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Adenosine versus intravenous calcium channel antagonists for supraventricular tachycardia (Review)

Alabed S, Sabouni A, Providencia R, Atallah E, Qintar M, Chico TJA

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[Intervention Review]

Adenosine versus intravenous calcium channel antagonists for supraventricular tachycardia

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ABSTRACT

Background

People with supraventricular tachycardia (SVT) frequently are symptomatic and present to the emergency department for treatment. Although vagal manoeuvres may terminate SVT, they often fail, and subsequently adenosine or calcium channel antagonists (CCAs) are administered. Both are known to be effective, but both have a significant side effect profile. This is an update of a Cochrane review previously published in 2006.

Objectives

To review all randomised controlled trials (RCTs) that compare effects of adenosine versus CCAs in terminating SVT.

Search methods

We identified studies by searching CENTRAL, MEDLINE, Embase, and two trial registers in July 2017. We checked bibliographies of identified studies and applied no language restrictions.

Selection criteria

We planned to include all RCTs that compare adenosine versus a CCA for patients of any age presenting with SVT.

Data collection and analysis

We used standard methodological procedures as expected by Cochrane. Two review authors independently checked results of searches to identify relevant studies and resolved differences by discussion with a third review author. At least two review authors independently assessed each included study and extracted study data. We entered extracted data into Review Manager 5. Primary outcomes were rate of reversion to sinus rhythm and major adverse effects of adenosine and CCAs. Secondary outcomes were rate of recurrence, time to reversion, and minor adverse outcomes. We measured outcomes by calculating odds ratios (ORs) and assessed the quality of primary outcomes using the GRADE approach through the GRADEproGDT website.

Main results

We identified two new studies for inclusion in the review update; the review now includes seven trials with 622 participants who presented to an emergency department with SVT. All included studies were RCTs, but only three described the randomisation process, and none had

blinded participants, personnel, or outcome assessors to the intervention given. Moderate-quality evidence shows no differences in the number of people reverting to sinus rhythm who were treated with adenosine or CCA (89.7% vs 92.9%; OR 1.51, 95% confidence interval (CI) 0.85 to 2.68; participants = 622; studies = 7; I^2 = 36%). Low-quality evidence suggests no appreciable differences in major adverse event rates between CCAs and adenosine. Researchers reported only one case of hypotension in the CCA group and none in the adenosine group (0.66% vs 0%; OR 3.09, 95% CI 0.12 to 76.71; participants = 306; studies = 3; I^2 = 0%). Included trials did not report length of stay in hospital nor patient satisfaction.

Authors' conclusions

Moderate-quality evidence shows no differences in effects of adenosine and calcium channel antagonists for treatment of SVT on reverting to sinus rhythm, and low-quality evidence suggests no appreciable differences in the incidence of hypotension. A study comparing patient experiences and prospectively studied adverse events would provide evidence on which treatment is preferable for management of SVT.

PLAIN LANGUAGE SUMMARY

Adenosine versus intravenous calcium channel antagonists for tachycardia in adults

Background

Supraventricular tachycardia (SVT) is a common abnormal rhythm of the heart that results in a very rapid heartbeat. This rhythm problem usually occurs in otherwise healthy people, and common symptoms include palpitations, light-headedness, and chest pain. Occasionally, SVT may also cause confusion or loss of consciousness. SVT can sometimes be treated with simple physical manoeuvres such as forced breath holding. When simple manoeuvres fail, SVT can be treated in the emergency department with a variety of drugs. The two most commonly used drug types are adenosine and calcium channel antagonists (CCAs) (verapamil is the most frequently used drug in this class).

Study characteristics

This review compares effectiveness and side effects of adenosine and CCAs in terminating SVT episodes. We included in the review seven trials involving 622 patients. Evidence is current to July 2017.

Key results

Combined analysis of these trials showed no differences between adenosine and CCAs in successfully treating SVT. This finding is based on moderate-quality evidence. A temporary drop in blood pressure that did not require treatment was reported in only one of 152 study participants treated with CCAs, and low-quality evidence suggests that no patients treated with adenosine experienced low blood pressure. We have no data on length of stay in hospital nor on patient satisfaction.

Conclusions

Moderate-quality evidence shows no differences in effects of adenosine and calcium channel antagonists for treatment of SVT on reverting to sinus rhythm, and low-quality evidence suggests no differences in cases of hypotension. None of these trials examined patient preferences, which is an important factor in deciding which drug is the 'best' treatment.

Summary of findings for the main comparison. Adenosine compared with calcium channel antagonists for supraventricular tachycardia

Adenosine compared with calcium channel antagonists for supraventricular tachycardia

Patient or population: patients with supraventricular tachycardia
Setting: emergency department
Intervention: adenosine
Comparison: calcium channel antagonists (CCAs)

Outcomes	Number of participants	Number of studies	Odds ratio (95% CI)	Absolute effects (95% CI)			Follow-up	Quality of the evidence (GRADE)	What happens
				With adenosine	With CCA	Difference			
Odds of reversion	622	7 RCTs	OR 1.51 (0.85 to 2.68)	89.7%	92.9% (88.1 to 95.9	3.2% lower odds of reversion with adenosine (95% CI 1.2 lower to 6.2 lower)	Until reversion occurred or predetermined maximum dose was reached	⊕⊕⊕⊖ MODERATE[a]	Higher odds of reversion indicate better effect.
Major adverse event: hypotension	306	3 RCTs	OR 3.09 (0.12 to 76.71)	0.0%	0.0% (0.0 to 0.0)	0.0% fewer (0 fewer to 0 fewer)	Up to 2 hours after infusion	⊕⊕⊖⊖ LOW[a,b]	Lower hypotension rate indicates fewer adverse events.
Length of stay in hospital	Not reported	0							
Patient satisfaction	Not reported	0							

CI: confidence interval; OR: odds ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect,
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]Quality of the evidence downgraded by one level for imprecision. Moderate to wide confidence intervals.
[b]Quality of the evidence downgraded by one level for study limitations. Judgements of high risk of bias in all studies, as none of the studies were blinded.

BACKGROUND

Description of the condition

Definitions

Supraventricular tachycardia (SVT) includes all tachyarrhythmias that originate in supraventricular tissue or incorporate supraventricular tissue in the re-entrant circuit and have sudden onset and termination. Atrioventricular nodal re-entrant tachycardia (AVNRT) and atrioventricular re-entrant tachycardia (AVRT) (such as Wolff-Parkinson-White syndrome) are two major types of SVT; other types include atrial tachycardia, paroxysmal atrial flutter, and paroxysmal atrial fibrillation (Jayam 2004). Most patients with SVT due to AVNRT or AVRT do not have associated structural heart disease (Ferguson 2003).

Epidemiology

SVT is a common arrhythmia with a prevalence of 2 per 1000 adults. The incidence of SVT is 36 per 100,000 people per year, and women have twice the risk of developing SVT compared with men (Orejarena 1998).

Clinical presentation and diagnosis

SVTs are often recurrent and occasionally persistent, and are a frequent cause of visits to emergency departments and primary care physicians' offices. Common symptoms of SVT include palpitations, anxiety, light-headedness, chest pain, neck pounding, and dyspnoea (Delacrétaz 2006; Medi 2009). For patients presenting with SVT, a 12-lead electrocardiogram (ECG) that shows a narrow complex tachycardia is essential for making the diagnosis and may reveal the mechanism of the arrhythmia.

Treatment

Treatment in stable, symptomatic patients is aimed at terminating the rhythm by decreasing conduction through the atrioventricular (AV) node. Increasing vagal tone by the Valsalva manoeuvre or by carotid sinus massage will effectively revert up to 53% of patients to sinus rhythm (Wen 1998). A modified Valsalva manoeuvre with leg elevation and supine positioning can further improve success (Appelboam 2015). A recent Cochrane review assessed effectiveness of the Valsalva manoeuvre in terminating SVT and showed a reversion success rate between 19.4% and 54.3% in two studies. However, evidence was insufficient overall to support its effectiveness in terminating SVT (Smith 2015). For patients in whom vagal manoeuvres are not effective, calcium channel antagonists (CCAs), adenosine, sotalol, beta-blockers, and magnesium sulphate have been shown to be more effective than placebo (Dougherty 1992; Gupta 1999; Jordaens 1991; Joshi 1995). However, for acute management, adenosine and non-dihydropyridine CCAs - verapamil and diltiazem - are the intravenous drugs of choice for termination of SVT (Mangrum 2002). The 2015 American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation and the 2015 European Resuscitation Council (ERC) Guidelines for Resuscitation for regular narrow complex SVT recommend use of adenosine if vagal manoeuvres have failed to terminate the SVT. CCAs are recommended as a second-line drug if adenosine is contraindicated or fails to terminate the SVT (Page 2016; Soar 2015). The decision as to which agent should be used is generally determined by clinician preference, personal experience, and institutional culture.

Description of the intervention

Adenosine and CCAs have been widely used in SVT with similar efficacy (Bolton 2000; Delaney 2011). Moreover, the previous version of this Cochrane review, which compared these agents, showed no significant differences in reversion rate between the two drugs (Holdgate 2006). However, adenosine is significantly more costly than most intravenous (IV) CCAs.

