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External electrical and pharmacological cardioversion for atrial fibrillation, atrial flutter or atrial tachycardias: a network meta-analysis (Protocol)

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[Intervention Protocol]

External electrical and pharmacological cardioversion for atrial fibrillation, atrial flutter or atrial tachycardias: a network meta-analysis

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ABSTRACT

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

To assess the efficacy and safety of pharmacological and electrical cardioversion for atrial fibrillation (AF).

BACKGROUND

Description of the condition

Atrial fibrillation (AF) is the most frequent arrhythmia seen in clinical practice, with a prevalence of 3% in recent community studies (Björck 2013; Haim 2015), and its prevalence is likely to rise in the next decades (Chugh 2014; Go 2011; Krijthe 2013; Lloyd-Jones 2004; Magnani 2011; Miyasaka 2006). This arrhythmia is associated with a high annual cost for healthcare systems (Maddox 2008), and is characterised by high clinical and biological heterogeneity, being responsible for causing a myriad of symptoms, like palpitations, shortness of breath, chest pain, syncope, among others (ESC Guidelines 2016). Unlike other arrhythmic disorders, AF is also associated with an increased risk of stroke and systemic embolism (Wolf 1978). Data from the Framingham study have shown that the presence of AF was an independent risk factor for death (odds ratio (OR) 1.9, 95% confidence interval (CI) 1.5 to 2.2 in females and OR 1.5, 95% CI 1.2 to 1.8 in men; Benjamin 1998).

Patients with AF episodes lasting more than seven days are usually described as having persistent AF. Paroxysmal AF is reserved for patients with self-terminating episodes that usually last for less than

48 hours (ACC/AHA/HRS Guidelines 2014; ESC Guidelines 2016). However, according to the European Society for Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) classification and despite the lower likelihood of spontaneous cardioversion, self-terminating episodes of less than seven days also fall in this category. Patients who remain in AF and where a rate control strategy has been chosen, meaning that they will likely remain in AF for the rest of the time, are defined as having permanent AF. Those patients having an AF episode lasting for more than one year, but where rhythm control is still being pursued are defined as having long-standing persistent AF.

On a pathophysiological level, since the publication of the landmark paper by Haïssaguere and colleagues (Haïssaguerre 1998), the pulmonary veins are thought to be the initiators of paroxysms of AF and radiofrequency ablation as an effective way of treating this arrhythmia. It is thought that unlike paroxysmal AF where a predominance of local triggers/drivers, particularly from the pulmonary veins, is thought to occur, in persistent AF, re-entry substrates (initially functional and then structural) predominate following electrical and structural remodelling of the atria (Iwasaki 2011). This was supported by early reports of significantly improved efficacy of pulmonary vein isolation in paroxysmal AF compared with persistent AF (Oral 2002). However, pulmonary veins may also be responsible for starting approximately 50% of AF episodes in patients with persistent AF, as suggested by the results of the STAR-AF II trial (Verma 2015).

Postablation atrial tachycardias (or flutters) are thought to occur because of macro- or micro-reentrant circuits developing around areas of previous ablation where focal recovery has led to the development of reentrant-prone areas (Pappone 2012).

Unlike atrial fibrillation, typical atrial flutter occurs as a result of a macro-reentrant circuit in the right atrium with an isthmus in the cavotricuspid area (Feld 1992). Atrial flutter may coexist in 80% of patients with AF (Tunick 1992). Based on observational emergency department data, this atrial arrhythmia is more likely to respond to electrical cardioversion than to pharmacological cardioversion (Scheuermeyer 2011).

Description of the intervention

The treatment of AF currently consists of using anticoagulants for preventing stroke and systemic embolism and strategies aiming to control patients' symptoms (ACC/AHA/HRS Guidelines 2014; ESC Guidelines 2016; NICE 2014). These strategies include two different approaches: rhythm control and rate control.

Rhythm control, which includes cardioversion (which can be electrical - i.e. direct-current cardioversion, or pharmacological - if antiarrhythmic agents are used), catheter ablation (usually pulmonary vein isolation) and antiarrhythmic agents, aims to restore the patient's rhythm back to normal (i.e. sinus rhythm), thus allowing the patient to recover atrial depolarisation and contraction, and atrioventricular synchrony. Hopefully this will increase the cardiac output, lead to a more controlled heart rate and resolve patients' symptoms. Unfortunately, these strategies under certain circumstances, like the presence of persistent AF, and structural heart disease, may be effective in less than 50% of patients, and sooner or later the rhythm will evolve to AF once again (Mont 2014; Verma 2015).

The other strategy, called rate control, consists of controlling the patient's ventricular rate, without making an attempt to interfere with the atrial arrhythmia. This seems to be the preferred alternative for asymptomatic patients, or those without a clear symptom-arrhythmia correlation, and for patients with low chances of remaining in sinus rhythm if the rhythm control strategy was used. Drugs (beta-blockers, calcium channel blockers, digoxin), or catheter ablation of the atrioventricular node and pacemaker implant can be used (ACC/AHA/HRS Guidelines 2014; ESC Guidelines 2016).

The 'Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)' (Wyse 2002), and the 'Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study (RACE)' (Van Gelder 2002), were two landmark trials comparing rate versus rhythm control strategies and their impact on outcomes. The results showed there was no discernible difference between the two treatment strategies in terms of outcomes. Some of the suggested explanations for the results of the rhythm control strategy were the suboptimal use of anticoagulation, and possible toxicity induced by the used antiarrhythmic agents (Blackshear 2003).

