Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation (Review)

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[Intervention Review]

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ABSTRACT

Background

Atrial fibrillation (AF) is the most frequent sustained arrhythmia. AF recurs frequently after restoration of normal sinus rhythm. Antiarrhythmic drugs have been widely used to prevent recurrence, but the effect of these drugs on mortality and other clinical outcomes is unclear.

Objectives

To determine, in patients who recovered sinus rhythm after AF, the effect of long-term treatment with antiarrhythmic drugs on death, stroke and embolism, adverse effects, pro-arrhythmia, and recurrence of AF.

Search methods

We updated the searches of CENTRAL on *The Cochrane Libary* (Issue 1 of 4, 2010), MEDLINE (1950 to February 2010) and EMBASE (1966 to February 2010). The reference lists of retrieved articles, recent reviews and meta-analyses were checked.

Selection criteria

Two independent reviewers selected randomised controlled trials comparing any antiarrhythmic with a control (no treatment, placebo or drugs for rate control) or with another antiarrhythmic, in adults who had AF and in whom sinus rhythm was restored. Post-operative AF was excluded.

Data collection and analysis

Two reviewers independently assessed quality and extracted data. Studies were pooled, if appropriate, using Peto odds ratio (OR). All results were calculated at one year of follow-up.

Main results

In this update, 11 new studies met inclusion criteria, making a total of 56 included studies, comprising 20,771 patients. Compared with controls, class IA drugs quinidine and disopyramide (OR 2.39, 95% confidence interval (95%CI) 1.03 to 5.59, number needed to harm (NNH) 109, 95%CI 34 to 4985) and sotalol (OR 2.47, 95%CI 1.2 to 5.05, NNH 166, 95%CI 61 to 1159) were associated with increased all-cause mortality. Other antiarrhythmics did not seem to modify mortality.

Several class IA (disopyramide, quinidine), IC (flecainide, propafenone) and III (amiodarone, dofetilide, dronedarone, sotalol) drugs significantly reduced recurrence of AF (OR 0.19 to 0.70, number needed to treat (NNT) 3 to 16). Beta-blockers (metoprolol) also reduced significantly AF recurrence (OR 0.62, 95% CI 0.44 to 0.88, NNT 9).

All analysed drugs increased withdrawals due to adverse affects and all but amiodarone, dronedarone and propafenone increased pro-arrhythmia. We could not analyse other outcomes because few original studies reported them.

Authors' conclusions

Several class IA, IC and III drugs, as well as class II (beta-blockers), are moderately effective in maintaining sinus rhythm after conversion of atrial fibrillation. However, they increase adverse events, including pro-arrhythmia, and some of them (disopyramide, quinidine and sotalol) may increase mortality. Possible benefits on clinically relevant outcomes (stroke, embolisms, heart failure) remain to be established.

PLAIN LANGUAGE SUMMARY

Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Atrial fibrillation is a disease where the heart rhythm is irregular (this is called arrhythmia) and too fast (this is called tachycardia, from the Greek "tachy" meaning fast). Atrial fibrillation may produce complications, either in the heart (heart failure, syncope) or in other organs (mainly causing embolisms, which is the formation of blood clots in the cavities of the heart that may then travel to other places, for example the brain).

Atrial fibrillation can be reverted, restoring normal heart rhythm, by using drugs or a controlled electrical shock. However, a major problem is that atrial fibrillation recurs frequently. A variety of drugs have been employed to avoid recurrences and keep normal heart rhythm. This systematic review looked at the effectiveness and safety of antiarrhythmic drugs used to prevent recurrences of atrial fibrillation.

We found 56 good quality studies testing various antiarrhythmic drugs, involving 20,771 patients. The cumulative data from these studies show that several drugs are effective at preventing recurrences of atrial fibrillation (quinidine, disopyramide, flecainide, propafenone, amiodarone, azimilide, dofetilide, dronedarone and sotalol), but all of them increased adverse effects. The data shows also that some of those drugs, one specific group called "class IA", which comprises quinidine and disopyramide, and sotalol, may cause a small increase in the number of deaths in treated patients. A limitation of the review was that the majority of the studies we found did not assess the complications most frequently seen with atrial fibrillation (embolisms and heart failure). Therefore, we can not know if treatment with antiarrhythmic drugs may have any effect reducing (or increasing) those complications.

It is unclear if the long-term benefits obtained with antiarrhythmic drugs outweigh their risks.

BACKGROUND

Atrial fibrillation is the most common sustained arrhythmia and its incidence increases substantially with age (Go 2001; Ruigomez 2002). Atrial fibrillation is associated with increased morbidity and mortality, due to stroke, other embolic complications, and heart failure (Benjamin 1998; Heeringa 2006; Krahn 1995; Stewart 2002). In developed countries, atrial fibrillation has grown progressively as a contributing cause of hospitalisation and death in the last few decades (MMWR 2003; Wattigney 2003).

In people who have atrial fibrillation, normal sinus rhythm is interrupted by periods of atrial fibrillation that may be either symptomatic or asymptomatic. Symptoms can be mild (e.g. palpitations, breathlessness or reduced effort capacity) or severe, causing syncope, heart failure or acute coronary syndrome. Many of the symptoms caused by atrial fibrillation are related to the degree of tachycardia and can be improved by either controlling heart rate (rate control strategy) or converting atrial fibrillation to normal sinus rhythm by electrical means or pharmacological (rhythm control strategy).

The length of periods in atrial fibrillation is highly variable within patients and between patients, and it is employed to classify this arrhythmia (ACC/AHA/ESC 2006; NICE 2006). If the arrhythmia terminates spontaneously atrial fibrillation is designated "paroxysmal", and may recur afterwards or not. When sustained beyond seven days, it is designated "persistent". Termination with pharmacological or electrical does not change the designation. When atrial fibrillation is first detected, and it is not known if it will resolve or persist, it is designated "recent onset" or simply "first detected". Finally, "permanent" atrial fibrillation refers to persistent atrial fibrillation in which cardioversion has failed or has not been attempted because it is considered that there is no more a possibility to restore sinus rhythm. An individual patient can show different classes of atrial fibrillation over time.

Many patients recover sinus rhythm spontaneously after an episode of recent onset atrial fibrillation, as many as 70% in some studies (Geleris 2001). Electrical and pharmacological cardioversion are very effective to restore sinus rhythm, even in long-standing persistent atrial fibrillation. However, a major problem is the recurrence of atrial fibrillation. The risk of recurrence of atrial fibrillation is dependent on age, duration of atrial fibrillation and the existence and severity of structural damage to the heart (Flaker 1995; Frick 2001). The overall rate of recurrence of atrial fibrillation without treatment is high: of patients who converted to sinus rhythm, only 20 to 30% will remain in sinus rhythm one year later (Gelder 1996; Golzari 1996).

