common cause of structural heart disease, although scar-related VT can occur in other myocardial diseases (Anderson 2019; Markman 2018).

VT, despite AADs, often recurs and can result in haemodynamic compromise and ICD therapies in the form of either shocks or ATP. Patients with recurrence have worse outcomes and a reduction in VT burden and ICD therapies is desirable. Therapeutic options include escalating antiarrhythmic drug therapy by increasing the dose, changing the drug, or adding a new drug. An alternative option is VT ablation (Sapp 2016). The most recent European Society of Cardiology (ESC) guidelines in management of VT and sudden cardiac death recommend catheter ablation or amiodarone therapy for treating recurrent ICD shocks caused by sustained monomorphic VT (Priori 2015). The Heart Rhythm Society/European Heart Rhythm Association (HRS/EHRA) consensus statement on catheter ablation for ventricular arrhythmias recommends catheter ablation for symptomatic sustained monomorphic VT, including VT terminated by an ICD, that recurs despite antiarrhythmic drug therapy or when antiarrhythmic drugs are not tolerated or not desired (Cronin 2019). The optimal choice of therapy between escalated drug therapy and VT ablation in reducing recurrent VT and ICD therapies amongst patients taking AADs is still uncertain and will be the focus of this review.

AAD therapy is almost universally used as first-line therapy for these patients; however, catheter ablation is increasingly recognised as a particularly important option in recurrent VT. In current day-to-day practice, catheter ablation is a key strategy for patients with VT when AADs are ineffective, not tolerated, or not desired by the patient. The purpose of this review is to examine the evidence, according to standardised Cochrane methodology, in order to establish the effectiveness of catheter ablation in managing recurrent VT compared to escalation of antiarrhythmic drugs. Whilst there are a number of published randomised control trials and meta-analyses within this field, we feel a comprehensive and up-to-date review, specifically in the context of IHD, rather than all structural heart disease, is required and would add to the literature (Al-Khatib 2015; Anderson 2019; Carbucicchio 2008; Deneke 2011; Izquierdo 2012; Kuck 2010; Kuck 2017; Kumar 2017; Mallidi 2011; Martinez 2020; Morawski 2017; Muser 2017; Nayyar 2013; Reddy 2007).

O B J E C T I V E S

To assess and compare the effects of catheter ablation for ventricular tachycardia (VT) with escalation of antiarrhythmic drugs (AADs) in patients with ischaemic heart disease (IHD).

M E T H O D S

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled trials (RCTs) that have compared the safety and efficacy of catheter ablation for VT versus antiarrhythmic drugs (AAD). We will include studies published as full text, as abstract only, and those which are unpublished. For the purpose of this review, we anticipate that sufficient RCTs have been conducted to answer this clinical question and therefore we will not include any non-randomised studies. We do not anticipate that we

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

4

will encounter any cluster-randomised trials. However, if such trials are identified, they will be included. We are not planning to include cross-over trials due to the risk of carry-over effect with AADs, such as amiodarone, which have long-term effects.

Types of participants

We will include studies that recruited patients with recurrent scar-related VT who are aged 18 years or above, with a history of IHD. In case only a subset of eligible participants are presented in a trial, we will contact study authors to request a full data set. If authors are unwilling or unable to provide additional information, we will include those studies in which at least 80% of included participants are eligible in our review.

We will exclude patients with non-ischaemic VT.

Types of interventions

We will compare all forms of catheter ablation for VT (with or without AAD therapy) in patients with structural heart disease to escalation of AAD therapy.

We will have two comparisons, the first is catheter ablations with AADs versus escalation (i.e. increased dose of current drug, addition of new drug, change of drug) of AADs alone; and the second is catheter ablations without AADs versus escalation of AADs alone.

We will include all forms of catheter ablation for VT, including endocardial as well as epicardial approaches, using both conventional as well as 3-dimensional mapping systems using radiofrequency. We will include both substrate and arrhythmia mapping strategies.

Concomitant therapies, including any heart failure treatment, such as medical therapy (drugs), as well as device therapy (pacemakers and defibrillators), and exercise or dietary treatments will be eligible, given that they are equally available to all participants.