A subanalysis of the AFFIRM trial suggested that being in sinus rhythm (independently of the treatment strategy) and receiving oral anticoagulation were associated with improved survival. Conversely, the use of antiarrhythmic agents was associated with increased mortality (Corley 2004). These data reinforce the main role of thromboembolic prophylaxis in AF patients and suggested that being in sinus rhythm should be pursued using a more effective approach, and with fewer adverse effects, than the antiarrhythmic agents used in this trial. However, inference about life-prolonging effects of being in sinus rhythm could be biased, because it may be assumed, that those in sinus rhythm were in a better general health condition than those in AF.

Subsequently, dronedarone an antiarrhythmic agent with a more favourable adverse effect profile (mainly on a thyroid and neurologic level) held some promise in the field. Despite being less effective than amiodarone (AF recurrence during a median of 7 months after successful cardioversion was 63.5% with dronedarone versus 42.0% with amiodarone; $P < 0.01$; Le Heuzey 2012), the results of dronedarone in the ATHENA trial (Hohnloser 2009), led to enthusiasm concerning this novel antiarrhythmic agent. This drug was associated with a reduction in the primary study endpoint of first hospitalisation due to cardiovascular effects or death (hazard ratio (HR) 0.76, 95% CI 0.69 to 0.84, $P < 0.001$), and it was also the first antiarrhythmic agent capable of reducing cardiovas-

cular death (HR 0.71, 95% CI 0.51 to 0.98, P = 0.03) and stroke (HR 0.66, 95% CI 0.46 to 0.96, P = 0.027) (Connolly 2009). However, in the PALLAS trial, dronedarone used in patients with permanent AF increased rates of heart failure, stroke, and death from cardiovascular causes (Connolly 2011). These results led to recommendations by the Food and Drug Administration (FDA) and the National Institute for Health and Care Excellence (NICE) for the drug not to be to used in patients with permanent AF (FDA 2011; NICE 2013).

Recent data from a large nationwide registry suggest that the rhythm control strategy, through catheter ablation, may also be associated with lower mortality and stroke incidence (Friberg 2016). However, referral bias for ablation could explain such findings. For the population of AF patients with left ventricular ejection fraction < 35% in the 'Catheter Ablation versus Standard conventional Treatment in patients with LEft ventricular dysfunction and Atrial Fibrillation (CASTLE-AF)' trial, there was a reduction of all-cause mortality in patients treated with catheter ablation (HR 0.53, 95% CI 0.32 to 0.86, P = 0.011; Marrouche 2018). Two ongoing randomised controlled trials (RCTs) on catheter ablation will provide further data on the benefit of catheter ablation as part of the rhythm control strategy (NCT00911508; NCT01288352). In sum, a growing body of evidence is now providing support to rhythm control strategies, and their use is likely to increase further within the next few years.

How the intervention might work

A cardioversion is a procedure whereby a sustained abnormal rhythm is reverted back to sinus rhythm by means of a synchronised internal or external shock (electrical cardioversion) (Lown 1962; Lown 1963), or by the action of antiarrhythmic drugs (pharmacological cardioversion) (Gunton 1964; Wenckbach 1923).

In pharmacological cardioversion, antiarrhythmic drugs are used instead to terminate atrial activity in the atria by interfering with effective refractory periods of atrial myocytes and terminating the propagation of AF micro-reentrant wavelets and blocking atrial arrhythmia triggers (Boriani 2004; Knight 2015).

In an electrical cardioversion, a selected amount of electric current (usually in joules) over a predefined number of milliseconds at the optimal moment of the cardiac cycle is delivered by way of pads (external cardioversion) or through an intravascular device (internal cardioversion) (Lévy 1992), halting the fibrillation activation fronts and allowing or giving rise to new wavefronts from the sinus node to resume and recover control (reversal of sinus rhythm) in case it works successfully (Cakulev 2010; Chen 1991; Knight 2015). Synchronisation with the R wave of the QRS complex is performed to prevent cardioversion-induced arrhythmias (e.g. ventricular fibrillation), which can occur if a shock is delivered to the vulnerable period of the T wave (R-on-T). Pads or patches can be positioned in anteroposterior or anterolateral positions (Kirchhof 2002). For electrical cardioversion, sedation is required, as the shock would be very painful for the patient if they were awake.

Cardioversion is usually performed under close monitoring in a hospital-based setting. This can occur in a cath lab, in an emergency department, or in an intensive care unit. Minimal requirements for procedural safety are electrocardiographic monitoring, regular measurement of blood pressure, and respiratory rate, and arterial oxygen saturation using a pulse oximeter. If the patient is unstable, with haemodynamic imbalance occurring as a result of the arrhythmia, it is performed urgently. However, more frequently, cardioversions are performed in stable patients on an elective basis (Knight 2017).

Possible complications include skin burn or skin irritation (for electrical cardioversion), muscle pain (for electrical cardioversion), sedation-related complications, proarrhythmia (unsynchronised cardioversion or drug-induced tachyarrhythmias), bradycardias (in case of severe sinus node disease), and postcardioversion cardiogenic shock or acute pulmonary oedema (as a result of post-shock cardiac stunning) (ACC/AHA/HRS Guidelines 2014; ESC Guidelines 2016; Knight 2015). Another possible complication is embolic stroke following the dislodgement of an intracardiac clot following cardioversion and/or the recovery of normal atrial contractility. For that reason, international guidelines have provided precise guidance on what precautions (anticoagulation and pre-procedural transoesophageal echocardiogram) are required to prevent this complication (ACC/AHA/HRS Guidelines 2014; ESC Guidelines 2016).