Adenosine has a half-life of less than a minute, and reversion to sinus rhythm may be short-lived, as a subsequent ectopic beat may reinitiate SVT. Many patients experience short-lived but unpleasant side effects following administration of adenosine, including dyspnoea, flushing, and, perhaps most dreadfully, a sense of impending death or doom that can be very frightening (Bolton 2000; Katzung 1995). The recommended adult dosage of adenosine for peripheral infusion is 6 mg, followed by a 12-mg dose if needed. Because of the ultrashort duration of action, cumulative effects of sequential doses are not seen (Ferguson 2003).

On the other hand, CCAs have been used in SVT for many years and are effective in up to 90% of patients (Bolton 2000; Delaney 2011). Calcium channel blockade causes negative inotropy and peripheral vasodilation, which may result in hypotension, particularly among patients with impaired left ventricular function. CCAs have a relatively long half-life of three to six hours, thus adverse effects may be prolonged. They are relatively contraindicated in patients who are already taking beta-blockers, as the combined effect may lead to significant bradycardia (Katzung 1995). The recommended dosage of verapamil is 5 mg IV over 2 minutes, followed in 5 to 10 minutes by a second dose of 5 to 7.5 mg. The recommended dosage of diltiazem is 20 mg, followed, if necessary, by a second dose of 25 to 35 mg; SVT termination should occur within 5 minutes of infusion completion (Ferguson 2003).

How the intervention might work

Both adenosine and CCAs inhibit conduction through the AV node, which facilitates termination of SVT. Adenosine is an endogenous nucleoside that acts by inhibiting cyclic adenosine monophosphate (cAMP)-mediated calcium influx and enhancing potassium conduction. This leads to inhibition of AV nodal conduction and expansion of the AV nodal refractory period. In contrast, CCAs act by blocking voltage-dependent calcium channels, thus reducing intracellular calcium and leading to blockade of calcium-dependent conduction through the AV node (Katzung 1995).

Why it is important to do this review

The previous version of this review showed that adenosine and CCAs are reasonably effective but have a significant side effect profile (Holdgate 2006). This review update looks at new studies conducted over the past 10 years and aims to further explore uncertainty while helping clinicians and decision makers to regulate the choice between adenosine and CCAs. Recent American and British guidelines recommend adenosine as first pharmacological treatment for stable patients with SVT after vagal manoeuvres are attempted (Blomstrom-Lundqvist 2003; Page 2016; Resuscitation Council (UK) 2015).

OBJECTIVES

To review all randomised controlled trials (RCTs) that compare effects of adenosine versus CCAs in terminating SVT.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include RCTs. We excluded studies reported to be randomised but exhibiting major violations in randomisation methods or treatment allocation, or major differences in baseline characteristics unlikely to have occurred by chance (Athar 2013; Riaz 2012). We contacted authors of studies with protocol violations or for whom we had questions regarding the randomisation process or approval. We excluded these studies from the analysis until we receive further information.

Types of participants

We included patients of any age with SVT diagnosed on 12-lead ECG within 24 hours of onset.

We excluded RCTs of patients with an SVT induced in the electrophysiology lab, as they do not meet the aim of this review, which focuses on SVT (see Differences between protocol and review section).

Types of interventions

We included all interventions that directly compare any intravenous CCA (e.g. verapamil, diltiazem) versus IV adenosine, at any dosage or infusion rate of either drug.

Types of outcome measures

Primary outcomes

1. Reversion to sinus rhythm
2. Major adverse events (defined as cardiac arrest, prolonged hypotension, symptomatic bradycardia requiring treatment, and acute cardiac failure)

Secondary outcomes

1. Time to immediate reversion to sinus rhythm
2. Rate of relapse to SVT within two hours following reversion
3. Length of stay in hospital
4. Minor adverse events (defined as any reported adverse events other than those defined above)
5. Patient satisfaction as measured on any validated scale

Search methods for identification of studies

Electronic searches

We updated searches conducted in 2006 for the original review (Appendix 1) by searching the following databases on 5 July 2017 for relevant RCTs (Appendix 2).

1. Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library (2017; Issue 6 of 12).
2. Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, and MEDLINE (Ovid, 1946 to 5 July 2017).
3. Embase (Ovid, 1980 to 2017 Week 27).

We applied the sensitivity-maximising version of the Cochrane RCT filter to our MEDLINE search, and we applied terms as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* to our Embase search (Lefebvre 2011). We imposed no restrictions on date or language of publication.

Searching other resources

We searched the following sources.

1. Reference lists of relevant identified publications.
2. Two databases of ongoing trials- ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) - on 7 July 2017 (Appendix 2).

Data collection and analysis

Selection of studies

Two review authors (MQ and AS) independently screened titles and abstracts for inclusion of all eligible studies identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. For disagreements, we asked a third review author (SA) to arbitrate. We retrieved full-text study reports/publications; two review authors (MQ and AS) independently screened the full texts and identified studies for inclusion, or recorded reasons for exclusion of ineligible studies. We resolved disagreements through discussion or through consultation with a third review author (SA). We identified and excluded duplicates and collated multiple reports of the same study, so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail and completed a PRISMA flow diagram and Characteristics of excluded studies tables.

We excluded all publications that were reviews, retrospective studies, or studies of observational design, as well as those that were not randomised, or did not focus on adenosine or CCAs or SVT.

Data extraction and management

Four review authors (MQ, AS, EA, and TJAC) extracted data for the eligible studies so that each eligible study was independently extracted by two authors. We extracted and collated data using a standardised, agreed upon data extraction form. Data collected include:

1. general information: publication type; title, authors, source, country, year of publication, trial dates, additional publications;
2. trial characteristics: design, setting, duration, types of interventions, types of outcome measures, aim of study, randomisation (and method), allocation concealment (and method), blinding (outcome assessors), check of blinding, funding/conflict of interest;
3. participants: unit of allocation, method of recruitment, inclusion criteria, exclusion criteria, total number and numbers in comparison groups, sex/age, ethnicity, severity of illness, subgroups reported, similarity of groups at baseline, withdrawals/losses to follow-up;

4. intervention: dosage, delivery, timing, administration rate, type of CCA, length of intervention, co-interventions, costs, compliance;
5. outcomes: outcomes as specified above, the main outcome assessed in the study, other events, length of follow-up; and
6. results: for outcomes assessed.

'Summary of findings' table

We used the GRADE approach, adopted by Cochrane, to interpret findings (Schünemann 2011). We used the GRADE profiler website (www.gradepro.org) to create a 'Summary of findings' table. Two review authors (SA, AS) independently assessed the quality of included studies.

With GRADEproGDT (GRADEproGDT 2015), evidence relative to each specific outcome is rated as having high, moderate, low, or very low quality. We started rating outcomes of all randomised trials as high quality and downgraded them depending on limitations in study design or execution, indirectness of evidence, unexplained heterogeneity, imprecision of results, and high probability of publication bias. By using GRADEproGDT, we produced a 'Summary of findings' table to show outcome-specific ratings and to present information about the overall quality of evidence.

We selected all primary outcomes for inclusion in the 'Summary of findings' table. In addition, we had planned to include length of stay in hospital and patient experience as patient-relevant outcomes, but included studies did not report this information.

Assessment of risk of bias in included studies

For this updated review, two review authors (MQ, AS, EA, and TJAC) independently carried out risk of bias assessment.

We assessed risk of bias of included trials, using the methods detailed in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We rated the risk of selection bias by assessing randomisation and allocation concealment. We rated performance, detection, and attrition bias by assessing blinding to treatment, blinding to outcome assessment, and losses to follow-up. We planned to assess selective reporting bias by cross-checking study outcomes against published protocols or trial registrations.

We coded each risk of bias criterion as having high risk, low risk, or unclear risk of bias, and we resolved disagreements by discussion. When necessary, we contacted study authors to try to clarify trial methods.

Measures of treatment effect

We followed the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions,* Sections 9.2 and 9.4, for measuring effects of different data types (Higgins 2011). For continuous outcomes (e.g. time to reversion), we calculated mean differences (MDs) and 95% confidence intervals (CIs), and for dichotomous outcomes (e.g. odds of reversion, adverse events), we calculated odds ratios (ORs) and 95% CIs.

Unit of analysis issues

Our unit of analysis was the participant. For cross-over trials, we included only data from the pre-cross-over phase, as time between drugs was short and did not allow drug washout. We did not encounter any cluster-randomised trials.

Dealing with missing data

When possible, we extracted data relevant to intention-to-treat analyses.

Assessment of heterogeneity

We analysed statistical heterogeneity by visually inspecting the forest plot and carrying out both Chi^2 and I^2 tests, as recommended in Chapter 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For the Chi^2 test on N-1 degrees of freedom, we defined $P < 0.1$ as showing substantial heterogeneity. We used the I^2 statistic to quantify statistical inconsistency and to assess the impact of heterogeneity on the meta-analysis. We determined that $I^2 > 50\%$ demonstrated high heterogeneity.

If no heterogeneity was present, we performed analysis using a fixed-effect model. When we detected substantial heterogeneity, we investigated possible sources of heterogeneity (e.g. study quality, outcome measures, participants, interventions). When the source of heterogeneity could not be explained, we did not combine study results.