Types of outcome measures

Definitions and measurement of clinical events will be according to the individual trials. Where a published report does not appear to report one of these outcomes, we will access the trial protocol and contact the trial authors to ascertain whether the outcomes were measured but not reported. We will include relevant trials that measured these outcomes but did not report the data at all. We will assess the outcomes at the longest follow-up point.

Primary outcomes

- Ventricular arrhythmia recurrence rate
- All-cause mortality
- Cardiovascular mortality

Secondary outcomes

- Cardiac rehospitalisation
- Appropriate ICD therapies (ICD shocks or ATP)

- Adverse events
  - acute procedural complications including
    - stroke
    - pericardial tamponade
    - major bleeding
  - related to AADs, including events requiring discontinuation and or other treatment to counteract the adverse event, such as
    - corneal microdeposits
    - thyroid dysfunction
    - liver dysfunction
    - pulmonary fibrosis
    - QT prolongation
    - Torsade de Pointes
- VT storm (defined as ≥ 3 episodes of VT, or shocks, or both, within 24 hours)

Recurrence of ventricular arrhythmias (VT and VF) will be accessed on ICD check logs. In patients with no ICDs, we will take into account all the documented ventricular arrhythmia events, whether on a 12-lead ECG, or any form of cardiac rhythm monitor, provided that the treating physicians were satisfied with the diagnosis of ventricular arrhythmia.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases for relevant trials, from their inception to the present, and we will impose no restriction on language or publication status.

- Cochrane Central Register of Controlled Trials (CENTRAL) (in the Cochrane Library)
- MEDLINE (Ovid, from 1946)
- Embase (Ovid, from 1980)
- Science Citation Index Expanded on the Web of Science (Clarivate Analytics, from 1900)

We will apply the Cochrane sensitivity-maximising RCT filter (Lefebvre 2021) to MEDLINE (Ovid) and adaptations of it to the other databases, except CENTRAL.

In order to identify ongoing or unpublished trials, we will search the following electronic databases.

- World Health Organisation (WHO) International Clinical Trials Registry Platform (www.who.int/ictrp/en)
- ClinicalTrials.gov (clinicaltrials.gov)
- Clinical Trials Register EU (www.clinicaltrialsregister.eu)

We will consider adverse events described in included studies only.

Searching other resources

We will handsearch reference lists of included trials and reviews on the topic of ablation in ventricular arrhythmia. We will also examine any relevant retraction statements and errata for included studies.

Data collection and analysis

We will perform the review and meta-analysis according to the recommendations in the *Cochrane Handbook for Systematic*

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

5

Reviews of Interventions (Higgins 2021a). We will include all eligible trials in the analysis, regardless of publication status.

Selection of studies

Two review authors (HA and GM) will independently screen titles and abstracts of all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, a third review author will be asked to arbitrate (SJ). We will retrieve the full-text publications and two review authors (HA and GM) will independently screen these to identify studies for inclusion and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a fourth review author (MAh). We will identify and exclude duplicates and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table (Liberati 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. One review author (JK, CB or GB) will extract study characteristics from included studies. We will extract the following study characteristics.

- Methods: study design, total duration of study, number of study centres and location, country published in, study setting, and date of study
- Participants: N randomised, N lost to follow-up/withdrawn, N analysed, mean age, age range, gender, inclusion criteria, and exclusion criteria, how they were randomised (allocation random, allocation sequence concealed, baseline differences between intervention groups (comments), awareness amongst participants and carers of the intervention, deviations from outcome due to trial context, whether these deviations were in both groups, the analysis done to estimate the effect of assignment to intervention, age, number of males and females, smoking status, hypertension, diabetes mellitus, high cholesterol, history of cardiovascular disease, left ventricular ejection fraction, history of previous reduced left ventricular function
- Interventions: intervention, comparison, concomitant medications, pacemaker type (Single chamber, dual chamber or biventricular pacemaker or cardiac resynchronisation therapy defibrillator (CRT-D)
- Outcomes: primary and secondary outcomes specified and collected, and time points reported, measurement methods and thresholds reported. We will also look specifically at missing data.
- Notes: funding for trial, and notable conflicts of interest of trial authors

Two review authors (HA and GM) will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving a third review author (GB). One review author (GM) will transfer data into the Review Manager file (Review Manager 2020). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the data extraction form. A second review author (MAh) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (GM, MAh) will independently assess risk of bias for each study using RoB 2, outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b). We will resolve any disagreements by discussion or by involving another review author (MB). We will assess the risk of bias of a specific result of a trial according to the domains of:

- bias arising from the randomisation process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome; and
- bias in selection of the reported result.