Factors known to affect the success of cardioversion include AF episode duration and left atrial size. AF lasting for more than three years is more likely to recur (Resnekov 1968), and AF lasting for less than a month is more frequently associated with cardioversion success (Dalzell 1990). AF is more likely to recur in dilated left atria (Olshansky 2005). In recent-onset AF, faster-acting agents like ibutilide and vernakalant seem to be more effective than sotalol (Vos 1998), or amidoarone (Camm 2011), respectively.

Why it is important to do this review

AF is a highly prevalent heart condition (Go 2011; Magnani 2011), and is the most frequent cause of hospital admission because of arrhythmia (Bialy 1992). Cardioversions are performed very frequently all around the world to revert the rhythm back to sinus. Development of new antiarrhythmic agents (vernakalant, vanorexine, antazoline), and growing evidence in recent years that pursuing a rhythm control strategy may improve outcomes (Corley 2004; Friberg 2016; Hohnloser 2009; Marrouche 2018), supports the idea that besides having an effect on symptoms, interventions to restore the rhythm back to sinus-like cardioversion may have an impact on prognosis, and therefore the use of cardioversion and other rhythm control strategies is likely to increase even further. As there are several options of performing a cardioversion (pharmacological or electrical, and within pharmacological cardioversion

there are several different drug options), it is important to clarify the efficacy of each of these techniques, and whether or not, one strategy shows better results, and therefore should be preferred.

In the clinical setting, the decision between using external electrical cardioversion and pharmacological cardioversion frequently depends on the clinician's preference and experience, internal protocols, and the availability of an anaesthetic support team to provide safe sedation when performing external electrical cardioversion. The International guidelines do not provide strong evidence or recommendations on which cardioversion strategy is more effective and should be preferred, except for the setting of haemodynamic instability, where electrical cardioversion is recommended (ACC/AHA/HRS Guidelines 2014; ESC Guidelines 2016), the guidelines fail to provide a recommendation on which should be favoured, electrical or pharmacological cardioversion. According to the ESC, and AHA/ACC "Level of Evidence A" applies to a recommendation which evidence comes from "Data derived from multiple randomised clinical trials or meta-analyses", "Level of Evidence B" to "Data derived from a single randomized clinical trial or large non-randomized studies", and "Level of Evidence C" to "Consensus of opinion of the experts and/or small studies, retrospective studies, registries". Out of the eight recommendations in the American guidelines, three have level C evidence and three have level B evidence (ACC/AHA/HRS Guidelines 2014), while the ESC guidelines present six out of eight recommendations with level B evidence, suggesting that quality of evidence for cardioversion-related practice is low. Performing a systematic review addressing the topic might allow for improvement of the level of evidence in future guidelines.

The previous reviews on electrical and pharmacological cardioversion of AF and flutter (Cordina 2005; Mead 2005), focused mainly on rhythm versus rate control strategy but did not focus on procedural data of cardioversion (efficacy, relapse rates, etc.), which means that this subject still needs to be covered in a Cochrane Review.

OBJECTIVES

To assess the efficacy and safety of pharmacological and electrical cardioversion for atrial fibrillation (AF).

METHODS

Criteria for considering studies for this review

Types of studies

We will undertake this systematic review according to the recommendations stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We will include randomised controlled trials (RCTs) at patient and cluster level which can be reported as full-text, published as abstract only, and unpublished data. However, we will not include cross-over trials as it is known that the different treatment alternatives can mutually affect each other, and could potentially contaminate the analysis (e.g. antiarrhythmic drugs in a patient with failed pharmacological cardioversion can remain in the bloodstream, and may increase the chances of success of a subsequent electrical cardioversion if performed shortly after).

Regarding the outcome stroke and/or systemic embolism, or mortality (if stroke/embolic related), we will exclude studies not following the current guidelines for thromboprophylaxis of thromboembolic events during cardioversion (ACC/AHA/HRS Guidelines 2014; ESC Guidelines 2016). These recommendations state that: for atrial fibrillation (AF) of unknown duration or lasting $\geq$ 48 hours, patients require a preprocedural transoesophageal echocardiogram to exclude the presence of intracardiac clots or three weeks of effective anticoagulation. Following cardioversion, four weeks of anticoagulation will be required.

Types of participants

All patients aged $\geq$ 18 years with AF of any type and duration, atrial flutter or other sustained related atrial arrhythmias, which are not occurring as a result of cardiac surgery or other potentially reversible causes (i.e. sepsis, hyperthyroidism, trauma, critically ill in intensive care, etc.)

Types of interventions

The intervention group must have received either external electrical cardioversion, or antiarrhythmic drugs aiming to perform pharmacological cardioversion.

We will perform the following three different types of main comparisons.

- External electrical cardioversion versus placebo.
- Pharmacological cardioversion versus placebo.
- Pharmacological cardioversion versus external electrical cardioversion.

If enough data are present in studies (at least more than 1 study for each specific comparison of antiarrhythmic drug or electrical cardioversion strategy), we will perform the following subcomparisons through direct or indirect comparisons.

- Pharmacological cardioversion (drug A) versus pharmacological cardioversion (drug B).
- Electrical cardioversion (anteroposterior patches) versus electrical cardioversion (anterolateral patches).
- Pharmacological cardioversion (drug A, or drug B, etc.) versus placebo.

- Electrical cardioversion (anteroposterior patches or anterolateral patches) versus placebo.
- Electrical cardioversion (anteroposterior patches or anterolateral patches) versus pharmacological cardioversion (drug A, or drug B, etc.)