Long-term antiarrhythmic therapy has been widely used to prevent the recurrence of atrial fibrillation. Antiarrhythmic drugs are usually grouped following the classification by Vaughan Williams (Vaughan Williams 1984) into four classes. Class I: drugs with direct membrane action (Na channel blockade), subdivided to IA, IB and IC, depending on specific effects on conduction and repolarisation; class II: sympatholytic drugs (i.e. beta-blockers); class III: drugs that prolong repolarisation; and class IV: calcium channel blockers. There is evidence that several class I and class III, and maybe class II antiarrhythmic drugs are more effective than placebo for maintaining sinus rhythm (Miller 2000; Nichol 2002). However, some questions remain.

It has been assumed that keeping patients in sinus rhythm would reduce the risks of embolism, stroke, heart failure or increased mortality that are associated with atrial fibrillation (Anter2009). However, this has not been proven and, unfortunately, many of the trials with antiarrhythmic drugs have focused only on maintenance of sinus rhythm and have not assessed other relevant outcomes (Connolly 2000). Overall, rhythm control strategy, using antiarrhythmics to maintain sinus rhythm, has not shown any clear benefits in clinical outcomes when compared in randomised controlled trials with a rate control strategy (e.g. mortality or stroke) (Cordina 2005; Denus 2005; Testa 2005).

Chronic treatment with antiarrhythmic drugs can be associated with severe adverse effects, including the potential induction of life-threatening arrhythmias. Adverse effects could compromise any benefits of maintaining sinus rhythm or even outweigh them, leading to worse outcomes overall. In fact, the results of some trials show a significantly increased mortality associated with the long term use of some antiarrhythmics, as in the case of quinidine (Coplen 1990; SPAF 1992) or flecainide (CAST 1991). Finally, it is not known if all antiarrhythmic drugs are equivalent in effectiveness and safety.

Many trials have studied long-term treatment with diverse antiarrhythmic drugs for maintaining sinus rhythm, sometimes compared to placebo, sometimes compared to other antiarrhythmic drugs. Attempts to summarise this evidence in systematic reviews or meta-analyses have been incomplete: they were combined in a narrative review (Golzari 1996), trials using different antiarrhythmics and with very dissimilar length of treatment were pooled together (Nichol 2002), and outcomes other than sinus rhythm maintenance were not evaluated (Miller 2000) Consequently, we planned to conduct a more exhaustive systematic review of randomised controlled trials studying long-term use of antiarrhythmic drugs to maintain sinus rhythm, and aimed to determine their effect not only on the recurrence of atrial fibrillation, but also on other important clinical outcomes. After the first publication of this review in 2007 several new large randomised controlled trials have been published. They have been systematically searched, assessed and when found adequate, included in this update.

OBJECTIVES

To determine the effect of long-term treatment with antiarrhythmic drugs in patients who have recovered sinus rhythm after having atrial fibrillation, on death, stroke and embolism, drug adverse effects and recurrence of atrial fibrillation.

The primary aim was to assess the effects of any antiarrhythmic drug compared with no antiarrhythmic treatment, that is no treatment, placebo, or treatment for rate control. If several antiarrhythmic drugs appeared to be effective the secondary aim was to compare them.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials with concealed allocation of participants to intervention or placebo. Studies that were not randomised or where allocation to treatment was not concealed were excluded. Cross-over studies and studies where duration of follow up was less than six months were also excluded.

Types of participants

Adults (>16 years) who had atrial fibrillation of any type and duration and in whom sinus rhythm had been restored, spontaneously or by any therapeutic intervention.

Patients with atrial fibrillation following cardiac surgery were excluded, as well as patients with any condition causing an expectancy of life of less than 12 months.

Types of interventions

To be included, studies must have randomly allocated patients to an intervention and a control group. The intervention group must have received oral long-term treatment with any available antiarrhythmic drugs, at an appropriate dosing regime, aimed at preventing new episodes of atrial fibrillation and maintaining sinus rhythm.

The control group, for the primary objective of the review, could use placebo, drugs for rate control (digoxin, calcium channel blockers, beta-blockers) or no treatment. For the secondary objective of evaluating differences between antiarrhythmic drugs, the control group could be any of the other antiarrhythmic drugs having shown effectiveness compared to no antiarrhythmic treatment.

Both groups, intervention and control, had to be similar with regard to cardiac disease (frequency, type and severity) and type of atrial fibrillation (especially duration). Also, both groups must have been treated equally, apart from the experimental therapy, that is:

(1) Guidelines used to manage initiation, discontinuation, dose and surveillance of anticoagulation had to be the same in both intervention and control groups;

(2) Management and drug used for hypertension and heart failure had to be similar.

Types of outcome measures

Primary outcomes

(1) Mortality (total mortality and mortality due to cardiovascular causes).

(2) Embolic complications (stroke and peripheral embolism combined).

(3) Adverse effects (withdrawals caused by adverse events and pro-arrhythmia, including any of the following: sudden death, any new symptomatic arrhythmia (including symptomatic bradycardia), aggravation of existing arrhythmias (i.e. rapid atrial fibrillation) and new appearance on electrocardiogram of QRS or QT widening leading to stopping treatment (Friedman 1998)).

Secondary outcomes

(1) Use of anticoagulation (number of patients started on long-term treatment with anticoagulants at the end of follow up).

(2) Recurrence of atrial fibrillation (number of patients who had a recurrence of atrial fibrillation during follow up).

It was planned to analyse all outcomes at six, 12 and 24 months, when data were available. If a trial did not measure outcomes at these exact time points then the nearest measure point, if close enough, was used (e.g. at nine or 15 months instead of 12 months).

Search methods for identification of studies

Electronic searches

The searches from 2005 (Appendix 1) have been updated and were re-run on 17 February 2010 (Appendix 2). We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* (Issue 1 of 4, 2010), MEDLINE (1950 to February 2010) and EMBASE (1966 to February 2010).

Searching other resources

In addition, the reference lists of retrieved studies were checked, as well as the reference lists of recent guidelines, meta-analyses and general reviews on atrial fibrillation.

No language restrictions were applied.

Data collection and analysis

Selection of studies

The titles (and abstracts where available) were read by either of the reviewers and any publication that seemed to possibly meet the above criteria was retrieved. Two independent reviewers read the full text of the studies retrieved and selected the trials that met the above stated criteria for inclusion. A pre-defined form was developed and used for this task. The selected trials were compared

and any discrepancy resolved by discussion and consensus. The articles finally selected for the review were checked to avoid data published in duplicate. Records of the selection process were kept and a PRISMA flowchart was prepared (PRISMA 2009).