Assessment of reporting biases

To assess the risk of publication bias, we had planned to construct funnel plots for each outcome with at least 10 trials; however, this was not possible owing to the limited number of included studies (Sterne 2011).

Data synthesis

We used Review Manager 5 software to perform data analysis (RevMan 5.3).

Subgroup analysis and investigation of heterogeneity

We planned subgroup analysis based on participant age, gender, duration of symptoms, intercurrent drug therapy, presence of underlying heart disease, prior treatments, and drug dosage to explore different effects amongst different groups. However, we found insufficient data to carry out these subgroup analyses.

Sensitivity analysis

We had planned to conduct sensitivity analyses on the primary outcomes to re-analyse exclusion of studies that we judged to be at high risk of bias across one or more domains of the Cochrane 'Risk of bias' tool. This was not possible, as all included studies had at least one domain with high risk of bias.

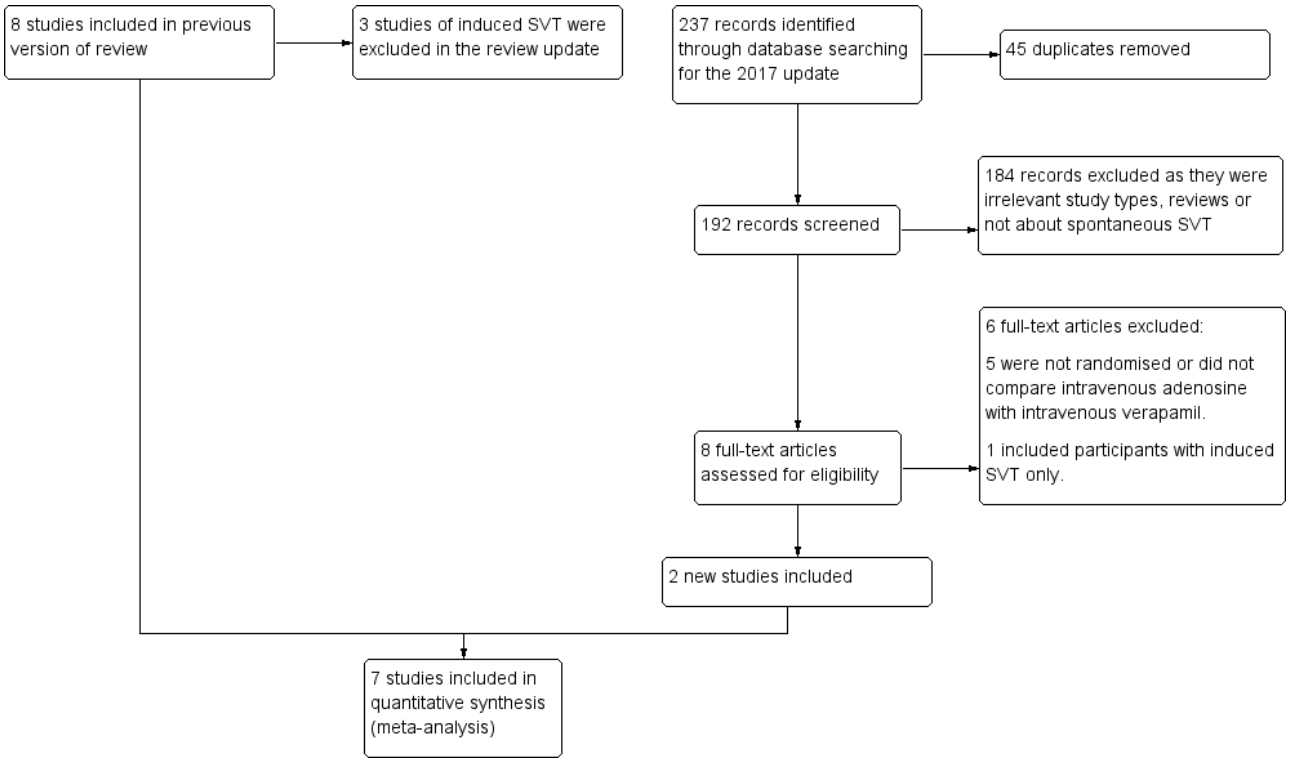
RESULTS

Description of studies

Results of the search

We identified 237 new references in our updated literature review. We screened 192 records on the basis of title and abstract after removing duplicates. We excluded most studies on abstract review because they were not RCTs or did not compare adenosine versus a CCA. We assessed eight full-text records and included two studies (Lim 2009; Vranic 2006). Figure 1 shows a flow chart of the updated search.

Figure 1. Study flow diagram.



We found no trials from reference checking and no ongoing trials upon searching ClinicalTrials.gov and the International Clinical Trials Registry Platform.

The original review included eight trials (Cabrera-Sole 1989; Cheng 2003; DiMarco 1990; Ferreira 1996; Gil Madre 1995; Greco 1982; Hood 1992; Kulakowski 1998). In this updated review, we excluded three of these, as they included patients with induced SVT (DiMarco 1990; Hood 1992; Kulakowski 1998). See Differences between protocol and review for clarification.

Included studies

Study designs

Four studies included a cross-over component in which the alternate study drug was administered if the first drug was unsuccessful (Lim 2009; Ferreira 1996; Gil Madre 1995; Greco 1982). The authors of one study did not report results after cross-over but counted them as showing failure of the initial treatment intervention (Lim 2009). Otherwise, we included only data from the pre-cross-over phase, as time between drugs was short and did not allow drug washout (particularly for verapamil). Another study included a third treatment arm given digitalis and did not provide data from this component of the trial (Greco 1982). The Lim trial,divided the CCA arm into verapamil and diltiazem (Lim 2009). We combined these arms in a single CCA group for the purposes of our meta-analysis.

The other three included studies reported that they were randomised and provided no further explanation (Cabrera-Sole 1989; Cheng 2003; Vranic 2006).

None of the included studies attempted blinding of participants or personnel.

Study design characteristics of the included studies can be found in the Characteristics of included studies tables.

Participants

The seven included trials were conducted in six different countries, were published between 1982 and 2009, and included 622 participants (Cabrera-Sole 1989; Cheng 2003; Ferreira 1996; Gil Madre 1995; Greco 1982; Lim 2009; Vranic 2006). All studies but one were conducted in adults (Greco 1982). Inclusion criteria for one trial included people above the age of 10. However, it was not possible to determine how many children younger than 18 were included in this trial (Lim 2009).

All included studies enrolled patients with SVT only.

Interventions

Four trials used adenosine in the form of ATP (adenosine triphosphate) (Cabrera-Sole 1989; Ferreira 1996; Gil Madre 1995; Greco 1982); the remaining five used adenosine. ATP is rapidly converted to adenosine (the free base form) following exogenous administration; 10 mg ATP is equipotent to 6 mg adenosine, and a linear dosage relationship has been noted between these two forms of the drug (Belhassen 1984; Faulds 1991). Verapamil was the CCA used in all trials. One trial included an arm of diltiazem that was analysed with verapamil in a combined CCA group (Lim 2009). One trial administered adenosine in doubling doses (3 mg-6 mg-12 mg), and another used dosing starting at 10 mg ATP (equivalent to 6 mg adenosine) followed by 20 mg ATP (Cheng 2003; Ferreira 1996). Two

trials gave adenosine 6 mg IV bolus followed by 12 mg IV bolus if SVT was not reverted with the first bolus (Lim 2009; Vranic 2006).

Cheng 2003, Ferreira 1996, and Gil Madre 1995 gave verapamil in 5-mg boluses. Cheng 2003 gave a 5-mg verapamil infusion over five minutes, Gil Madre 1995 in three minutes, Riaz 2012a in two minutes, and Ferreira 1996 in one minute. One trial did not specify whether the 5-mg verapamil bolus was infused over time or was given as an injection (Vranic 2006).

Verapamil was given at a fixed dose of 10 mg in Cabrera-Sole 1989. Another trial administered adenosine by slow intravenous infusion at a rate of 1 mg per minute up to a maximum dose of 20 mg while assessing the rhythm every two minutes (Lim 2009).

One trial administered diltiazem by slow intravenous infusion at a rate of 2.5 mg per minute up to a maximum dose of 50 mg, while assessing the rhythm every two minutes (Lim 2009).

Outcomes

All trials reported reversion to sinus rhythm as the main outcome. Researchers reported continuous ECG monitoring or ECG recording in Cheng 2003, Gil Madre 1995, Greco 1982, and Vranic 2006. Infusions were given until successful conversion to sinus rhythm occurred without further details on how this was assessed in Cabrera-Sole 1989, Ferreira 1996, and Lim 2009. Investigtors in all included studies monitored heart rate and blood pressure throughout infusion.

No studies reported length of stay in hospital nor outcomes derived from patient satisfaction surveys.

Excluded studies

We excluded five studies after acquiring full texts (Athar 2013; Gill 2014; Riaz 2012; Shaker 2015; Turkoglu 2009).

Riaz 2012 mentions randomisation only in the title and provides no further explanation in the Methods section. We contacted study authors for further clarification. This study mentions that a lottery method was used as the allocation method without providing further explanation about what this involved. When contacted, study authors described potentially significant differences in baseline characteristics (four-year difference in age and no P for comparison) and explained that no other baseline comparisons were available). We deemed that this trial did not use an appropriate randomisation method and therefore excluded it from this review.