Groups of patients being compared (intervention and placebo), need to be similar with regard to cardiac disease (frequency, type and severity) and type of atrial fibrillation (especially duration). Also, groups should receive similar treatment apart from the intervention being assessed, that is - similar treatment regarding: 1. the guidelines used to manage initiation, discontinuation, dose and surveillance of anticoagulation; 2. management and drugs used for hypertension and heart failure.
We will exclude trials of internal cardioversion versus pharmacological cardioversion or internal cardioversion versus placebo. However, trials including a mix of patients undergoing internal cardioversion, and at least two more interventions among the following (external electrical cardioversion, pharmacological cardioversion, and placebo) can still be included, if procedural data and outcome data on patients treated with internal cardioversion are provided separately, allowing exclusion of such patients.
Reasons for excluding internal cardioversion are: the need of having either an implantable cardioverter defibrillator or equivalent device, or an intravascular catheter with cardioverting capacity. These occur in very specific scenarios, and therefore are out of the scope of this review.

Types of outcome measures

Primary outcomes

- Maintenance of sinus rhythm until hospital discharge or end of study follow-up

Maintenance of sinus rhythm can be demonstrated through absence of symptoms and predischarge 12-lead electrocardiogram (ECG) in sinus rhythm, or through telemetry monitoring.

Secondary outcomes

- Stroke, systemic embolism, or transient ischaemic attack occurring within the first 30 days following cardioversion, reported as a composite rather than individual outcomes as the 3 outcomes all share the same mechanism;
- 30-day all-cause mortality
- Acute procedural success, defined as at least 30 seconds of sinus rhythm following cardioversion
- 30-day cardiovascular mortality
- Duration of hospitalisation
- Development of ventricular arrhythmias following cardioversion while in hospital
- Development of bradyarrhythmias following cardioversion while in hospital
- Quality of life, measured with any validated scale within the first year post cardioversion.
- Heart failure admission within the next month
- Immediate (< 24 hours) procedure-related complications
- Complications deemed to be related to the procedure occurring within the first week.

Complications can be either rhythm-related as mentioned above, or skin burn or skin irritation, sedation-related complications, cardiogenic shock and acute pulmonary oedema.
Reporting one of more of the outcomes listed here in the trial is not an inclusion criterion for the review. 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 in the review as part of the narrative which measured these outcomes but did not report the data at all, or not in a usable format.

Search methods for identification of studies

Electronic searches

We will search the following sources, from their inception, to identify relevant trials.

1. CENTRAL (Cochrane Register of Studies (CRS Web)).
2. MEDLINE (Ovid).
3. Embase (Ovid).
4. Conference Proceedings Citation Index-Science (CPCI-S) (Web of Science).

We will adapt the preliminary search strategy for MEDLINE (Ovid) for use in the other databases (Appendix 1). We will apply the Cochrane sensitivity-precision RCT filter to MEDLINE (Ovid) and adaptations of it to the other databases (Lefebvre 2011), except CENTRAL. We will impose no restrictions with regard to language of publication or publication status. We will also examine any relevant retraction statements and errata for included studies.
We will not perform a separate search for adverse effects of electrical or pharmacological cardioversion used for the treatment of AF. We will consider adverse effects described in included studies only.

Searching other resources

We will search three clinical trial registers: ClinicalTrials.gov (clinicaltrials.gov); the WHO ICTRP (who.int/ictrp/en); and the ISRCTN registry (ISRCTN), for ongoing or unpublished trials.
For identified studies with status of registration not present in any of the three aforementioned registries, we will look for additional

evidence of registration in national trial registries, and clinical trial registries listed on the US Department of Health and Human Services webpage (HHS 2015).

We will check the reference lists of all included studies and any relevant systematic reviews identified.

Data collection and analysis

Selection of studies

As the first step of screening, we will apply the machine learning classifier (RCT model) (Wallace 2017), available in the Cochrane Register of Studies (CRS-Web) (Cochrane 2017a). The classifier assigns a probability (from 0 to 100) to each citation of being a true RCT. For citations that are assigned a probability score of less than 10, the machine learning classifier currently has a specificity/recall of 99.99% (Wallace 2017). Cochrane Crowd will screen citations with a score of nine or less (Cochrane 2017b). Cochrane Crowd will return any citations that are deemed to be potential RCTs to the authors for screening. The titles and abstracts of all remaining entries assigned a score of 10 or above will be screened in duplicate and independently by two review authors (JT and AI or NP) and will only be rejected if the review author can determine that they definitely do not meet the inclusion criteria. We will obtain full-texts for all potentially eligible papers following assessment of the abstracts. Two review authors (JT and AI or NP) will independently assess each paper. We will use Covidence for accelerating the process of title and abstract screening. If we exclude a trial after analysis of its full paper, we will add a record of the study and the reason for excluding it to a document. Differences between the two review authors in the selection process will be resolved by discussion or by a third review author (RP or SBW) if agreement cannot be reached.

Data extraction and management

Two review authors (NP, AI or JT) will extract data independently using a data collection form specifically developed for this task. When necessary, we will contact authors of primary studies for additional information. We will check the completed data forms for agreement and will resolve any differences by discussion and consensus. When agreement is not reached, a third review author (RP or SBW) will be contacted for a final decision. We will pilot the data collection form with a sample of included studies to assess its accuracy and adequacy to the protocol.

In addition to data relating to the outcomes of the review, we will collect information on the following.