Data extraction and management

Two reviewers extracted data independently using a data collection form specifically developed for this task. When necessary, the authors of primary studies were contacted for additional information. The completed data forms were checked for agreement and differences resolved by discussion and consensus.

In addition to data relating to the outcomes of the review, we collected information on the following:

(1) Study methods and designs (randomisation, allocation concealment and blinding);

(2) Baseline characteristics of patients (age, gender, frequency and type of heart disease, echocardiographic measures, duration and type of atrial fibrillation - as defined in each study, knowing that definitions employed have not been always consistent);

(3) Details of treatments (method of cardioversion employed, time interval between conversion to sinus rhythm and initiation of intervention, antiarrhythmic drugs used and dose, treatment used in control group, concomitant treatments (beta-blockers, angiotensin converting enzyme inhibitors, antiplatelets and warfarin); and

(4) Follow-up duration, patients lost to follow up and withdrawals.

Assessment of risk of bias in included studies

Two reviewers independently assessed the methodological quality of the selected studies, attending to the adequacy of allocation concealment, which was ranked as A (adequate), B (unclear) or C (inadequate), following the Cochrane Handbook (Higgins 2005). Any differences of opinion were resolved by discussion and consensus.

Measures of treatment effect

Odds ratio, for all outcomes (all are dichotomous variables). If results for any outcome were significant and control group levels of outcomes were broadly similar, we calculated also the number needed to treat (NNT) or number needed to harm (NNH) to prevent or produce, respectively, one adverse outcome for the specified duration of treatment, using the pooled odds ratio and pooled rate from control groups.

Dealing with missing data

Data were analysed on the basis of intention-to-treat. By default, available case analysis was used (missing patients were considered not to experience an event). Nevertheless, worst-case scenario intention-to-treat-analysis (all missing patients considered as events) was also calculated for all outcomes to test if any potential difference might have arisen due to losses to follow up.

Assessment of heterogeneity

Heterogeneity was tested using the Mantel-Haenszel chi-squared test and the I-square statistic (Higgins 2011). If significant heterogeneity was found, we searched for an explanation based on the differences in clinical characteristics of the included studies. If the studies were found to be clinically very dissimilar they were not statistically combined.

Assessment of reporting biases

A funnel plot was used to test for the presence of publication bias, based on the data for the primary outcome of total mortality.

Data synthesis

Data were pooled using RevMan software (version 5.0.25). If no heterogeneity was found, Peto odds ratio was calculated for all outcomes, using a fixed-effect model. If heterogeneity between studies was observed, odds ratios was calculated using a random-effects model.

Data for all antiarrhythmic drugs were pooled and analysed individually (each specific drug) and also grouped by pharmacological class, following the classification of Vaughan-Williams (Vaughan Williams 1984).

Subgroup analysis and investigation of heterogeneity

Predefined subgroup analyses were:

(1) Paroxysmal atrial fibrillation and persistent atrial fibrillation;

(2) Patients with heart failure, opposed to patients who had never developed heart failure;

(3) Studies where warfarin was mandatory versus those where warfarin was discretionary; and

(4) Patients with a structurally normal heart ("lone" atrial fibrillation).

Sensitivity analysis

Sensitivity analysis were performed by selectively pooling:

(1) Studies having the best methodological quality; and

(2) Studies including the greatest number of patients (i.e. >200 patients).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

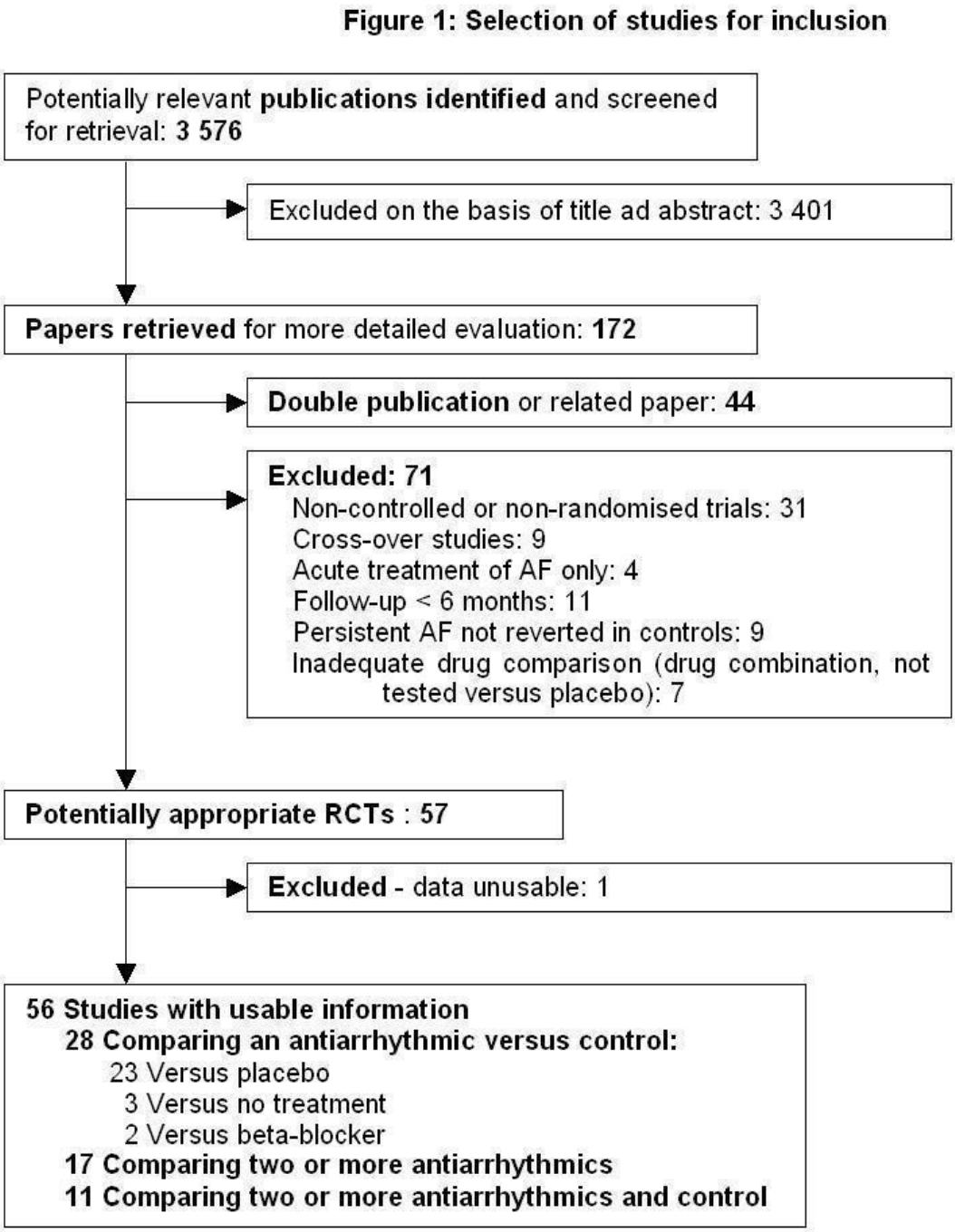
We found a total of 3 576 references, and assessed 172 articles in more detail. Articles in Chinese, English, French, Italian, German, Spanish and Swedish were retrieved, translated when needed, and assessed. Finally, 56 studies fulfilled inclusion criteria and had useable data. They comprised 20,771 patients in total.