We will assess the risk of bias for the outcomes of the included trials that will be included in our summary of findings table.

We will use the signalling questions in the RoB 2 tool and rate each domain as 'low risk of bias', 'some concerns' or 'high risk of bias'. We will summarise the risk of bias judgements across different studies for each of the domains listed for each outcome. The overall risk of bias for the result is the least favourable assessment across the domains of bias.

We will be interested in quantifying the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended (the 'intention-to-treat effect'). When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

We will be using the RoB 2 Excel tool to carry out our assessment (RoB 2 Excel 2019). Due to the large amount of data generated by the RoB 2 tool, we will be unable to list all of this in the full review, apart from a RoB 2 table giving overall risk of bias. We will however list all the consensus decisions for the signalling questions in a supplemental data file. For cluster-RCTs, we will use the RoB 2 tool as it is and add an additional domain specific for cluster-RCTs from the archived version of the tool (Domain 1b - 'Bias arising from the timing of identification and recruitment of participants') (RoB 2 for cluster-randomized trials 2021), and use the signalling questions from the archived version and the guidance in the *Cochrane Handbook* (Higgins 2021a).

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs).

Unit of analysis issues

We will be including multiple-arm RCTs as well as cluster-RCT trials. We will overcome unit of analysis error in a cluster-randomised trial by conducting the analysis at the same level as the allocation. We will analyse the data considering each cluster as a unit of analysis. However, in cluster-RCTs in which the unit of analysis is not reported, we will calculate the effective sample size using an intracluster correlation coefficient (ICC; Higgins 2021c).

If we have trials that could contribute multiple, correlated, comparisons with multiple treatment arms we will combine groups to create a single pair-wise comparison for analysis.

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

6

Regarding multiple observations on patients, we will select the longest follow-up from each study.

Dealing with missing data

We will record any missing data on our data collection form. We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). If we do not receive a response, we will evaluate the data missing due to participants' dropout using intention-to-treat analysis (ITT).

Where possible, we will use the RevMan calculator to calculate missing standard deviations using other data from the trial, such as CIs, based on methods outlined in the *Cochrane Handbook* (Higgins 2021a). If we cannot obtain this information, we will impute those values by taking the mean of the variance of other studies reporting on the same outcome using the same methodology.

If important information is missing, such as number of participants, means, or standard deviations, but standard error, 95% CI or P values are reported, we will calculate an effect estimate, when appropriate, using the generic inverse variance method (Higgins 2021a). We will do this for all studies with missing standard deviations/errors.

We will then undertake a sensitivity analysis excluding those studies with a high level of missing data for that outcome. We will consider missing data to be substantial if the outcome data were missing for > 20% of the participants. We will compare the rates of missing data between groups to determine if asymmetry is present.

Assessment of heterogeneity

We will assess heterogeneity among the studies using the Chi^2 test from the forest plot. Heterogeneity may be indicated if there is a statistically significant result (P < 0.10). However, if the studies included in the review have small sample sizes, then careful interpretation of the Chi^2 test is needed. In this situation, we will use the I^2 statistic, which measures the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error/chance. The inconsistency among the studies will be quantified as:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity (Higgins 2021a).

If we identify substantial or considerable heterogeneity (indicated by an I^2 value > 50%) we will report it and explore possible causes by prespecified sensitivity analysis.

For random-effects meta-analysis, we will examine the extent of variation among the effect estimates of the different studies using Tau^2.

Assessment of reporting biases

If we are able to pool > 10 trials, we will create and examine a funnel plot to explore possible small study biases for the primary outcomes.

Data synthesis

We will include all studies in the primary analysis, and to assess the potential effects of studies at high risk we will carry out sensitivity analyses (Higgins 2021a). We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. We will use a random-effects model due to the high probability of heterogeneity in the RCTs that will be included in this review.