1. Study methods and design (randomisation, allocation, concealment and blinding).
2. Information on the number of people eligible, N randomised, N completing treatment, N analysed, and N lost to follow-up (by treatment arm, and specifying reasons).
3. Baseline characteristics of patients (age, gender, episode/symptoms duration, prevalence and aetiology of heart disease, ECG data on left ventricular systolic and diastolic function and left atrial size, duration and type of AF, and used definitions for type of AF, presence of diabetes, hypertension, previous stroke, known coronary artery disease, CHA_2DS_2VASc score). The CHA2DS2VASc score is a marker of thromboembolic risk in AF patients, and is composed of the following risk factors: congestive heart failure, hypertension, age (over 65 years, or over 75 years), diabetes mellitus, stroke or transient ischaemic attack, and presence of vascular disease (Lip 2010).
4. Setting of cardioversion: emergency room/accident and emergency.
5. Details of treatment: method of cardioversion employed (direct-current cardioversion: energy, pad position and waveform - mono or biphasic; pharmacological cardioversion: antiarrhythmic drug and doses), information on preprocedural anticoagulation (duration - pre and postcardioversion, and type of anticoagulation and doses / international normalized ratio - INR - target), treatment used in control group and concomitant medication (beta-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blocker antagonists, aldosterone receptor blockers, antiplatelets and anticoagulants, and pretreatment with antiarrhythmic drugs in patients undergoing electrical cardioversion).
6. Follow-up: duration, patients lost to follow-up and withdrawals, method used for rhythm monitoring (implantable loop recorder, 24 hours, 48 hours, 7-day Holter or others).
7. Funding.
8. Information on published protocol/clinical trial register entry.
9. Planned outcomes, reported outcomes.
10. Trial authors' conflicts of interest.

One review author (JT) will transfer data into the Review Manager file (RevMan 2014). 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 (AI or NP) will spot-check study characteristics for accuracy against the trial report. We will compare magnitude and direction of effects reported in the study with those in the review for confirming data accuracy (Higgins 2016).

Assessment of risk of bias in included studies

We will use the instructions given in the *Cochrane Handbook for Systematic Reviews of Interventions* in our evaluation of the methodology and the risk of bias of the included trials (Higgins 2011). Two review authors (RP, SBW) will independently assess risk of bias for each included study. Disagreements will be resolved by

consultation with a third review author (PL) or by general consensus. We will apply the Cochrane 'Risk of bias' tool by assessing the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will judge each potential source of bias as 'high', 'low' or 'unclear' and report quote(s) from the study together with justification(s) for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed.

When considering the treatment effects, we will take into account the risk of bias for the studies contributing to that outcome. We will consider the implications of missing outcome data from individual participants per outcome, such as high dropout rates (for example, above 15%) or disparate attrition rates (for example, a difference of 10% or more between study arms).

We will classify studies with low risk of bias in all domains as being at low risk. We will make an exception for blinding of participants and personnel, which we believe will be difficult for cardioversion strategies, as electrical cardioversion requires sedation. Studies presenting high risk of bias in this item can still receive the final classification of low risk of bias. If studies present any other additional domains classified as high risk, we will classify the study as high risk of bias. We will contact study authors in situations where we consider the risk unclear. If there is no clarification provided by the authors, we will consider this high risk. We will discuss in the final review the limitations of the expected lack of 'blinding of participants and personnel' for conclusions (Hróbjartsson 2014; Pocock 2015).

We will still consider studies with presence of bias in the 'blinding of outcome assessment' low risk of bias regarding all primary endpoints and secondary endpoints, except those related to quality of life and complications, as we believe that for objective outcomes like death, stroke or hospitalisation, this will not lead to relevant bias.

Measures of treatment effect

Dichotomous outcomes

We will calculate risk ratios (RRs) for having an event with 95% confidence intervals (CIs) for dichotomous outcomes.

Continuous outcomes

We will use end values in preference to change in values/scores in our analyses, if these are both reported in the same study. We will calculate the mean differences (MDs) or the standardised mean differences (SMDs) with 95% CIs for continuous outcomes. We will only use the SMD for those outcomes where a MD is inappropriate (Higgins 2011).

For studies where these data are not available, and only median and interquartile range are reported, we will narratively describe skewed data reported as medians and interquartile ranges.

Outcomes reported in different scales

For outcomes like quality of life, where different scales may be used for reporting, we will pool data using SMD.

Relative ranking

While performing the network meta-analysis we will estimate the probabilities for each intervention of being at each possible rank. Then we will obtain a treatment hierarchy using the probability of each intervention being the best treatment by using ranking of treatments (R (R 2017), metameta, command netrank (Rücker 2015)) based on P scores, the frequentist analogue of the Surface Under the Cumulative RAnking curve (SUCRA) (Rücker 2015). We will create a relative ranking of the competing interventions for all the available endpoints.

Number needed to treat

We will calculate the number needed to treat for an additional beneficial outcome (NNTB) or number needed to harm for an additional harmful outcome (NNTH) for the specified duration of treatment. This will be done for all comparisons, irrespectively of the significant status of the observed differences (Altman 1998). This will be estimated as the reciprocal of the absolute risk difference for the particular outcome between treated subjects and the control or placebo group-that is, 1(risk of outcome in placebo group−risk of bad outcome in treated group) (Laupacis 1998). Similarly, when comparing two active treatments, the treatment whose rank is closer to the placebo arm rank, will be the reference treatment.

We will provide absolute risk reduction or difference and the respective 95% CIs alongside with NNTB and NNTH.

Unit of analysis issues

All included trials will be randomised at the individual participant level. We will reduce patient numbers in cluster-randomised trials to an effective sample size, as described by Hauck 1991.

For studies with multiple-arm interventions and if more than two meet the inclusion criteria, we will combine them into electrical, pharmacological or placebo for the main analysis, and perform pairwise comparisons; subsequently, for the specific intervention analysis (by antiarrhythmic type or electrical cardioversion strategy), we will compare different arms among themselves pairwise.

Dealing with missing data

We will contact investigators or study sponsors to obtain any missing data. We will compute standard deviations (SDs) from other reported statistics whenever these are available.