Compared with the previous publication of this review in 2007, which searched until May 2005, 999 more references were read, 25 new articles were assessed in detail and 11 new randomised controlled trials were included (A-COMET-I 2006, A-COMET-II 2006, A-STAR 2006, ATHENA 2009, DAPHNE 2008, DYONISOS 2010, EMERALD 2000, Nergardh 2007, Niu 2006, PITAGORA 2008, SVA-4 2008). Studies classed in our previous version as awaiting classification (EMERALD 2000) and ongoing (A-COMET-I 2006, A-COMET-II 2006) were now included. The 11 new included trials studied several drugs (amiodarone, azimilide, dofetilide, dronedarone, metoprolol and sotalol) and added 8,212 more patients. Seven of the new studies compared one or two antiarrhythmic drugs with placebo, one compared sotalol with beta-blockers and 3 compared two different antiarrhythmics.

Agreement between reviewers was good, for both selecting studies and extracting data.

Figure 1 illustrates the selection of articles, following the PRISMA model. Details of each included study are shown in the Characteristics of included studies table, and the reasons for exclusion are shown in the Characteristics of excluded studies table.

Figure 1. Figure 1. PRISMA chart



Included studies

Patients

Entry criteria differed between studies in several aspects. In some trials atrial fibrillation was documented in the past but patients were in sinus rhythm at inclusion, while in other trials patients were in atrial fibrillation and needed to be converted to sinus rhythm (only those converted were included in the review). The duration of atrial fibrillation when persistent, or the time from the last documented episode of atrial fibrillation when paroxysmal, were highly variable (from 1 month to 1 year, or even no time limit in some studies). Some of the studies required atrial fibrillation to be symptomatic, others did not. A few studies (six in total) enrolled both atrial fibrillation or atrial flutter. When available, only data from patients with atrial fibrillation was used.

Regarding the type of atrial fibrillation, eight studies included exclusively paroxysmal or recent onset atrial fibrillation, 23 studies included only persistent atrial fibrillation, and the remaining 25 included both types. Overall, 42.4% of the pooled population had persistent or permanent atrial fibrillation. The proportion of patients having underlying heart disease varied widely, from 29% to 100%, with only one study selectively including patients without structural heart disease (FAPIS 1996). Mean left ventricle ejection fraction was greater than 50% in almost all trials, with four exceptions (DIAMOND 2001; Kalusche 1994; Nergardh 2007; Plewan 2001). The most frequent diseases were coronary disease (5% to 50% of patients), hypertension, and valvular abnormalities (less frequent in recent studies).

Interventions

Twenty eight trials (cumulating 13 404 patients) compared an antiarrhythmic with a control, 11 trials (4 458 patients) compared two different antiarrhythmics and a control, and 17 trials (2 904 patients) compared two or more antiarrhythmics with each other. The comparison used in the 39 trials with control groups was a placebo in 33 trials, beta-blockers in two (DAPHNE 2008; Plewan 2001), digoxin in one (Steinbeck 1988), and no treatment at all in three trials (Hillestad 1971; Sodermark 1975; Van Gelder 1989). Drugs included in this review, for which at least one well designed randomised controlled trial was found, were: (a) class IA: quinidine, disopyramide; (b) class IB: aprindine, bidisomide; (c) class IC: flecainide, propafenone; (d) class II (beta-blockers): metoprolol; (e) class III: amiodarone, azimilide, dofetilide, dronedarone and sotalol.

Outcomes

All studies had data about mortality, all but two (ASAP 2003; PITAGORA 2008) about atrial fibrillation recurrence rates, and the majority presented data for adverse effects, either withdrawals or pro-arrhythmia. All-cause mortality and cardiovascular mortality were virtually identical in all studies, so we reported only all-cause mortality. Other outcomes were, unfortunately, very infrequently reported: stroke was reported only in nine trials, heart failure in seven trials, and actual frequency of anticoagulation in none.

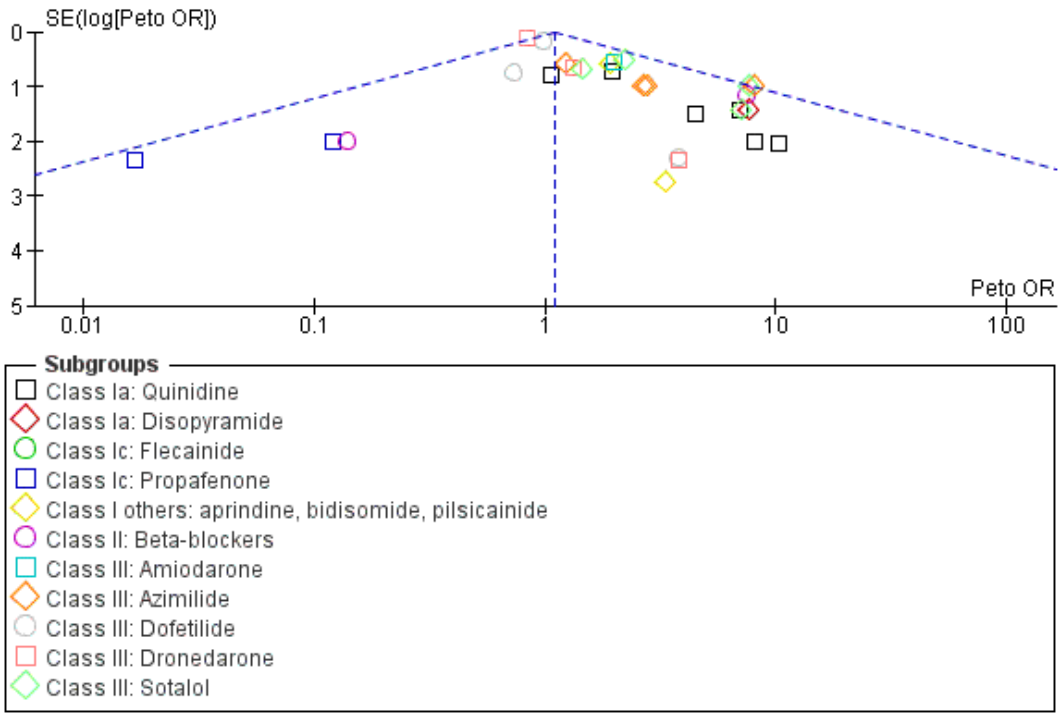
Follow up

The most frequent length of follow up was one year. It was shorter in 15 trials (six to nine months). Four trials followed patients for two years or more (AFFIRM Substudy 2003; Kochiadakis 2000; Kochiadakis 2004a; Kochiadakis 2004b). Therefore we decided to extract and pool all outcomes at one year of follow up. For studies with shorter duration of follow up, the last observation available was employed.