Athar 2013 reports a quasi-experimental trial, with participants "randomly" allocated to two groups. However, study authors did not conceal allocation, as randomised participants received the alternate study drug (rather than the allocated drug) if they had a personal preference for the other drug owing to previous exposure. This article makes no further mention and provides no details of randomisation; multiple attempts to contact study authors were met with no response for clarification.

Gill 2014 makes no mention of randomisation; our attempts to contact study authors for clarification resulted in no response. Shaker 2015 was an RCT that compared IV adenosine versus IV adenosine and oral verapamil. Turkoglu 2009 enrolled only participants with induced SVT.

We excluded three studies that were initially included in the original review, as they enrolled patients with induced SVT (DiMarco 1990; Hood 1992; Kulakowski 1998). See Differences between protocol and review for clarification.

We have provided study design characteristics of all excluded studies in the Characteristics of excluded studies tables.

Risk of bias in included studies

For details on risk of bias in included studies, see 'Risk of bias' tables (Characteristics of included studies). We have presented information on overall risk of bias in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

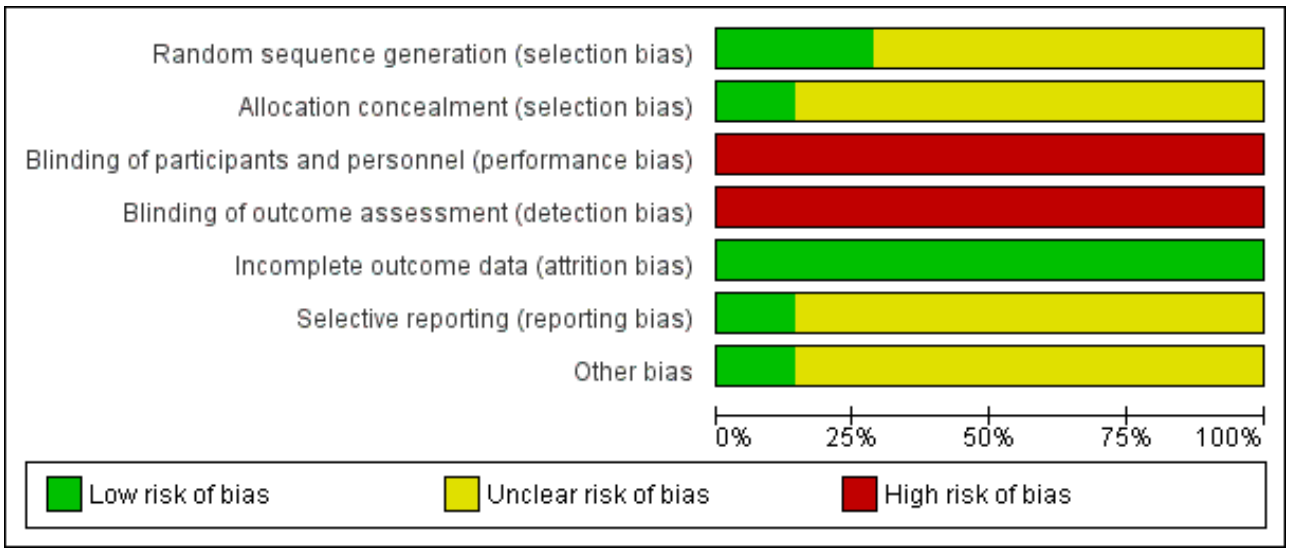
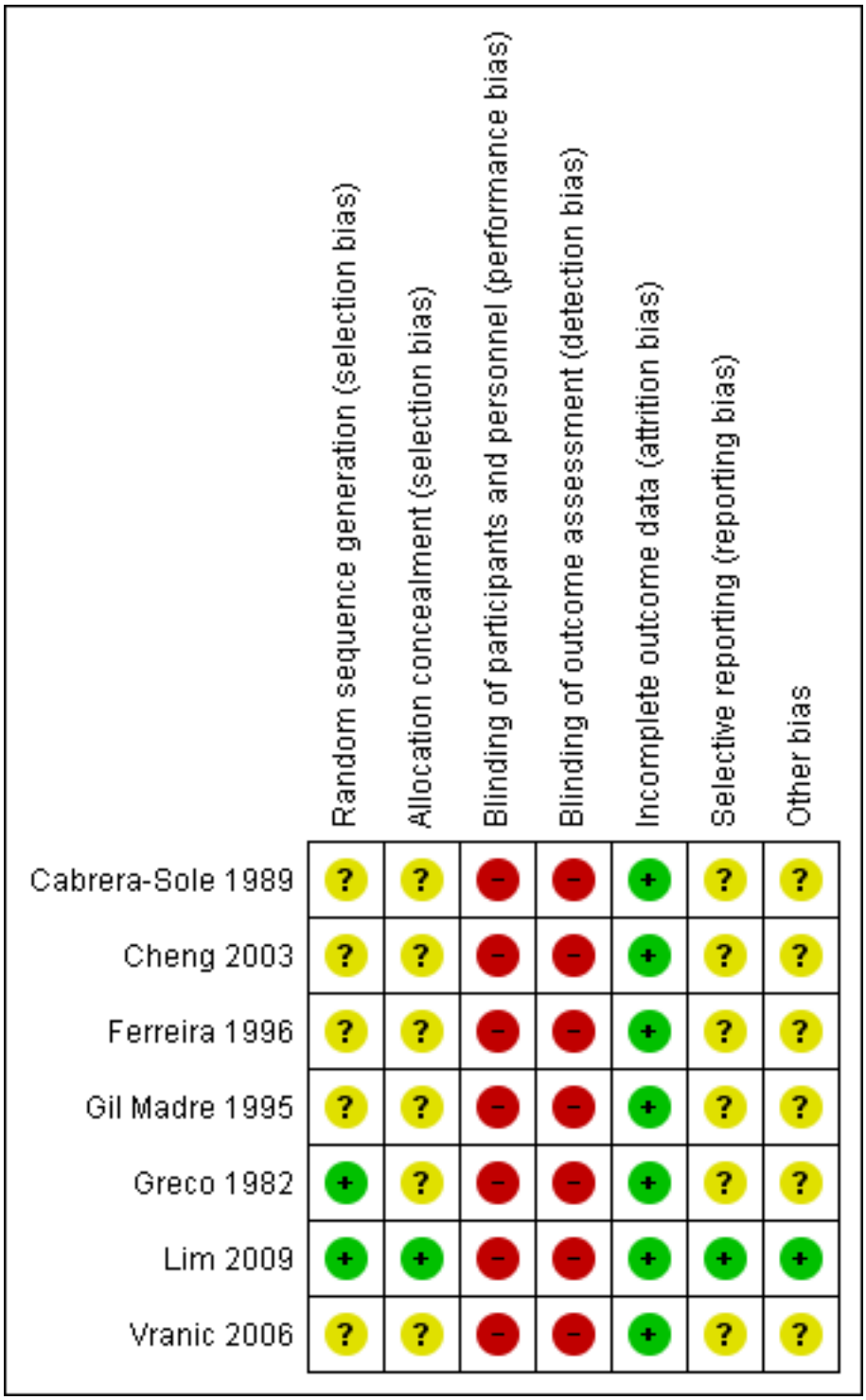


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

Two trials described the randomisation process (Greco 1982; Lim 2009). Investigators used a random numbers table to allocate participants to treatment in Greco 1982. A nurse drawing a serialised sealed envelope performed randomisation In Lim 2009.

All included studies provided data showing that participants in both drug groups were of similar age and had similar physiological parameters at the time of enrolment.

Allocation concealment

Only one trial reported adequate allocation concealment using an envelope method (Lim 2009). The remaining six trials did not provide sufficient information to reveal whether allocation concealment was adequate.

Blinding

We rated blinding as introducing high risk of bias in all included studies, as none reported blinding of participants, caregivers, outcome assessors, or investigators. As these two drugs are usually given by different methods (adenosine as a rapid bolus, and CCAs as a slower IV infusion), it would be possible to achieve blinding only by using a double-dummy method, which would require substantial resources. However, no investigators discussed this issue.

Incomplete outcome data

Trialists applied all interventions and assessed all outcomes in the emergency department during admission of patients. All studies reported outcomes for all included patients and reported no withdrawals or dropouts; therefore we rated risk of attrition bias as low for all studies.

Selective reporting

No protocols for included studies were available for cross-checking of reported study outcomes versus published protocols. All included trials described outcomes in the Methods sections.

We found a prospective trial registration in clinicaltrials.gov for Lim 2009. Planned outcomes included conversion to sinus rhythm as a primary outcome, and recurrence of SVT and vital signs as secondary outcomes. Trial authors reported these outcomes in the published article.

Other potential sources of bias

Inclusion and exclusion criteria

All trials described inclusion criteria, although most studies stated that a diagnosis of SVT was the main inclusion criterion without defining SVT by rate or QRS width, and provided no time limit on duration of symptoms. All but one study described exclusion criteria well (Cabrera-Sole 1989).