If a meta-analysis is not possible, we will analyse our data using non-statistical methods, including investigation of the similarities and the differences between the findings of different studies. We will use the following steps (Campbell 2020).

- Describe the included studies and summarise the features of each study in the same order.
- Group the studies by intervention, population groups and settings.
- Tabulate results in order to identify patterns across the included studies.
- Transform the data into a common statistical format.
- Translate the data: we will use thematic or content analysis in identifying areas in common between studies.

Subgroup analysis and investigation of heterogeneity

We will explore heterogeneity using subgroup analyses (if we identify ≥ 10 studies) according to the following parameters.

- Male versus Female
- Age (< 70 years versus ≥ 70 years)
- Left ventricular ejection fraction on ECG (< 35% and ≥ 35%)

We will use the formal test for subgroup differences in RevMan Web 2020, and base our interpretation on this. We will report the results of subgroup analyses quoting the Chi^2 statistic and P value.

Sensitivity analysis

We plan to carry out the following sensitivity analyses, to test whether key methodological factors or decisions have affected the main result.

- We only include randomised studies with low risk or some concerns and carry out a sensitivity analysis.
- We will examine both fixed-effect model and random-effects model meta-analyses.
- We plan to explore the impact of missing data.

If we identify studies with missing data that were unobtainable, we will repeat the analyses excluding them to find their impact on the primary analyses.

Summary of findings and assessment of the certainty of the evidence

The following are preselected outcomes to be included in the summary of findings tables: ventricular arrhythmia recurrence rate, all-cause mortality, cardiovascular mortality, appropriate ICD therapy, and acute procedural complications (including stroke, pericardial tamponade and major bleeding).

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

7

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes. We will use RoB 2 to assess the certainty of the evidence for both GRADE and the summary of findings table. We will use the overall RoB 2 judgement to feed into GRADE. We will use GRADEpro software to create a GRADE table, (GRADE pro GDT 2021). We will justify all decisions to downgrade the quality of studies using footnotes, and we will make comments to aid readers' understanding of the review where necessary (Schünemann 2021).

Judgements about evidence certainty will be made by two review authors (HA, GM) working independently, with disagreements resolved by discussion or involving a fourth review author (SJ or PL). We plan to extract study data, format our comparisons in data tables, and prepare summary of findings tables before writing the results and conclusions of our review. In case a meta-analysis is not possible, we will present the results as a narrative summary of findings table.

ACKNOWLEDGEMENTS

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

8

REFERENCES

Additional references

Al-Khatib 2015

Al-Khatib SM, Daubert JP, Anstrom KJ, Daoud EG, Gonzalez M, Saba S, et al. Catheter ablation for ventricular tachycardia in patients with an implantable cardioverter defibrillator (CALYPSO) pilot trial. *Journal of Cardiovascular Electrophysiology* 2015;**26**(2):151–7.

Anderson 2019

Anderson RD, Ariyarathna N, Lee G, Virk S, Trivic I, Campbell T, et al. Catheter ablation versus medical therapy for treatment of ventricular tachycardia associated with structural heart disease: Systematic review and meta-analysis of randomized controlled trials and comparison with observational studies. *Heart Rhythm* 2019;**16**(10):1484-91.

Anter 2014

Anter E, Josephson M. Ischaemic Heart Disease. In: Zipes DP, Jalife J, editors(s). Cardiac Electrophysiology: from cell to bedside. 6th edition. Vol. **1**. Philadelphia: Elsevier Saunders, 2014:849-57.

Bonny 2017

Bonny A, Tibazarwa K, Mbouh S, Wa J, Fonga R, Saka C, et al. Epidemiology of sudden cardiac death in Cameroon: the first population-based cohort survey in sub-Saharan Africa. *International Journal of Epidemiology* 2017;**46**:1230-8.

Boriani 2001

Boriani G, Lubinski A, Capucci A, Niederle R, Kornacewicz-Jack Z, Wnuk-Wojnar AM, et al. A multicentre, double-blind randomized crossover comparative study on the efficacy and safety of dofetilide vs sotalol in patients with inducible sustained ventricular tachycardia and ischaemic heart disease. *European Heart Journal* 2001;**22**(23):2180-91.

Brady 2005

Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *New England Journal of Medicine* 2005;**352**(3):225-37.