Risk of bias in included studies

The funnel plot (Figure 2) showed asymmetry, with less small studies in the left side (more small studies showing a trend to more deaths on active treatment). However, this is the contrary to what is expected when publication bias is present (usually, small studies with negative results are underreported) and we do not have a satisfactory explanation for the asymmetry observed in the funnel plot.

Figure 2. Funnel plot of comparison: All-cause mortality, by individual antiarrhythmics, compared vs control.



All included studies were randomised controlled trials. Quality of allocation concealment was adequate in 16 trials, in the remaining 40 it was unclear or the procedure not well reported. The majority of trials comparing an antiarrhythmic versus a control were blinded (out of 39 trials, 26 were double-blind and five single-blind, the remaining 8 being open-label). In contrast, most trials comparing two or more different antiarrhythmics were open-label (14 out of 17).

The percentage of patients lost to follow-up was reported in 42 out of the 56 included trials and was small (5% to 10%). However, virtually all studies followed patients until atrial fibrillation recurred or until treatment was stopped for any cause, and no longer. Data for some outcomes, like mortality, are therefore not extensive.

Conflict of interest could exists: almost all the studies included in the review were founded by the company manufacturing the antiarrhythmic drug tested.

Effects of interventions

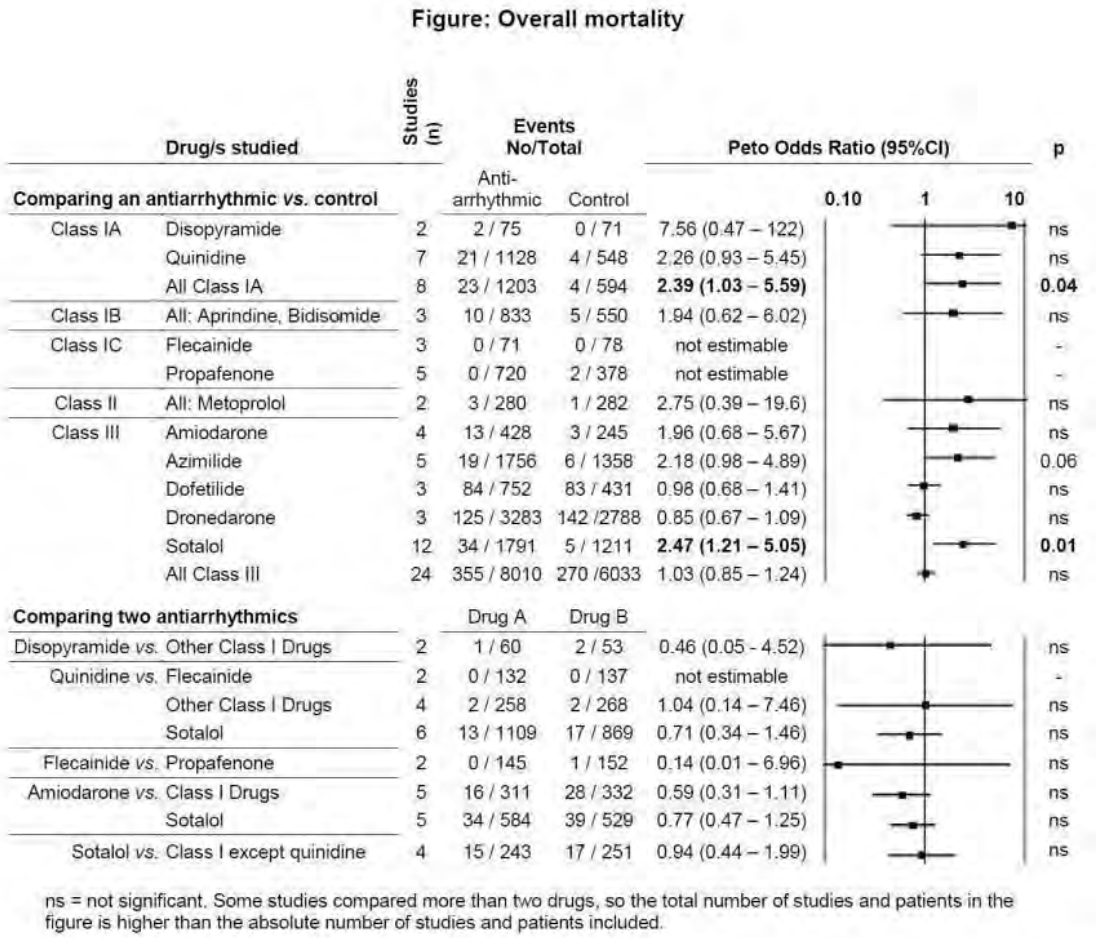
All outcomes are calculated at one year of follow-up.

Imputing missing patients as events (the worst-case intention-to-treat scenario) did not modify results in general, so the best-case intention-to-treat analysis (missing patients counted as being free of events) is reported as the default, and where differences exist details are given.

Mortality

Results for mortality are summarized in Analysis 1.1 and Figure 3. The all-cause mortality rate was low (0% to 5.1% at 1 year). The only exception to this general low mortality was the DIAMOND study (DIAMOND 2001). It recruited only patients with advanced heart failure and had a mortality of 31% at one year.

Figure 3. Overall mortality



Quinidine, compared with controls, showed a non-significant but clear trend to increase mortality (OR 2.26, 95% CI 0.93 to 5.45, P = 0.07). This trend became significant if missing patients were counted as deaths (OR 2.29 95% CI 1.05 to 5.01, P = 0.04), and when all drugs of class IA (quinidine and disopyramide) were combined (OR 2.39, 95% CI 1.03 to 5.59, P = 0.04) (Analysis 1.5). The corresponding NNH for combined class IA drugs was 109 patients treated for one year to have one excess death, with a wide 95% CI of 34 to 4895 patients.