Publication bias

A funnel plot was not appropriate for assessment of publication bias, as this review includes fewer than 10 studies (Sterne 2011).

Conflicts of interest and funding

Only one study included a declaration of interests and reported its source of financial support (Lim 2009). Trial authors reported the absence of any conflicts of interests and receipt of funding from the Department of Clinical Research of Singapore General Hospital for costs of adenosine and diltiazem.

Effects of interventions

See: **Summary of findings for the main comparison** Adenosine compared with calcium channel antagonists for supraventricular tachycardia

Odds of reversion

All seven studies reported odds of reversion or 'efficacy' of adenosine versus CCA as an outcome measure, noting no difference in the odds of reversion to sinus rhythm among participants treated with adenosine or CCA (Analysis 1.1: 89.7% vs 92.9%; odds ratio (OR) 1.51, 95% confidence interval (CI) 0.85 to 2.68; participants = 622; studies = 7; I^2 = 36%). This result is based on evidence of moderate quality (Summary of findings for the main comparison).

Low heterogeneity between trials can be explained by differences in doses of adenosine and verapamil given. All but one study used sequentially increasing doses of each trial drug until reversion occurred or the predetermined maximum dose was reached, whichever occurred first (Cabrera-Sole 1989). Six trials reported odds of reversion as overall cumulative reversion for participants who received one or more doses of each drug. Trialists in one study used a fixed dose of each drug with no escalation of drug dosage in the absence of reversion (Cabrera-Sole 1989).

Major adverse events

Three trials reported outcomes of hypotension, noting only one episode of hypotension with CCA and none with adenosine (Analysis 1.5: 0.66% vs 0%; OR 3.09, 95% CI 0.12 to 76.71; participants = 306; studies = 3; I^2 = 0%) (Cabrera-Sole 1989; Ferreira 1996; Lim 2009). This result is not precise, and the confidence interval is wide. These results are based on evidence of low quality (Summary of findings for the main comparison).

Two of the three trials reporting hypotension specifically excluded patients with systolic blood pressure (BP) < 90 mmHg at enrolment. A hypotensive episode in one trial occurred at infusion of 7.5 mg of verapamil and did not require specific treatment (Lim 2009).

Only one study specifically reported absence of major bradycardia in either group (Ferreira 1996). No studies reported acute heart failure.

The only paediatric study reported that two participants experienced cardiac arrest after receiving treatment with verapamil (Greco 1982). One was an infant with cyanotic heart disease and electrolyte disturbances, the other was an infant already receiving treatment with a beta-blocker for Wolff-Parkinson-White syndrome. Both children were successfully resuscitated.

Time to reversion

Average time to reversion was reported in four studies (Cheng 2003; Ferreira 1996; Lim 2009; Vranic 2006). Each study showed a statistically significantly shorter time to reversion with adenosine than with verapamil. Average time to reversion in all studies combined was 44 seconds for adenosine and 394 seconds for CCAs. Very high heterogeneity between studies made pooling of results inappropriate. This heterogeneity may be due to differences in timing and dosing protocols between trials. Cheng 2003 reported 'average time after dose'; trialists did not report how time to reversion was estimated in two trials (Lim 2009; Vranic 2006).

Relapse rate

Four studies reported rate of relapse to SVT following reversion to sinus rhythm (Ferreira 1996; Gil Madre 1995; Lim 2009; Vranic 2006). Results show no differences in relapse rates between adenosine and CCAs (Analysis 1.3: 3.3% vs 1.14%; OR 0.38, 95% CI 0.09 to

1.69; participants = 358; studies = 4; I^2 = 0%). Two studies reported the period of observation following drug administration as 2 hours and 24 hours, respectively (Lim 2009; Vranic 2006). Ferreira 1996 reported relapse at 10 minutes for one participant given adenosine but did not mention time to relapse for the other participant given verapamil.

Length of stay in hospital

None of the included studies reported this outcome.

Minor adverse events

Studies reported numbers of specific adverse events rather than numbers of participants experiencing minor adverse events. Reported minor adverse events included chest tightness, nausea, shortness of breath, headache, and flushing. As patients might experience several different minor adverse events, double counting and exaggeration of estimated effects may occur. Therefore, we have not provided a total pooled estimate of minor adverse event subgroups.

Three trials reported that chest tightness occurred more frequently among participants treated with adenosine compared with verapamil (Analysis 1.4.1: 11.7% vs 0%; OR 0.09, 95% CI 0.02 to 0.50; participants = 222; studies = 3; I^2 = 0%) (Cheng 2003; Ferreira 1996; Gil Madre 1995).

Two trials reported shortness of breath, noting no differences between adenosine and CCAs (Analysis 1.4.2: 6.9% vs 1.2%; OR 0.23, 95% CI 0.04 to 1.37; participants = 171; studies = 2; I^2 = 0%) (Cheng 2003; Gil Madre 1995). These trials also reported nausea and headache, but high heterogeneity for these outcomes made pooling of results inappropriate.

Flushing as reported in trial was higher in the adenosine group (Analysis 1.4.3: 61.5% vs 0%; OR 0.01, 95% CI 0.00 to 0.24; participants = 50; studies = 1; I^2 = 0%) (Gil Madre 1995).

Greco 1982 also reported nausea, chest tightness, shortness of breath, and headache at higher rates among participants treated with adenosine. However, data included results from a non-randomised component of the study; therefore, we did not include these outcomes in the pooled analysis.

Two trials did not report any minor adverse events (Lim 2009; Vranic 2006).

Patient satisfaction

None of the included studies reported this outcome.

Subgroup analysis

We found insufficient data to carry out intended subgroup analyses.

Sensitivity analysis

All included studies had one or more component at high risk of bias; therefore, a sensitivity analysis for studies with low risk of bias was not possible.

DISCUSSION

Summary of main results

Adenosine and CCA efficiency

Our review aimed to examine the relative efficacy and safety of adenosine and calcium channel antagonists (CCAs) for patients presenting with supraventricular tachycardia (SVT). We included seven trials with 622 participants.

We used three outcomes to compare efficiency of these agents: odds of reversion, time to reversion, and relapse rates. Reversion and relapse rates were similar with adenosine and CCAs. We could not reliably examine time to reversion in a pooled analysis owing to severe heterogeneity. Time to reversion was on average less than a minute with adenosine and longer than six minutes with CCAs. The difference between these two treatments is probably of little clinical significance for patients who are haemodynamically stable.

Adverse effects

Investigators reported only one episode of hypotension among patients treated with verapamil and none in those treated with adenosine. Two cardiac arrests occurred in a paediatric study published in the 1980s, in clinical circumstances for which current practice guidelines would not recommend verapamil without expert consultation (ACLS 2015).

Minor adverse events occurred more frequently with adenosine and affected approximately one in ten patients. No studies specifically defined minor adverse events. Study authors relied on post hoc reporting; therefore, it is possible that the actual rate was higher than was reflected in the data. From a medical perspective, short-lived symptoms such as chest pain may be perceived as minor; however, no studies explored patients' perception of the relative severity of these events. No study commented on the sense of impending death or doom associated with adenosine treatment.

Patient-centred outcomes

The two outcomes for which we could find no data (i.e. patient satisfaction and length of hospital stay) may be helpful in the clinical decision as to which treatment should be used. From the patient's perspective, the risk of brief but unpleasant side effects, such as feeling close to death, may be unacceptable.

Overall completeness and applicability of evidence

The main gap in current knowledge involves patient preference. None of the included studies reported results on patient experiences.

Quality of the evidence

The GRADE approach shows that the quality of the evidence is moderate for the odds of reversion outcome (i.e. the result is likely to be close to the true effect but can be substantially different). The quality of evidence is low for the outcome of rate of major adverse events, but this result should be viewed with caution (Summary of findings for the main comparison). Reasons for downgrading the quality of evidence for adverse events were the presence of high risk of bias in the blinding domain for all included studies and imprecision of results with wide confidence intervals. As studies objectively assessed reversion to sinus rhythm using electrocardiograms (ECGs), lack of blinding of participants

or outcome assessors is not expected to have an impact on this endpoint.

Authors of all seven included studies stated that these were randomised trials; however, randomisation was poorly or incompletely reported. Only two studies specified how randomisation was undertaken (Greco 1982; Lim 2009). One study described allocation concealment (Lim 2009). None of the included studies were blinded. Most included trials used a cross-over design; however we have provided only pre-cross-over data in this review.

Potential biases in the review process

We performed a comprehensive literature search to find all relevant trials for inclusion in this review. Two review authors independently performed the literature search, selected studies, extracted data, and assessed risk of bias to minimise review bias. We contacted study authors to request further information when needed.

We conducted the review according to the previously published protocol. However, in some ways, we deviated from the protocol during the review process. We have documented deviations under Differences between protocol and review.

Agreements and disagreements with other studies or reviews

Delaney 2011 is a systematic review and meta-analysis of adenosine versus verapamil for treatment of stable SVT. This review included eight studies (Cabrera-Sole 1989; Cheng 2003; DiMarco 1990; Ferreira 1996; Gil Madre 1995; Hood 1992; Kulakowski 1998; Lim 2009). Review authors concluded that both adenosine and verapamil are effective and safe and included studies with induced SVT that we excluded from our review.