Campbell 2020

Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 2020;**368**:l6890.

Carbucicchio 2008

Carbucicchio C, Santamaria M, Trevisi N, Maccabelli G, Giraldi F, Fassini G, et al. Catheter ablation for the treatment of electrical storm in patients with implantable cardioverter-defibrillators: short- and long-term outcomes in a prospective single-center study. *Circulation* 2008;**117**(4):462–9.

Chen 2005

Chen ZM, Pan HC, Chen YP, Peto R, Collins L, Jiang LX, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;**366**(9497):1622–32. [DOI: doi: 10.1016/S0140-6736(05)67661-1.]

Cheung 2018

Cheung JW, Yeo I, Ip JE, Thomas G, Liu CF, Markowitz SM, et al. Outcomes, costs, and 30-day readmissions after catheter ablation of myocardial infarct–associated ventricular tachycardia in the real world: Nationwide Readmissions Database 2010 to 2015. *Circulation: Arrhythmia and Electrophysiology* 2018;**11**:11. [DOI: https://doi.org/10.1161/CIRCEP.118.0067542018;11Abstract]

Connolly 2006

Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, et al. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC study: a randomized trial. *JAMA* 2006;**295**(2):165-71.

Cronin 2019

Cronin EM, Bogun FM, Maury P, Peichl P, Chen M, Namboodiri N, et al. 2019 HRS/EHRA/APHRS/LAHRS expert consensus statement on catheter ablation of ventricular arrhythmias. *Europace* 2019;**21**(8):1143-4.

Darbar 2014

Darbar D. Standard Antiarrhythmic Drugs. In: Zipes DP, Jalife J, editors(s). Cardiac Electrophysiology: from cell to bedside. 6th edition. Vol. **1**. Philadelphia: Elsevier Saunders, 2014:1095-110.

De Bakker 2000

De Bakker JM. Pathophyiological correlates of ventricular tachycardia in hearts with healed myocardial infarct. In: Zipes DP, Jalife J, editors(s). Cardiac Electrophysiology: from cell to bedside. WB Saunders, 2000.

Deneke 2011

Deneke T, Shin D, Lawo T, Bösche L, Balta A, Anders H, et al. Catheter ablation of electrical storm in a collaborative hospital network. *American Journal of Cardiology* 2011;**108**(2):233–9.

Dorian 2004

Dorian P, Borggrefe M, Al-Khalidi HR, Hohnloser SH, Brum JM, Tatla DS, et al. Placebo-controlled, randomized clinical trial of azimilide for prevention of ventricular tachyarrhythmias in patients with an implantable cardioverter defibrillator. *Circulation* 2004;**110**(24):3646–54. [DOI: doi: 10.1161/01.CIR.0000149240.98971.A8]

Echt 1991

Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *New England Journal of Medicine* 1991;**324**(12):781–8. [DOI: doi: 10.1056/NEJM199103213241201]

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

9

Copyright © 2021 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Cochrane
Library

Trusted evidence.
Informed decisions.
Better health.

Cochrane Database of Systematic Reviews

Exner 2001

Exner DV, Pinski SL, Wyse DG, Renfroe EG, Follmann D, Gold M, et al. Electrical storm presages nonsudden death: the antiarrhythmics versus implantable defibrillators (AVID) trial. *Circulation* 2001;**103**(16):2066-71.

Fishman 2010

Fishman GI, Chugh SS, DiMarco JP, Albert CM, Anderson ME, Bonow RO, et al. Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. *Circulation* 2010;**122**(22):2335-48.

Gillis 2004

Gillis AM. Class I antiarrhythmic drugs: quinidine, procainamide, disopyramide, lidocaine, mexiletine, flecained and propafenone. In: Zipes D, Jalife J, editors(s). Cardiac Electrophysiology: from cell to bedside. Vol. **4**. Philadelphia: Elsevier Saunders, 2004:911–7.

GRADE pro GDT 2021 [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), 2021. Available at gradepro.org.

Higgins 2021a

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Higgins 2021b

Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA, editor(s). Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Higgins 2021c

Higgins JP, Eldridge S, Li T, editor(s). Chapter 23: Including variants on randomised trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Hua 2009

Hua W, Zhang LF, Wu YF, Liu XQ, Guo DS, Zhou HL, et al. Incidence of sudden cardiac death in China: analysis of 4 regional populations. *Journal American College of Cardiology* 2009;**54**(12):1110-8.