We will analyse the data on the basis of intention-to-treat. By default, we will use available case analysis (missing patients will be considered as not to have experienced an event). Nevertheless, we will also carry out the worst-case scenario intention-to-treat-analysis (all missing patients considered as having events) for the three outcomes of interest mentioned below, to test if any potential difference might have arisen due to losses to follow-up.

The outcomes of interest for these analyses will be:

- maintenance of sinus rhythm until hospital discharge;
- stroke, systemic embolism, or transient ischaemic attack

occurring within the first 30 days following cardioversion; and

- 30-day all-cause mortality.

Assessment of heterogeneity

For each direct comparison we will primarily investigate forest plots to visually assess any sign of heterogeneity. We will secondly assess the presence of statistical heterogeneity by the Chi^2 test (threshold $P < 0.10$) and measure the quantities of heterogeneity by the I^2 statistic (Higgins 2002; Higgins 2003). The importance of the observed value of I^2 depends on both magnitude and direction of effects and strength of evidence for heterogeneity, and uncertainty in the value of I^2 is substantial when the number of studies is small (Higgins 2011). We will follow the recommendations for thresholds in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

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

We will compare potential effect modifiers using descriptive statistics to assess similarity of trials within and across comparisons. This will allow us to assess whether or not the 'transitivity assumption' is met (whether it is equally likely that any patient in the network could have been given any of the treatments in the network), and if differences in the prevalence of effect modifiers are leading to heterogeneity.

We will use the Q statistic for quantifying heterogeneity/inconsistency of the whole network. We will then further decompose this into Q value within designs (within studies of the same design) and between designs (within studies of different designs).

Assessment of reporting biases

We will assess publication bias and other reporting biases by visual inspection of funnel plots for primary outcomes if we include at least 10 trials (Higgins 2011). Using visual assessment of the asymmetry of the funnel plot and the regression asymmetry test (Egger 1997), we will assess the risk of bias.

Data synthesis

Direct comparison

First, we will perform conventional pairwise meta-analyses for all outcomes and comparisons, provided that at least two studies are available; we will use statistical software, Review Manager 5 (Review Manager 2014), provided by Cochrane, for these analyses.

We will include all studies in our initial analyses and conduct a sensitivity analysis of studies at low risk of bias. If the results are similar, we will base our primary conclusions on the overall analysis. If they differ, we will base our primary conclusions on studies at low risk of bias.

We will use a random-effects model as the primary analysis for calculating RRs and MDs. The choice of the random-effects model allows accounting for between-study heterogeneity, and in case this is not present, results will be equal to those of the fixed-effect model. If the studies are found to be clinically very dissimilar, the pooled measure will be difficult to interpret and we may decide that we should avoid statistically combining them in a meta-analysis (Higgins 2011).

We will perform subgroup analyses if we detect any source of heterogeneity.

Network meta-analysis

We will rank the specific interventions included in the review through a network analysis for each of the outcomes listed in the 'Type of outcome measures' section. One of the review authors (IN) has expertise in the area, and expert opinion will be sought for clarification of questions which may arise during the course of the analyses.

It is the authors' belief that providing both data for direct comparisons of the different interventions, and a ranking of the differently available treatments for each of the outcomes will be more informative for clinicians and patients when making decisions regarding the clinical situation discussed in this review.

Network meta-analysis combines direct evidence within trials and indirect evidence across trials (Mills 2012). This method synthesises information from a network of trials addressing the same question but involving different interventions. For a given comparison, for example, electrical cardioversion versus placebo, direct evidence is obtained from studies that compare these two treatments directly. In addition, indirect evidence for the electrical cardioversion versus placebo comparison can be obtained by synthesising studies comparing electrical cardioversion versus pharmacological cardioversion and placebo versus pharmacological cardioversion (Caldwell 2005; Higgins 1996). Network meta-analysis combines

evidence into a single effect size, and under certain assumptions it can increase the precision in the estimates, while randomisation is respected. It is important that there are no major differences between the trials (clinical characteristics of the patients, settings, inclusion and exclusion criteria, study methods) making different comparisons other than the treatments being compared. The main assumptions for this to occur are homogeneity, similarity, transitivity, and consistency. It is important that the results of trials on the same comparison are homogeneous, so they can be used for indirect comparisons. Even though it is of importance that trials are similar enough to be considered together, not only in design but also regarding effect modifiers, we do not require perfect homogeneity between studies to enable a useful analysis. In sum, we require a reasonable belief that heterogeneity between studies, and between studies and the target population, is not likely to materially affect the estimates and inference. Left atrium size and AF duration may have an effect on the results of cardioversion. Therefore, their distribution should be similar among the two direct comparisons used for obtaining the indirect comparison. Finally, consistency can be assessed when direct and indirect data are available for a particular comparison of interventions. When consistency is present, the effect of a given treatment should be similar whether it is measured by direct or indirect comparison (Catala-Lopez 2014; Cipriani 2013).

We will perform network meta-analyses within a frequentist framework, assuming an equal heterogeneity parameter τ across all comparisons, and we will account for correlations induced by multi-arm studies (Lu 2006; Salanti 2009).

Similarly to the direct comparison part of the review, we will include all studies in our initial network meta-analysis and conduct a sensitivity analysis of studies at low risk of bias. If the results are similar, we will base our primary conclusions on the overall analysis. If they differ, we will base our primary conclusions on studies at low risk of bias.

We will perform the analysis using R, version 3.4.2 (R 2017), netmeta package (netmeta); the codes and description of the methodology can be found in netmeta, Neupane 2014, and Schwarzer 2015. As a measure that reflects ranking and the uncertainty, we will use ranking of treatments (netrank command on R 2017; package netmeta) based on frequentist analogue of the Surface Under the Cumulative RAnking curve (SUCRA) (Rücker 2015). This measure, expressed as percentage, shows the relative probability of an intervention being among the best options.