However, sensitivity analysis of studies on quinidine and class IA drugs, selectively pooling trials with adequate allocation concealment or those including more than 200 patients, left only two studies (PAFAC 2004; SOPAT 2004) in which no difference in mortality compared with controls was apparent. These two trials employed a lower dose of quinidine (320 to 480 mg/day) than other studies (800 to 1800 mg/day), and combined quinidine with verapamil.

Sotalol also showed a significant increase in associated mortality compared with controls (OR 2.47, 95% CI 1.21 to 5.05, P = 0.01). This increase was confirmed In all sensitivity analysis, either counting missing patients as deaths (OR 2.14, 95% CI 1.40 to 3.25, P = 0.0004), pooling high-quality trials only (OR 2.78, 95% CI 1.00 to 7.69, P = 0.05) or pooling trials with more than 200 patients only (OR 1.97, 95% CI 1.03 to 3.75, P = 0.04) (Analysis 1.11 and Analysis 1.12). The corresponding NNH for sotalol was 166 patients treated for 1 year to have 1 excess death, the 95% CI being also wide: 61 to 1159 patients.

A strong but non-significant trend to increased mortality appeared also with azimilide compared with controls (OR 2.18, 95% CI 0.98, 4.89, P = 0.06). This trend persisted in all sensitivity analysis.

Very little data on mortality was found on class IC drugs. We

retrieved only three small randomised trials (146 patients total) on flecainide that fulfilled inclusion criteria, in which no death at all was reported in any treatment group. We found more studies fulfilling criteria (five, 998 patients) on propafenone but only two deaths in patients taking placebo and no death in patients taking propafenone were reported. As the data obtained on mortality on flecainide and propafenone seemed incomplete, we choose not to analyse this outcome for both drugs.

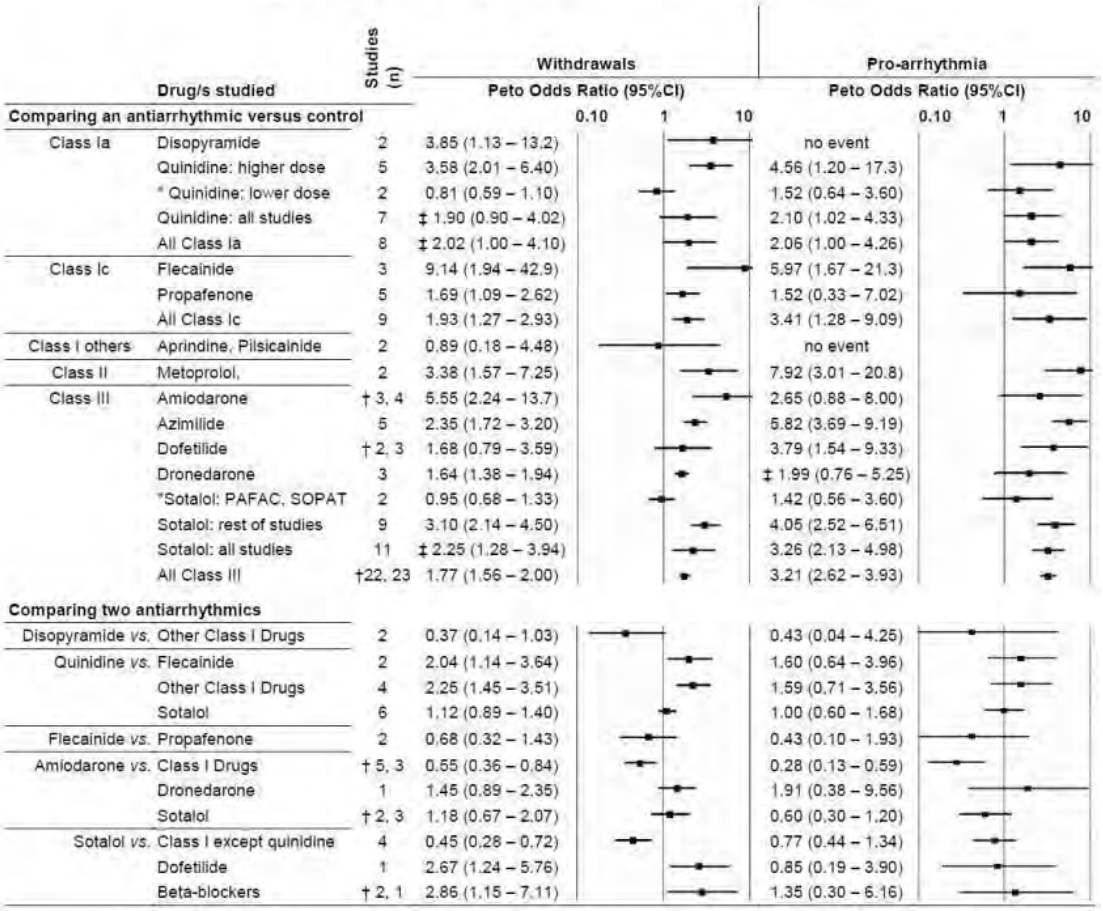
No other significant difference in mortality was apparent with respect to the remaining drugs analysed: beta-blockers, amiodarone, dofetilide and dronedarone. In direct comparisons between antiarrhythmics, no significant difference was found neither (Analysis 1.9). No heterogeneity between studies was detected in this outcome.

Adverse effects (withdrawals and pro-arrhythmia)

Results for adverse effects are summarized in Analysis 2.1, Analysis 3.1 and Figure 4. Compared to controls, withdrawals due to adverse effects were more frequent with all drugs, except aprindine, pilsicainide (both with results from one study only) and dofetilide (Analysis 2.1). Substantial heterogeneity between studies was detected for quinidine (I2 = 76%, P = 0.0003) and sotalol (I2 = 65%, P = 0.03). In both cases heterogeneity was due to the effect of PAFAC and SOPAT trials (PAFAC 2004; SOPAT 2004), in which neither quinidine nor sotalol showed significant differences in withdrawals compared with placebo. PAFAC and SOPAT trials employed lower doses of quinidine but usual doses of sotalol (320 mg/day). All the remaining studies of quinidine or sotalol did show a significant increase in withdrawals from treatment because of adverse effects.

Figure 4. Withdrawals due to adverse events and Pro-arrhythmia

Figure: Withdrawals due to adverse effects and Proarrhythmia.



* PAFAC and SOPAT trials in both cases, which showed heterogeneity compared with other studies on quinidine or on sotalol.

† When the number of studies pooled were different for the two outcomes, the number combined to evaluate withdrawals are given first, followed by those combined to evaluate pro-arrhythmia.

‡ Odds ratio calculated by random effects model, as test for heterogeneity between pooled studies was significant.