Izquierdo 2012

Izquierdo M, Ruiz-Granell R, Ferrero A, Martinez A, Sanchez-Gomez J, Mascarell B, et al. Ablation or conservative management of electrical storm due to monomorphic ventricular tachycardia: differences in outcome. *Europace* 2012;**14**(12):1734–9.

Josephson 2016

Josephson ME. Catheter and surgical ablation in the therapy of arrhythmias. In: Josephson ME, editors(s). Clinical Cardiac Electrophysiology: techniques and interpretations. Fifth edition. Philadelphia: Wolters Kluwer, 2016:764-92.

Khurshid 2018

Khurshid S, Choi SH, Weng LC, Wang EY, Trinquart L, Benjamin EJ, et al. Frequency of cardiac rhythm abnormalities in a half million adults. *Circulation: Arrhythmia and Electrophysiology* 2018;**11**(7):e006273. [DOI: https://doi.org/10.1161/CIRCEP.118.006273]

Koplan 2009

Koplan BA, Stevenson WG. Ventricular tachycardia and sudden cardiac death. *Mayo Clinic Proceedings* 2009;**84**(3):289-97. [PMID: https://pubmed.ncbi.nlm.nih.gov/19252119/]

Kowey 2011

Kowey PR, Crijns HJ, Aliot EM, Capucci A, Kulakowski P, Radzik D, et al. Efficacy and safety of celivarone, with amiodarone as calibrator, in patients with an implantable cardioverter-defibrillator for prevention of implantable cardioverter-defibrillator interventions or death: the ALPHEE study. *Circulation* 2011;**124**(24):2649-60.

Kuck 2010

Kuck KH, Schaumann A, Eckhardt L, Willems S, Ventura R, Delacretaz E, et al. Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomised controlled trial. *Lancet* 2010;**375**:31–40.

Kuck 2017

Kuck KH, Tilz RR, Deneke T, Hoffman BA, Ventura R, Hansen PS, et al. 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). *Circulation: Arrhythmia and Electrophysiology* 2017;**10**:e004422.

Kumar 2017

Kumar S, Fujii A, Kapur S, Romero J, Mehta NK, Tanigawa S, et al. Beyond the storm: comparison of clinical factors, arrhythmogenic substrate, and catheter ablation outcomes in structural heart disease patients with versus those without a history of ventricular tachycardia storm. *Journal of Cardiovascular Electrophysiology* 2017;**28**:56–67.

Lefebvre 2021

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

10

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**(7):e1000100.

Mallidi 2011

Mallidi J, Nadkarni GN, Berger RD, Calkins H, Nazarian S. Meta-analysis of catheter ablation as an adjunct to medical therapy for treatment of ventricular tachycardia in patients with structural heart disease. *Heart Rhythm* 2011;**8**(4):8503–10.

Manzoni 2015

Manzoni GM, Castelnuovo G, Compare A, Pagnini F, Essebag V, Proietti R. Psychological effects of implantable cardioverter defibrillator shocks. A review of study methods. *Frontiers of Psychology* 2015;**6**:39. [DOI: . doi:10.3389/fpsyg.2015.00039]

Markman 2018

Markman, McBride DA, Liang JJ. Catheter ablation for ventricular tachycardia in patients with structural heart disease. *USC* 2018;**28**:3.

Martinez 2020

Martinez BK, Baker WL, Konopka A, Giannelli D, Coleman CI, Kluger J, et al. Systematic review and meta-analysis of catheter ablation of ventricular tachycardia in ischemic heart disease. *Heart Rhythm* 2019;**17**:E206-19.

Morawski 2017

Morawski S, Pruszkowska P, Sredniawa B, Lenarczyk R, Kalarus Z. Longterm outcome of catheter ablation and other form of therapy for electrical storm in patients with implantable cardioverter-defibrillators. *Journal of Interventional Cardiac Electrophysiology* 2017;**50**:227–34.