We will obtain a network plot to ensure that the trials are connected by treatments using the netgraph command. Participants can be randomised to any intervention in the network/all eligible interventions are jointly randomisable.

We plan to perform a network meta-analysis of the formed triangular network of interventions (electrical cardioversion versus pharmacological cardioversion versus placebo), and then, if enough studies are present for specific treatment options (i.e. at least 2 studies for specific antiarrhythmic agents or cardioversion strategies), we will expand the three nodes and perform a network meta-analysis of the formed expanded network of treatment options (different antiarrhythmic drugs, different cardioversion strategies, etc.)

There are limitations in the use of the network meta-analysis methodology and it is essential to check the assumptions of the analysis before drawing conclusions. In order to estimate network inconsistency locally, we will use the Bucher method (Bucher 1997; ITC 2008), as described in Dias 2013. To evaluate the presence of inconsistency in the entire network, we will give the generalised heterogeneity statistic Q_{total} and the generalised I^2 statistic, as described in Schwarzer 2015. We will use the decomp.design command in the R package netmeta for decomposition of the heterogeneity statistic into a Q statistic for assessing the heterogeneity between studies with the same design and a Q statistic for assessing the design's inconsistency to identify the amount of heterogeneity/inconsistency within as well as between designs (netmeta; R 2017). Furthermore, we will create a net heat plot (Krahn 2013), a graphical tool for locating inconsistency in network meta-analysis, using the command 'netheat' in the R package netmeta (netmeta; R 2017). We will give Q_{total} and its components as well as net heat plots based on random-effects models to identify differences between these approaches.

We will assess quality of evidence in the network meta-analysis using the CINeMA approach (CINeMA; Cipriani 2013). This considers the five GRADE domains: study limitations, indirectness, inconsistency, imprecision and publication bias.

'Summary of findings' tables

We will use the GRADE system to assess the quality of the body of evidence associated with seven selected outcomes in our review (Guyatt 2008), constructing 'Summary of findings' tables using the GRADEPro GDT 2015 software and CINeMA. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality measure of a body of evidence considers within-study risk of bias, the directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias. We will include all studies in our initial analyses and conduct a sensitivity analysis with studies at low risk of bias in all domains except for 'blinding of participants and personnel'. If the results are similar, we will base our primary 'Summary of findings' tables and primary conclusions on the overall analysis. If they differ, we will base our primary 'Summary of findings' tables and primary conclusions on studies with low risk of bias or alternatively, studies with low risk of bias in all 'Risk of bias' domains except 'blinding of participants and personnel' (Gluud 2006; Kjaergard 2001; Lundh 2017; Moher 1998; Savovi 2012; Schulz 1995; Wood 2008).

The decision to downgrade a trial should result from a consensus between two review authors (RP and SBW), and whenever needed

a third review author (PL) will intervene. We will add a footnote to the 'Summary of findings' table to explain which domains were taken into account in the decision.

A SoF table will be completed for the mixed treatment comparison using CINeMA and for each of the pairwise comparisons using GRADEPro GDT 2015 (pharmacological cardioversion versus placebo; electrical cardioversion versus placebo; pharmacological cardioversion versus electrical cardioversion; and subcomparisons if enough data are available on different antiarrhythmic agents and electrical cardioversion pad position), and for the following seven outcome measures, as that is the maximum permitted: maintenance of sinus rhythm until hospital discharge or end of study follow-up; stroke, systemic embolism, or transient ischaemic attack occurring within the first 30 days following cardioversion; 30-day all-cause mortality; acute procedural success; 30-day cardiovascular mortality; duration of hospitalisation; and complications within the first week.

Subgroup analysis and investigation of heterogeneity

We will investigate possible heterogeneity through subgroup analyses. These will be conducted for all endpoints where heterogeneity is considered of potential importance (I^2 > 40%), and subgroups will include the following.

1. Type of AF or atrial arrhythmias
   i) non-valvular AF versus valvular AF
   ii) patients with AF versus patients with atrial flutter
   iii) patients with paroxysmal AF versus patients with persistent AF
2. Presence of previous catheter ablation procedure
   i) patients with previous ablation procedures
   ii) ablation naïve patients
3. Concomitant clinical comorbidities
   i) patients with heart failure versus patients without heart failure
   ii) patients with diabetes mellitus versus patients without diabetes mellitus
4. Patch/pad position for electrical cardioversion
   i) patches in anteroposterior position
   ii) patients in anterolateral position (standard position)
5. Ongoing antiarrhythmic drug therapy*
   i) amiodarone
   ii) vernakalant
   iii) dronedarone
   iv) azimilide
   v) flecainide
   vi) dofetilide
   vii) vanoxerine
   viii) other antiarrhythmic drugs
6. Antiarrhythmic status precardioversion in patients undergoing electrical cardioversion
   i) no antiarrhythmics
   ii) antiarrhythmics precardioversion
7. Antiarrhythmic status postcardioversion
   i) discontinued antiarrhythmic agents
   ii) non-discontinued antiarrhythmics postcardioversion
8. Structural Heart Disease
   i) patients with structurally normal heart (lone atrial fibrillation)
   ii) patients with structural changes (cardiomyopathy, valvular heart disease, etc.)

*We will pool data for all antiarrhythmic drugs and analyse it individually (for each specific drug), and also group it by pharmacological class, following the classification of Vaughan Williams (Vaughan Williams 1984).