AUTHORS' CONCLUSIONS

Implications for practice

For people with SVT

We found no evidence of differences in effects of adenosine and calcium channel antagonists (CCAs) for treatment of supraventricular tachycardia (SVT). Our results are based on evidence of moderate quality. We found that adenosine is associated with more frequent minor adverse events such as chest pain.

For clinicians

Adenosine is the safer option in clinical situations for which verapamil is clearly contraindicated, as when people who have hypotension and poor left ventricular function are already taking beta-blockers, when individuals have other tachyarrhythmias such as broad complex tachycardia, or when a rapid effect is essential (as in very unstable or highly symptomatic patients). Verapamil is suggested for patients with asthma, as well as for stable patients in whom an extra 5 minutes is not likely to result in a worse clinical outcome, patients treated with adenosine in the past who experienced uncomfortable side effects that they would rather avoid if possible, patients who relapsed to SVT shortly after receiving adenosine because of frequent ectopics, and patients with frequent atrial or ventricular ectopics that could trigger a new episode of arrhythmia.

For funders and policy makers

Although current guidelines recommend adenosine as the first treatment choice, we could not confirm its superiority versus CCAs (Blomstrom-Lundqvist 2003; Page 2016; Resuscitation Council (UK) 2015). Therefore, future updated versions of these guidelines might consider the evidence presented in this review.

Implications for research

The main gap in our current knowledge involves which treatment patients prefer. Studies comparing patient experiences and adverse events are needed to fully answer whether one treatment is preferable in the management of SVT.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cabrera-Sole 1989

Methods	RCT
Participants	Age not stated, presumed adult Gp 1: 44 participants Gp 2: 43 participants Inclusion criteria: SVT Exclusion criteria: not stated
Interventions	Gp 1: ATP 20 mg bolus Gp 2: verapamil 10 mg bolus
Outcomes	Reversion rate Minor A/E
Notes	Country: Spain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation performed, but method not specified
Allocation concealment (selection bias)	Unclear risk	Information insufficient to determine whether allocation concealment was adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment was not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No attempt at blinding intervention was made.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up, withdrawals, dropouts, or protocol deviations were reported.
Selective reporting (reporting bias)	Unclear risk	No study protocol was available for comparison of intended study outcomes vs reported outcomes.
Other bias	Unclear risk	No mention of funding and no mention of possible conflicts of interest

Cheng 2003

Methods	RCT
Participants	Adults 18 to 75 years Gp 1: 60 participants (29 M) Gp 2: 62 participants (25 M) Inclusion criteria: paroxysmal SVT Exclusion criteria: heart block; asthma; emphysema; tea/coffee; taking beta-blocker, Ca antagonist, or other antihypertensive or antiarrhythmics; pregnancy or breastfeeding

Cheng 2003 *(Continued)*

Interventions	Gp 1: Adenosine 3 mg, then 6 mg, then 9 mg every 1 to 2 minutes if no response to previous dose. Mean dose 9.63 mg Gp 2: Verapamil 5 mg over 5 minutes, repeated if no reversion by 15 minutes. Mean dose 7.15 mg
Outcomes	Reversion rate Time to reversion Minor A/E
Notes	Country: China

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation mentioned, but method not specified
Allocation concealment (selection bias)	Unclear risk	Information insufficient to determine whether allocation concealment was adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment was not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No attempt at blinding intervention was made.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up, withdrawals, dropouts, or protocol deviations were reported.
Selective reporting (reporting bias)	Unclear risk	No study protocol was available for comparison of intended study outcomes vs reported outcomes.
Other bias	Unclear risk	No mention of funding and no mention of possible conflicts of interest

Ferreira 1996

Methods	RCT with cross-over design
Participants	Adults Gp 1: 25 (8 M) Gp 2: 25 (9 M) Inclusion criteria: paroxysmal SVT presenting to ED Exclusion criteria: SBP < 90, low output state, CCF, UAP, recent MI, taking dipyridamole or methylxanthine
Interventions	Gp 1: ATP 10 mg, then 20 mg bolus if needed. Mean dose 10.8 mg Gp 2: Verapamil infused at 5 mg/min up to 15 mg if needed. Mean dose 9.38 mg
Outcomes	Reversion rate Time to reversion Recurrence rate Minor A/E

Ferreira 1996 *(Continued)*

	Major A/E
Notes	Country: Brazil

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation mentioned, but method not specified
Allocation concealment (selection bias)	Unclear risk	Information insufficient to determine whether allocation concealment was adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment was not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No attempt at blinding intervention was made.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up, withdrawals, dropouts, or protocol deviations were reported.
Selective reporting (reporting bias)	Unclear risk	No study protocol was available for comparison of intended study outcomes vs reported outcomes.
Other bias	Unclear risk	No mention of funding and no mention of possible conflicts of interest

Gil Madre 1995

Methods	RCT with cross-over design
Participants	Adults (25 M,25 F) Gp 1: 26 participants Gp 2: 24 participants Inclusion criteria: SVT without haemodynamic instability, unresponsive to vagal manoeuvres Exclusion criteria: SBP < 80, current treatment with beta-blockers or Ca antagonists, known ventricular dysfunction, asthma, recent treatment with dipyridamole
Interventions	Gp 1: ATP 5 mg, then 10 mg, then 20 mg every 1 minute if previous dose not effective Gp 2: 5 mg over 3 minutes, repeated after 10 minutes if no response to first dose
Outcomes	Reversion rate Relapse rate Minor A/E
Notes	Country: Spain

Risk of bias

Bias	Authors' judgement	Support for judgement

Gil Madre 1995 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomisation mentioned, but method not specified
Allocation concealment (selection bias)	Unclear risk	Information insufficient to determine whether allocation concealment was adequate
Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment was not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No attempt at blinding intervention was made.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up, withdrawals, dropouts, or protocol deviations were reported.
Selective reporting (reporting bias)	Unclear risk	No study protocol was available for comparison of intended study outcomes vs reported outcomes.
Other bias	Unclear risk	No mention of funding and no mention of possible conflicts of interest

Greco 1982

Methods	RCT with cross-over design
Participants	Children < 13 years Gp 1: 20 participants Gp 2: 23 participants Inclusion criteria: presentation with paroxysmal SVT Exclusion criteria: shock or response to vagal manoeuvre
Interventions	Gp 1: ATP titrated to effect, mean dose 7.46 mg Gp 2: verapamil titrated to effect, mean dose 2.09 mg
Outcomes	Reversion rate Minor A/E
Notes	Two-part study; only participants in second part included, as no randomisation in first part Country: Italy

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Information insufficient to determine whether allocation concealment was adequate

Greco 1982 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Treatment was not blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	No attempt at blinding intervention was made.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up, withdrawals, dropouts, or protocol deviations were reported.
Selective reporting (reporting bias)	Unclear risk	No study protocol was available for comparison of intended study outcomes vs reported outcomes.
Other bias	Unclear risk	No mention of funding and no mention of possible conflicts of interest

Lim 2009

Methods	RCT with cross-over design
Participants	233 participants with spontaneous regular narrow complex tachycardia and failed Valsalva manoeuvres Gp 1: 104 participants on adenosine, mean age 50.6 ± 17.0, 42% males Gp 1: 102 participants on verapamil (57 people) and diltiazem (59 people). Mean age 48.9 ± 18.3, 40% males 27 excluded from analysis after enrolment, as they had an arrhythmia other than SVT Inclusion criteria: at least 10 years of age with regular narrow complex tachycardia and an electrocardiographic (ECG) diagnosis of SVT, not converted by vagal manoeuvres (Valsalva manoeuvre or carotid sinus massage or both) Exclusion criteria: signs of impaired cerebral perfusion (e.g. altered mental state) or acute pulmonary oedema
Interventions	Gp 1: adenosine, initially a 6-mg bolus, then a 12-mg bolus after 2 minutes, if needed Gp 2: verapamil and diltiazem Verapamil: slow intravenous infusion at a rate of 1 mg per minute, up to a maximum dose of 20 mg Diltiazem: slow intravenous infusion at a rate of 2.5 mg per minute, up to a maximum dose of 50 mg Refractory cases were crossed-over if initial intervention was not successful after repeated admissions. These cases were counted as failures of the intervention and were not included in the final analysis.
Outcomes	Reversion rate Relapse rate: recurrences during 2-hour observation period Major adverse event: hypotension
Notes	ED of the Singapore General Hospital Country: Singapore

Lim 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by a nurse who drew a serialised sealed envelope.
Allocation concealment (selection bias)	Low risk	Participants were randomised with the use of sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Interventions were given by different methods, and no attempt at blinding intervention was made.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Twenty-seven participants were excluded from analysis, as they were found not to have SVT after enrolment. Therefore, 15% of participants were not analysed in the groups to which they were randomised. However, as participants were randomised, excluded patients were closely distributed across intervention groups and had similar reasons for exclusion.
Selective reporting (reporting bias)	Low risk	The main outcomes reported are the same as those planned at a prospective trial registration.
Other bias	Low risk	Study authors declared no conflicts of interest. The Department of Clinical Research, Singapore General Hospital, funded adenosine and diltiazem.