Muser 2017

Muser D, Liang JJ, Pathak RK, Magnani S, Castro SA, Tatsuya H, et al. Long-term outcomes of catheter ablation of electrical storm in nonischemic dilated cardiomyopathy compared with ischemic cardiomyopathy. *JACC: Clinical Electrophysiology* 2017;**3**(7):767–78.

Nayyar 2013

Nayyar S, Ganesan AN, Brooks AG, Sullivan T, Roberts-Thomson KC, Sanders P. Venturing into ventricular arrhythmia storm: a systematic review and meta-analysis. *European Heart Journal* 2013;**34**:560–9.

Pacifico 1999

Pacifico A, Hohnloser SH, Williams JH, Tao B, Saksena S, Henry PD, et al. Prevention of implantable-defibrillator shocks by treatment with sotalol. *New England Journal of Medicine* 1999;**340**:1855–62. [DOI: doi: 10.1056/NEJM199906173402402.]

Peichl 2014

Peichl P, Wichterle D, Pavlu L, Cihak R, Aldhoon B, Kautzner J. Complications of catheter ablation of ventricular tachycardia: a single-center experience. *Circulation: Arrhythmia and Electrophysiology* 2014;**7**:684-90. [DOI: https://doi.org/10.1161/CIRCEP.114.001530]

Priori 2015

Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). *European Heart Journal* 2015;**36**(41):2793–867.

Reddy 2007

Reddy VY, Reynolds MR, Neuzil P, Richardson AW, Taborksy M, Jongnaranjsin K, et al. Prophylactic catheter ablation for the prevention of defibrillator therapy. *New England Journal of Medicine* 2007;**357**:2657–65.

Review Manager 2020 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration Review Manager 5 (RevMan 5). Version 5.4. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2020.

RevMan Web 2020 [Computer program]

The Cochrane Collaboration Review Manager Web (RevMan Web). Version 1.22. The Cochrane Collaboration, 2020. Available at revman.cochrane.org.

RoB 2 Excel 2019

Higgins JP, Savović J, Page MJ, Sterne JA, on behalf of the RoB2 Development Group. Excel tool to implement RoB 2. www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2 2019.

RoB 2 for cluster-randomized trials 2021

RoB 2 for cluster-randomized trials. www.riskofbias.info/welcome/rob-2-0-tool/rob-2-for-cluster-randomized-trials 2021.

Roy 1986

Roy D, Marchand E, Theroux P, Waters DD, Pelletier GB, Cartier R, et al. Long term reproducibility and significance of provokable ventricular arrhythmias after myocardial infarction. *Journal of the American College of Cardiology* 1986;**8**:32-9.

Sacher 2010

Sacher F, Wright M, Tedrow UB, O'Neill MD, Jais P, Hocini M, et al. Wolff–Parkinson–White ablation after a prior failure: a 7-year multicentre experience. *EP Europace* 2010;**12**(6):835–41. [DOI: https://doi.org/10.1093/europace/euq050]

Sapp 2016

Sapp JL, Wells GA, Parkash R, Stevenson WG, Blier L, Sarrazin JF, et al. Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs. *New England Journal of Medicine* 2016;**375**:111-21. [DOI: DOI: 10.1056/NEJMoa1513614]

Schünemann 2021

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

11

JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook.

Scirica 2007

Scirica BM, Morrow DA, Hod H, Murphy SA, Belardinelli L, Hedgepeth CM, et al. Effect of ranolazine, an antianginal agent with novel electrophysiological properties, on the incidence of arrhythmias in patients with non ST-segment elevation acute coronary syndrome: results from the Metabolic Efficiency With Ranolazine for Less Ischemia in Non ST-Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction 36 (MERLIN-TIMI 36) randomized controlled trial. *Circulation* 2007;**116**:1647–52. [DOI: doi: 10.1161/CIRCULATIONAHA.107.724880]

Stevenson 1993

Stevenson WG, Khan H, Sager P, Saxon LA, Middlekauf HR, Natterson PD, et al. Identification of reentry circuit sites during catheter mapping and radiofrequency ablation of ventricular tachycardia late after myocardial infarction. *Circulation* 1993;**88**:1647–70.

Stevenson 1998

Stevenson WG, Friedman PL, Kocovic D, Sager PT, Saxon LA, Pavri B. Radiofrequency catheter ablation of ventricular tachycardia after myocardial infarction. *Circulation* 1998;**98**:308–14.