We will conduct a significance test for assessing for differences between two or more subgroups (Borenstein 2008; Review Manager 2014).

Sensitivity analysis

We will perform sensitivity analyses by selectively pooling:

- studies having the best methodological quality (low risk of bias);
- studies including the greatest number of patients (i.e. studies in the highest quartile of participants);
- trials with evidence of registration considered irrefutable and with registration occurring before the start of study enrolment; and
- trials with evidence of registration considered irrefutable and with registration occurring at any time.

At least two studies fulfilling one of these prerequisites will be required for performing these four sensitivity analyses.

- A worst-case scenario to assess the effect of missing data (we will consider missing cases to have relapsed AF or developed the above mentioned outcomes).

The outcomes of interest for these analyses will be:

- maintenance of sinus rhythm until hospital discharge;
- stroke, systemic embolism, or transient ischaemic attack occurring within the first 30 days following cardioversion; and
- 30-day all-cause mortality.

We will accept as irrefutable evidence the following sources.

1. Trial registration: for studies that began enrolment on or after 1 July 2008 based on World Health Organization (WHO) (Sim 2006; WHO 2006; WHO 2012) and the International Committee of Medical Journal Editors' recommendations (Laine 2007); we will search on ClinicalTrials.gov (clinicaltrials.gov), the WHO International Clinical Trials Registry Platform (ICTRP) (who.int/ictrp/en), and the ISRCTN registry (ISRCTN). For studies not identified in these databases, we will perform additional searches on national trial registries or other registries available on the US Department of Health and Human Services (HHS 2015).

2. Letters from ethics committees or trial authors confirming the study was approved by an ethics committee as a 'randomised trial'.

3. Evidence of trial registration in a different database provided by authors.

4. Publication of a peer reviewed protocol prior to the publication of the trial results.

We will contact authors for information on trial registration, and how this has been done (alternative trial registration database, etc).

Studies which began enrolment prior to the specified date, will have to address points 2, 3 or 4. Studies starting enrolment on or after 1 July 2008 will have to comply with points 1 and 2.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Preliminary MEDLINE search strategy

1 Electric Countershock/
2 Cardioversion*.tw.
3 countershock*.tw.
4 electroversion*.tw.
5 defibrillation*.tw.
6 exp Anti-Arrhythmia Agents/
7 (anti arrhythmi* or antiarrhythmic* or antifibrillatory).tw.
8 ((cardiac or myocardial) adj2 (depressant* or dysrhythmia)).tw.
9 exp Adrenergic beta-Antagonists/
10 (beta adj2 (adrenergic* or antagonist* or block* or receptor*)).tw.
11 acebutolol.tw.
12 Adenosine.tw.
13 Ajmaline.tw.
14 amiodarone.tw.
15 atenolol.tw.
16 azimilide.tw.
17 bisoprolol.tw.
18 Carvedilol.tw.
19 digoxin.tw.
20 diltiazem.tw.
21 disopyramide.tw.
22 dofetilide.tw.
23 Dronedarone.tw.
24 Encainide.tw.
25 esmolol.tw.
26 flecainide.tw.
27 ibutilide.tw.
28 Lidocaine.tw.
29 metoprolol.tw.
30 Mexiletine.tw.
31 moricizine.tw.
32 nadolol.tw.
33 Nebivolol.tw.
34 oxprenolol.tw.
35 Phenytoin.tw.
36 procainamide.tw.
37 propafenone.tw.
38 propranolol.tw.

39 quinidine.tw.
40 sotalol.tw.
41 Timolol.tw.
42 Tocainide.tw.
43 verapamil.tw.
44 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45 Atrial Fibrillation/
46 Atrial Flutter/
47 ((atrial or atrium or auricular) adj3 (fibrillat* or flutter*)).tw.
48 45 or 46 or 47
49 44 and 48
50 randomized controlled trial.pt.
51 controlled clinical trial.pt.
52 randomized.ab.
53 placebo.ab.
54 clinical trials as topic.sh.
55 randomly.ab.
56 trial.ti.
57 50 or 51 or 52 or 53 or 54 or 55 or 56
58 exp animals/ not humans.sh.
59 57 not 58
60 49 and 59

CONTRIBUTIONS OF AUTHORS

RP: developed the concept of this protocol, completed the draft protocol and modified the protocol according to the feedback obtained from other authors.

DC: provided clinical feedback on the elaboration of the protocol.

JT: provided feedback on the elaboration of the protocol.

KKR: provided clinical and methods feedback on the elaboration of the protocol.

NP: provided clinical and methods feedback on the elaboration of the protocol.

AI: provided clinical and methods feedback on the elaboration of the protocol.

GEM: provided clinical and methods feedback on the elaboration of the protocol.

IIFN: provided methods feedback on the elaboration of the protocol.

SBW: provided clinical feedback on the elaboration of the protocol.

PL: provided clinical feedback on the elaboration of the protocol.

CAM: provided clinical feedback on the elaboration of the protocol.

All authors have read and approved the protocol.

DECLARATIONS OF INTEREST

RP: none known

DC: none known

JT: none known

KKR: none known

NP: none known

AI: none known

GEM: none known

IIFN: none known

SBW: received unrestricted grant support from Medtronic Canada, Boston Scientific, and Abbott, for work unrelated to the review topic, and consulting fees from Arca Biopharma for work on an atrial fibrillation clinical trial

PL: receives speaker fees and educational grant funding from Boston Scientific, and educational grant funding from Medtronic for work unrelated to the content of this Cochrane Review

CAM: declared conflicts not related with the current work

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NOTES

This review supersedes two reviews that were in need of updating but have been merged and started as a new review (Cordina 2017; Mead 2017)