Vranic 2006

Methods	RCT
Participants	Adults with spontaneous SVT or WPW 64 consecutive patients with diagnosis of acute SVT or WPW syndrome Males 48.4% Mean age of men was 47 ± 12 years, and women 48 ± 12 years Inclusion criteria: older than 18 years of age with abrupt onset of SVT lasting 20 to 30 minutes Exclusion criteria: presence of atrial flutter, asthma or chronic obstructive pulmonary disease, long-term use of dipyridamole or theophylline derivatives, pregnant or breastfeeding women, any heart disease apart from coronary artery disease (different forms of stenotic lesions of major arteries or veins), heart failure or pulmonary heart disease, history of bleeding diathesis, stroke, hypertension over 200/110 mmHg, severe diseases of liver or renal function (anamnestic data), confirmed malignancies, severe genetic diseases, severe anaemia, alcohol or narcotic addiction, psychiatric disorders, AV block of second or third degree, sick sinus syndrome
Interventions	Gp 1: adenosine IV bolus of 6 mg, then 12 mg if needed

Vranic 2006 *(Continued)*

	Gp 2: verapamil or IV 5 mg up to maximum dose of 10 mg if needed
Outcomes	Cardioversion into sinus rhythm Duration to sinus rhythm conversion Relapse Biomarkers outcomes
Notes	Intensive care unit and emergency centre at Clinical Center of Serbia Country: Serbia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation and randomisation method not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Interventions given by different methods and no attempt at blinding intervention made
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Interventions were applied and outcomes were assessed within the department. No losses to follow-up, withdrawals, or dropouts were reported.
Selective reporting (reporting bias)	Unclear risk	No study protocol was available for comparison of intended study outcomes vs reported outcomes.
Other bias	Unclear risk	No mention of funding and no mention of possible conflicts of interest

A/E: adverse events.
ATP: adenosine triphosphate.
AV: atrioventricular.
CCF: congestive cardiac failure.
ECG: electrocardiogram.
ED: emergency department.
MI: myocardial infarction.
RCT: randomised controlled trial.
SBP: systolic blood pressure.
SVT: supraventricular tachycardia.
UAP: unstable angina pectoris.
WPW: Wolff-Parkinson-White.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Athar 2013	Not an RCT, as allocation to treatment was changed according to previous patient experience with adenosine/verapamil. In addition, significant differences in baseline characteristics suggest that no appropriate randomisation method was used. Study authors have not yet replied to our request for further data/information.
Ballo 2004	Retrospective chart review and no relevant outcomes measured
Belhassen 1984	Review article, not a trial
Conti 1995	Editorial only
DiMarco 1990	Included participants with induced SVT
Garratt 1989	Not a randomised trial. Participants with induced SVT were given adenosine, then were re-induced and given verapamil.
Gill 2014	Not a randomised trial
Hood 1992	Included participants with induced SVT
Kulakowski 1998	Included participants with induced SVT
Rankin 1991	Review article, not a trial
Riaz 2012	Significant differences in baseline characteristics suggest that no appropriate randomisation method was used. Study authors have not yet replied to our request for further data/information.
Sellers 1987	Retrospective chart review
Sethi 1994	Not a randomised trial. Participants with induced SVT were given adenosine, then were re-induced and given verapamil.
Shaker 2015	Comparison of intravenous adenosine vs intravenous adenosine with oral verapamil
Trappe 1997	Comparison of adenosine vs ajmaline (class 1A antiarrhythmic). No calcium antagonist arm included
Turkoglu 1996	Not a randomised trial
Turkoglu 2009	Only participants with induced SVT were included.

RCT: randomised controlled trial.
SVT: supraventricular tachycardia.

DATA AND ANALYSES

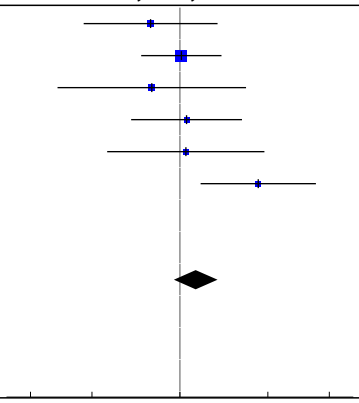
Comparison 1. Adenosine vs CCA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Odds of reversion	7	622	Odds Ratio (M-H, Fixed, 95% CI)	1.51 [0.85, 2.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Time to reversion (seconds)	4		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Relapse to SVT post reversion	4	358	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.09, 1.69]
4 Minor adverse events	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Chest tightness	3	222	Odds Ratio (M-H, Fixed, 95% CI)	0.09 [0.02, 0.50]
4.2 Shortness of breath	2	171	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.04, 1.37]
4.3 Flushing	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.01 [0.00, 0.24]
5 Hypotension	3	306	Odds Ratio (M-H, Fixed, 95% CI)	3.09 [0.12, 76.71]

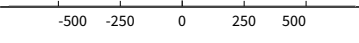
Analysis 1.1. Comparison 1 Adenosine vs CCA, Outcome 1 Odds of reversion.

Study or subgroup	CCA n/N	Adenosine n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Cabrera-Sole 1989	39/43	42/44		19.92%	0.46[0.08,2.68]
Cheng 2003	54/62	52/60		35.18%	1.04[0.36,2.97]
Ferreira 1996	23/25	24/25		9.91%	0.48[0.04,5.65]
Gil Madre 1995	20/24	21/26		17.33%	1.19[0.28,5.08]
Greco 1982	21/23	18/20		8.64%	1.17[0.15,9.14]
Lim 2009	100/102	90/104		9.02%	7.78[1.72,35.16]
Vranic 2006	31/31	33/33			Not estimable
Total (95% CI)	**310**	**312**		**100%**	**1.51[0.85,2.68]**
Total events: 288 (CCA), 280 (Adenosine)					
Heterogeneity: Tau^2=0; Chi^2=7.76, df=5(P=0.17); I^2=35.59%					
Test for overall effect: Z=1.42(P=0.16)					



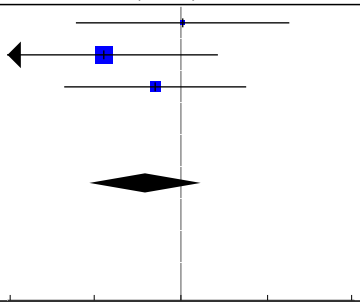
Analysis 1.2. Comparison 1 Adenosine vs CCA, Outcome 2 Time to reversion (seconds).

Study or subgroup	CCA N	CCA Mean(SD)	Adenosine N	Adenosine Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Cheng 2003	62	414.4 (191.2)	60	34.2 (19.5)		380.2[332.35,428.05]
Ferreira 1996	25	248 (152.5)	25	29.6 (11.6)		218.4[158.45,278.35]
Lim 2009	102	397.8 (0)	104	88.8 (0)		Not estimable
Vranic 2006	31	514 (229.2)	33	21.5 (2.6)		492.5[411.81,573.19]



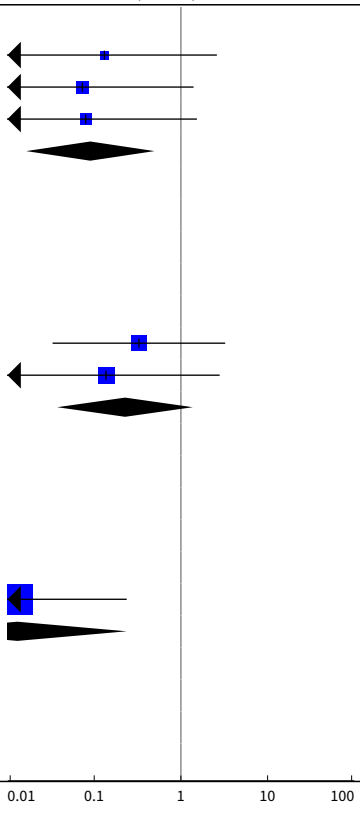
Analysis 1.3. Comparison 1 Adenosine vs CCA, Outcome 3 Relapse to SVT post reversion.

Study or subgroup	CCA n/N	Adenosine n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Ferreira 1996	1/23	1/24		15.02%	1.05[0.06,17.76]
Gil Madre 1995	0/20	3/21		53.53%	0.13[0.01,2.67]
Lim 2009	1/102	2/104		31.46%	0.5[0.05,5.66]
Vranic 2006	0/31	0/33			Not estimable
Total (95% CI)	**176**	**182**		**100%**	**0.38[0.09,1.69]**
Total events: 2 (CCA), 6 (Adenosine)					
Heterogeneity: Tau^2=0; Chi^2=1.03, df=2(P=0.6); I^2=0%					
Test for overall effect: Z=1.27(P=0.21)					



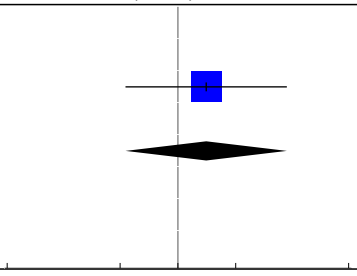
Analysis 1.4. Comparison 1 Adenosine vs CCA, Outcome 4 Minor adverse events.