Tran 2019

Tran HV, Ash AS, Gore JM, Darling CE, Kiefe CI, Goldberg RJ, et al. Twenty-five year trends (1986-2011) in hospital incidence and case-fatality rates of ventricular tachycardia and ventricular fibrillation complicating acute myocardial infarction. *American Heart Journal* 2019;**208**:1-10.

Tung 2010

Tung R, Boyle NG, Shivkumar K. Catheter ablation of ventricular tachycardia. *Circulation* 2010;**122**(3):e389-91. [DOI: doi:10.1161/CIRCULATIONAHA.110.963371]

Van Herendael 2010

Van Herendael H, Pinter A, Ahmad K, Korley V, Mangat I, Dorian P. Role of antiarrhythmic drugs in patients with implantable cardioverter defibrillators. *Europace* 2010;**12**(5):618-25.

Wilber 1995

Wilber DJ, Kopp DE, Glascock DN, Kinder CA, Kall JG. Catheter ablation of the mitral isthmus for ventricular tachycardia associated with inferior infarction. *Circulation* 1995;**92**:3481–9.

A P P E N D I C E S

Appendix 1. Preliminary MEDLINE (Ovid) search strategy

1 Catheter Ablation/ (31971)

2 ablation.tw. (91851)

3 1 or 2 (98798)

4 exp Tachycardia, Ventricular/ (16753)

5 ventricular tachycardia*.tw. (23543)

6 VT.tw. (15924)

7 4 or 5 or 6 (40464)

8 3 and 7 (4828)

9 randomized controlled trial.pt. (509746)

10 controlled clinical trial.pt. (93762)

11 randomized.ab. (486190)

12 placebo.ab. (209433)

13 drug therapy.fs. (2220320)

14 randomly.ab. (337049)

15 trial.ab. (512719)

16 groups.ab. (2069665)

17 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (4749461)

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

12

18 exp animals/ not humans.sh. (4718676)

19 17 not 18 (4121094)

20 8 and 19 (561)

CONTRIBUTIONS OF AUTHORS

Mohamed Abbas (MAb), Mahmood Ahmad (MAh), Gordon Begg (GB), Haseeb Arif (HA) and Gavin Manmathan (GM) conceived, designed and drafted the protocol.

Jayant Kakarla (JK), Chris Benson (CB), Simon James (SJ), Andrew Thornley (AT), Matthews Bates (MB), Darragh Twomey (DT), Amitava Banerjee (AB) and Pier Lambiase (PL) provided general advice and revised the protocol.

All authors agreed on the final protocol version.

DECLARATIONS OF INTEREST

JK declares having no conflicts.

CB declares having no conflicts.

MAb declares having no conflicts.

GB declares support for clinical fellowship post at James Cook University Hospital by Medtronic and travel and subsistence (no direct monies paid to me) for attendance at Abbott educational meetings in UK and Europe.

DT declares funding from Abbott Medical and Menarini for conference attendance.

AT declares educational bursaries for travel and accommodation for conferences from Abbott, Medtronic and Boston Scientific.

MB declares funds by Abbott as an expert panel member on the topic of atrial fibrillation management as well as departmental funding for meeting attendance to enable abstract presentation (Medtronic, Boston Scientific, Abbott, Biosense).

MAh declares having no conflicts.

HA declares having no conflicts.

AB declares research funding from Astra Zeneca to look at overlap between chronic renal impairment, diabetes and heart failure. Astra Zeneca has no financial interest in the findings of the current review. I control how the funds are spent. AB also declares the role of trustee of the South Asian Health Foundation.

GPRM declares having no conflicts.

PDL declares grants by Boston Scientific and Medtronic as well as speaker fees by Boston Scientific.

SJ declares having no conflicts.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- Cochrane Collaboration , UK

  This project was supported by the British Heart Foundation (BHF) Clinical Research Collaborative BHF CRC via Cochrane Collaboration. The views and opinions expressed in this protocol are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, BHF, National Health Service (NHS) or the Department of Health, UK.

Catheter ablation versus escalation of antiarrhythmic medications for management of ventricular tachycardia in patients with ischaemic heart disease (Protocol)

13