Some studies compared more than two drugs, so the total number of studies in the table is superior to the absolute number of studies and patients included.

All studied antiarrhythmics showed increased pro-arrhythmic effects (counting both bradyarrhythmias and tachyarrhythmias attributable to treatment), with the exceptions of amiodarone, dronedarone and propafenone (Analysis 3.1). Pooled events rates varied depending on the antiarrhythmic used, from 4% to 23% for withdrawals due to adverse effects and from 1% to 12% for pro-arrhythmia. The NNH, the mean number of patients needed to treat for one year to have one excess withdrawal due to adverse effects from treatment were nine with quinidine, 15 with sotalol, 22 with dronedarone and 26 with amiodarone or propafenone. The NNH for pro-arrhythmia ranged between 17 with flecainide and 156 with dofetilide, being 39 with sotalol and 85 with quinidine.

In direct comparisons between antiarrhythmics (Analysis 2.6 and Analysis 3.6), quinidine caused more withdrawals than the other class I drugs (OR 2.25, 95% CI 1.45 to 3.51, P = 0.0003) but not more pro-arrhythmia. Amiodarone produced significantly fewer withdrawals (OR 0.55, 95% CI 0.36 to 0.84, P = 0.006) and less pro-arrhythmic events (OR 0.28, 95% CI 0.13 to 0.59, P = 0.0007) than class I drugs combined. However, compared to placebo, amiodarone had a high OR for increasing withdrawals (OR 5.55, 95% CI 2.24 to 13.7). Significant heterogeneity between studies comparing two antiarrhythmic drugs was frequent in the analysis of withdrawals. This heterogeneity is probably explained by the differences in criteria for stopping treatment and withdrawal of patients when adverse effects appeared.

Sensitivity analysis did not modify results for withdrawals and pro-arrhythmia.

Atrial fibrillation recurrence

Results for atrial fibrillation recurrence are summarized in Analysis 4.1 and Figure 5. All studied class IA, class IC and class III drugs significantly reduced recurrences of atrial fibrillation. Metoprolol, based in two studies (562 patients), also showed a significant effect in reducing the number of atrial fibrillation recurrences (OR 0.62, 95% CI 0.44 to 0.88, P = 0.008). In contrast, class IB drugs did not show any difference with controls.

Figure 5. Atrial fibrillation recurrence

Figure: Atrial fibrillation recurrence

	Drug/s studied	Studies (n)	Events No/Total		Peto Odds Ratio (95%CI)	p
Comparing an antiarrhythmic versus control			Anti-arrhythmic	Control	0.10 1 10	
Class Ia	Disopyramide	2	40 / 75	49 / 71	0.52 (0.27 – 1.01)	0.05
	Quinidine	7	741 / 1106	417 / 518	0.51 (0.40 – 0.65)	<0.001
	All Class Ia	8	781 / 1181	449 / 564	0.51 (0.40 – 0.64)	<0.001
Class Ib	All: Aprindine, Bidisomide	2	639 / 781	453 / 540	0.84 (0.63 – 1.13)	ns
Class Ic	Flecainide	3	31 / 71	56 / 78	0.31 (0.16 – 0.60)	<0.001
	Propafenone	5	376 / 720	276 / 378	0.37 (0.28 – 0.48)	<0.001
	All Class Ic	9	443 / 843	342 / 466	0.36 (0.28 – 0.45)	<0.001
Class II	Metoprolol	2	172 / 280	203 / 282	0.62 (0.44 – 0.88)	0.008
Class III	Amiodarone	4	200 / 428	209 / 245	0.19 (0.14 – 0.27)	<0.001
	Azimilide	4	604 / 797	656 / 805	0.70 (0.55 – 0.90)	0.005
	Dofetilide	3	448 / 752	363 / 431	0.30 (0.23 – 0.39)	<0.001
	Dronedarone	2	648 / 982	353 / 461	0.59 (0.46 – 0.75)	<0.001
	Sotalol	12	1197 / 1791	955 / 1211	0.51 (0.43 – 0.60)	<0.001
	All Class III	22	3097 / 4750	2536 / 3153	0.46 (0.42 – 0.51)	<0.001
Comparing two antiarrhythmics			Drug A	Drug B		
Disopyramide *vs.*	Other Class I Drugs	2	26 / 60	27 / 53	0.76 (0.36 – 1.60)	ns
Quinidine *vs.*	Flecainide	2	103 / 132	99 / 137	1.38 (0.79 – 2.41)	ns
	Other Class I Drugs	4	176 / 258	168 / 268	1.30 (0.90 – 1.87)	ns
	Sotalol	6	715 / 1109	556 / 869	0.92 (0.76 – 1.11)	ns
Flecainide *vs.*	Propafenone	2	49 / 145	56 / 152	0.87 (0.54 – 1.40)	ns
Amiodarone *vs.*	Class I Drugs	5	142 / 311	229 / 332	0.36 (0.26 – 0.50)	<0.001
	Dronedarone	1	116 / 255	163 / 249	0.45 (0.31 – 0.63)	<0.001
	Sotalol	3	218 / 463	303 / 447	0.43 (0.33 – 0.56)	<0.001
Sotalol *vs.*	Class I except quinidine	4	150 / 243	157 / 251	0.98 (0.67 – 1.45)	ns
	Dofetilide	1	74 / 108	196 / 321	1.38 (0.88 – 2.16)	ns
	Beta-blockers	2	88 / 103	83 / 130	1.10 (0.64 – 1.90)	ns

ns = not significant. Some studies compared more than two drugs, so the total number of studies and patients in the table is superior to the absolute number of studies and patients included.

Substantial heterogeneity (I2 = 76%, P = 0.02) between studies was detected for dofetilide. Moderate, non-significant inconsistency (I2 = 52%, P = 0.15) appeared between the two studies on metoprolol. In both cases, dofetilide and metoprolol, all studies showed the same direction of the effect (i.e. to a reduction of atrial fibrillation recurrences) and the heterogeneity seems probably caused by the differences in the characteristics of recruited patients.

Pooled recurrence rates of atrial fibrillation at one year were high: 69% to 84% in controls not receiving antiarrhythmic treatment, reduced to 43% to 67% in patients treated with antiarrhythmics. The corresponding average NNT for one year, to avoid one recurrence of atrial fibrillation, were three with amiodarone, four with flecainide, five with dofetilide and propafenone, eight with quinidine and sotalol, 10 with dronedarone and metoprolol and 17 with azimilide (the 95% CI varied between 2 and 60).