Study or subgroup	CCA n/N	Adenosine n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 Chest tightness					
Cheng 2003	0/62	3/60		25.01%	0.13[0.01,2.6]
Ferreira 1996	0/25	5/25		38.24%	0.07[0,1.4]
Gil Madre 1995	0/24	5/26		36.74%	0.08[0,1.53]
Subtotal (95% CI)	**111**	**111**		**100%**	**0.09[0.02,0.5]**
Total events: 0 (CCA), 13 (Adenosine)					
Heterogeneity: Tau^2=0; Chi^2=0.09, df=2(P=0.96); I^2=0%					
Test for overall effect: Z=2.76(P=0.01)					
1.4.2 Shortness of breath					
Cheng 2003	1/60	3/61		47.01%	0.33[0.03,3.24]
Gil Madre 1995	0/24	3/26		52.99%	0.14[0.01,2.8]
Subtotal (95% CI)	**84**	**87**		**100%**	**0.23[0.04,1.37]**
Total events: 1 (CCA), 6 (Adenosine)					
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.65); I^2=0%					
Test for overall effect: Z=1.62(P=0.11)					
1.4.3 Flushing					
Gil Madre 1995	0/24	16/26		100%	0.01[0,0.24]
Subtotal (95% CI)	**24**	**26**		**100%**	**0.01[0,0.24]**
Total events: 0 (CCA), 16 (Adenosine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.93(P=0)					
Test for subgroup differences: Chi^2=2.7, df=1 (P=0.26), I^2=25.96%					



Analysis 1.5. Comparison 1 Adenosine vs CCA, Outcome 5 Hypotension.

Study or subgroup	CCA n/N	Adenosine n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Cabrera-Sole 1989	0/25	0/25			Not estimable
Ferreira 1996	0/25	0/25			Not estimable
Lim 2009	1/102	0/104		100%	3.09[0.12,76.71]
Total (95% CI)	**152**	**154**		**100%**	**3.09[0.12,76.71]**
Total events: 1 (CCA), 0 (Adenosine)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					



APPENDICES

Appendix 1. Search strategy 2006

CENTRAL on the Cochrane Library
#1 ADENOSINE
#2 adenosin*
#3 (#1 or #2)
#4 TACHYCARDIA SUPRAVENTRICULAR
#5 (supraventricular next arrhythmia*)
#6 tachycardia*
#7 tachyarrhythmi*
#8 (idioventricular next rhythm*)
#9 supraventric*
#10 svt
#11 psvt
#12 (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11)
#13 (#3 and #12)

Ovid MEDLINE search strategy
1 exp Adenosine/
2 adenosin$.tw.
3 1 or 2
4 exp Tachycardia, Supraventricular/
5 supraventricular tachycardia$.tw.
6 supraventricular arrhythmia$.tw.
7 supraventricular tachyarrhythmi$.tw.
8 sinus tachycardia$.tw.
9 svt.tw.
10 psvt.tw.
11 or/4-10
12 3 and 11

Ovid Embase
1 exp Adenosine/
2 adenosin$.tw.
3 1 or 2
4 Heart Supraventricular Arrhythmia/
5 Supraventricular Tachycardia/
6 Paroxysmal Supraventricular Tachycardia/
7 supraventricular tachycardia$.tw.
8 supraventricular arrhythmia$.tw.
9 supraventricular tachyarrhythmi$.tw.
10 sinus tachycardia$.tw.

11 svt.tw.
12 psvt.tw.
13 or/4-12
14 3 and 13

Appendix 2. Search strategy 2017

CENTRAL
#1 MeSH descriptor Adenosine explode all trees
#2 adenosin*
#3 (#1 OR #2)
#4 MeSH descriptor Tachycardia, Supraventricular explode all trees
#5 tachycardia*
#6 supraventricular next arrhythmia*
#7 tachyarrhythmi*
#8 idioventricular next rhythm*
#9 supraventric*
#10 svt
#11 psvt
#12 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
#13 (#3 AND #12)
#14 (#13), from 2010 to 2017

MEDLINE
1. exp Adenosine/
2. adenosin$.tw.
3. 1 or 2
4. exp Tachycardia, Supraventricular/
5. supraventricular tachycardia$.tw.
6. supraventricular arrhythmia$.tw.
7. supraventricular tachyarrhythmi$.tw.
8. sinus tachycardia$.tw.
9. svt.tw.
10. psvt.tw.
11. or/4-10
12. 3 and 11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. drug therapy.fs.
18. randomly.ab.
19. trial.ab.
20. groups.ab.
21. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. exp animals/ not humans.sh.
23. 21 not 22
24. 12 and 23
25. (2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).ed.
26. 24 and 25

Embase
1. adenosine/
2. adenosin$.tw.
3. 1 or 2
4. supraventricular tachycardia/
5. heart supraventricular arrhythmia/
6. paroxysmal supraventricular tachycardia/
7. supraventricular tachycardia$.tw.
8. supraventricular arrhythmia$.tw.
9. supraventricular tachyarrhythmi$.tw.
10. sinus tachycardia$.tw.

11. svt.tw.
12. psvt.tw.
13. or/4-12
14. 3 and 13
15. random$.tw.
16. factorial$.tw.
17. crossover$.tw.
18. cross over$.tw.
19. cross-over$.tw.
20. placebo$.tw.
21. (doubl$ adj blind$).tw.
22. (singl$ adj blind$).tw.
23. assign$.tw.
24. allocat$.tw.
25. volunteer$.tw.
26. crossover procedure/
27. double blind procedure/
28. randomized controlled trial/
29. single blind procedure/
30. 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
31. (animal/ or nonhuman/) not human/
32. 30 not 31
33. 14 and 32
34. (2010* or 2011* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017*).dd, em.
35. 34 and 35

Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/)

adenosine And supraventricular tachycardia

WHAT'S NEW

Date	Event	Description
17 July 2017	New citation required and conclusions have changed	Exclusion of induced SVT Included 2 new studies and added GRADEproGDT quality assessment.
5 July 2017	New search has been performed	New search

HISTORY

Protocol first published: Issue 1, 2005
Review first published: Issue 4, 2006

Date	Event	Description
4 July 2016	New search has been performed	Converted to new review format

CONTRIBUTIONS OF AUTHORS

S Alabed: selection of studies, data extraction and analysis, and review writing and editing.
A Sabouni: selection of studies and data extraction.
R Providencia: review editing and clinical expertise.
E Atallah: co-writing of review and data extraction.

M Qintar: review editing, selection of studies, data extraction, and clinical expertise.
T JA Chicho: review editing, data extraction, and clinical expertise.

DECLARATIONS OF INTEREST

SA: none known.

AS: none known.

RP: has received a research grant from Medtronic for a clinical epidemiology study on sudden cardiac death, and proctored and lectured for Medtronic and Pfizer, respectively, on topics related to atrial fibrillation. However, these topics are not directly related to treatment of supraventricular arrhythmias (which do not include atrial fibrillation) in A&E.

EA: none known.

MQ: none known.

T JA C: none known.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- National Institute for Health Research (NIHR), UK.

  S Alabed currently holds an NIHR Academic Clinical Fellowship (ACF)
- National Institutes of Health (NIH), USA.

  M Qintar is supported by The National Heart, Lung, and Blood Institute of the NIH under Award Number T32HL110837

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between original review in 2006 and update in 2017

The main changes in review methods compared with those used in the original review include the following.

1. Excluding studies of induced SVT: We excluded studies involving induced SVTs as they are not relevant to patients presenting acutely to the emergency department. Patients with inducible SVT may not necessarily be affected by SVT in their daily life. Induced SVTs can be terminated with pacing manoeuvres, whereas spontaneous SVTs treated in emergency rooms/A&E may last for hours and may require IV treatment for control.
2. Excluding quasi-randomised trials: Although the review protocol mentioned inclusion of quasi-RCTs, we decided to exclude trials with major violations in randomisation methods or treatment allocation. We also excluded studies reported to be randomised but showing no data on baseline differences between treatment interventions, and those in which major differences occurred at a rate of > 1 per 20 comparisons (which makes them unlikely to have occurred by chance) (Carlisle 2015; Carlisle 2017). When we had concerns about study methods, we excluded the study if study authors did not respond to our requests for clarification.
3. Using odds ratio instead of Peto odds ratio: The *Cochrane Handbook for Systematic Reviews of Interventions* discourages use of the Peto odds ratio and recommends use of the odds ratio instead (Higgins 2011).
4. Summary of findings tables: We prepared these in accordance with new requirements provided in the *Cochrane Handbook for Systematic Reviews of Interventions*.
5. Search for ongoing trials: The protocol and the original review did not plan or perform this.
6. Remove "in adults" from title: The protocol did not attempt to include adults only, and the original review included only one study in children (Greco 1982).

INDEX TERMS

Medical Subject Headings (MeSH)

Adenosine [adverse effects] [*therapeutic use]; Anti-Arrhythmia Agents [adverse effects] [*therapeutic use]; Calcium Channel Blockers [adverse effects] [*therapeutic use]; Emergency Service, Hospital [statistics & numerical data]; Hypotension [chemically induced]; Randomized Controlled Trials as Topic; Tachycardia, Supraventricular [*drug therapy]; Verapamil [adverse effects] [therapeutic use]

MeSH check words

Adult; Humans