In direct comparisons between antiarrhythmics (Analysis 4.5), amiodarone reduced recurrences of atrial fibrillation significantly more than combined class I drugs (OR 0.36, 95% CI 0.26 to 0.50, P < 0.00001), more than dronedarone (OR 0.45, 95% CI 0.31 to 0.63, P < 0.00001, results based in one single trial, 504 patients), and more than sotalol (OR 0.43, 95% CI 0.33 to 0.56, P < 0.00001). No other significant difference appeared in comparisons between antiarrhythmics.

Results for atrial fibrillation recurrence were unchanged in sensi-

tivity analysis.

Other outcomes and subgroup analysis

Chronic anticoagulation with warfarin was mandatory (i.e. every patient receiving anticoagulation therapy throughout the whole follow-up period) in only three studies (Channer 2004; Hillestad 1971; Van Gelder 1989). In the rest, the decision on anticoagulation was left to the judgement of the attending physician. Unfortunately, no trial reported the actual frequency of anticoagulation in the different treatment groups during follow up.

Only six of the 30 studies comparing antiarrhythmics with a control reported stroke outcomes (ATHENA 2009; Benditt 1999; Hillestad 1971; Karlson 1998; Lloyd 1984; Sodermark 1975) but it is uncertain that reporting was complete. No significant difference was found, except in the ATHENA study, where stroke was significantly less frequent in the group treated with dronedarone (1.2% per year) than in the placebo group (1.8% per year, P = 0.027). The remaining 5 studies reported six strokes in 650 patients in the control groups, and 20 strokes in 1755 patients treated with antiarrhythmics. Seven trials reported some data on the incidence of heart failure (ATHENA 2009; DYONISOS 2010; FAPIS 1996; Hohnloser 1995; Kuhlkamp 2000; PRODIS 1996; Reimold 1993) which was low and without differences between groups.

Subgroup analysis of patients with persistent atrial fibrillation replicated the results obtained in the entire population. Other planned subgroup analysis (patients with heart failure, studies where warfarin was mandatory versus those where it was discretionary, patients with a structurally normal heart) were not possible, as separate data for each group of patients was seldom available.

DISCUSSION

Summary of main results

In the update of this systematic review we have found and included 11 new randomised controlled trials. They comprised 8,212 more patients and added more data on amiodarone, azimilide, dofetilide, dronedarone, metoprolol and sotalol, leading to new results on the effectiveness of beta-blockers to reduce recurrences of atrial fibrillation and on the risk of increased mortality with sotalol.

The updated results confirm our previous findings that antiarrhythmic drugs belonging to class IA, class IC and class III are effective at reducing recurrence of atrial fibrillation, by a relative 20 to 50% compared to patients not receiving antiarrhythmics. Of all these drugs, amiodarone seemed to be the most effective in preventing recurrences of atrial fibrillation, as it obtained the lowest OR and in direct comparisons was better than combined class I drugs and other class III antiarrhythmics. Less information is available about the relative effectiveness of other antiarrhythmics between themselves. In any case, the overall effectiveness of antiarrhythmics is limited: atrial fibrillation still recurred in 44% to 67% of treated patients at one year.

What is new is the finding, based in the pooled data from two randomised controlled trials of high quality (Kuhlkamp 2000; Nergardh 2007) that metoprolol, a beta-blocker, showed a significant reduction of atrial fibrillation recurrences. The estimated OR and NNT for metoprolol were greater (this is, less effectiveness to reduce recurrences) than amiodarone, class IC drugs or dofetilide, but not far from class IA drugs and some class III antiarrhythmics. Besides, no significant difference to prevent recurrences was found in two trials that compared sotalol with beta-blockers, metoprolol or atenolol in one trial (DAPHNE 2008), bisoprolol in the other one (Plewan 2001). The effect of beta-blockers in reducing recurrences of atrial fibrillation could be due to the ability of beta-blockers to suppress atrial extrasystoles, known to be a frequent cause of paroxysmal atrial fibrillation (Haïssaguerre 1998), or to their effect in improving cardiac remodeling associated to concomitant heart diseases, e.g. coronary disease or heart failure.

However, the primary aim of this review was to know if long-term treatment with antiarrhythmics carried other clinical benefits to patients, in addition to maintenance of sinus rhythm. Consequently, we focused on mortality, stroke, embolisms and also on treatment potential adverse effects as main outcomes.

Concerning mortality, we found that no antiarrhythmic produced a benefit in mortality and that two different antiarrhythmics, class IA drugs and sotalol, appeared to be associated with a small, but significant, increase in mortality.

Class IA drugs (quinidine and disopyramide together) showed a significant increase on mortality. These results were not replicable when only the PAFAC and SOPAT studies were analysed. These two trials are recent, high quality, large (848 and 1033 patients, respectively) studies that compared quinidine, sotalol, and placebo and showed no increase in mortality in the active treatment groups. They differed also from others trials studying quinidine and sotalol in that they showed no increase in adverse effects or withdrawals with these drugs. A possible explanation is that both studies used a lower dose of quinidine than earlier trials and that quinidine was combined with verapamil, which has been shown to reduce some of the pro-arrhythmic effects of quinidine, such as accelerated atrioventricular conduction. Finally, the proportion of patients having structural heart disease was lower in the PAFAC and SOPAT studies than in earlier trials.

The overall cumulated evidence on class IA antiarrhythmics suggests that long-term use of these drugs may mildly increase mortality (NNH 109, 95 % CI 34 to 4985), with the possible exception of low dose quinidine combined with verapamil, although this exception requires confirmation. A previous meta-analysis by Coplen et al also found that quinidine increased mortality (Coplen 1990). Another meta-analysis, by Nichol et al, found no difference

in mortality with any antiarrhythmic, but most of the trials they pooled had very short follow-up periods (Nichol 2002).

Sotalol had showed, in our previous results, a trend to increase mortality that was not consistent in sensitivity analysis. In this updated review, after the addition of three new randomised trials, the increase in mortality associated with long-term use of sotalol become significant and remained significant in all sensitivity analysis, which suggests this effect is real. Again, the absolute increase in deaths seems small, with an estimate average NNH of 166. A recent meta-analysis, using a mixed treatment comparison method (where the estimates obtained from direct and indirect comparisons in a network of trials are combined) also found a significant increase in mortality associated with sotalol (Freemantle 2011). Quinidine was not studied in the meta-analysis by Freemantle et al.

Finally, considering that trends observed today could become significant results in a future with the addition of new research, as the case of sotalol proves, it is important to note the clear trend to increased mortality observed with the use of azimilide, even if not significant.

With respect to adverse effects, virtually all the antiarrhythmics showed more withdrawals due to adverse effects than controls. Concerning pro-arrhythmia, only amiodarone, dronedarone and propafenone showed no difference with controls. It is important to note that we employed an extended definition of pro-arrhythmia that included severe, symptomatic, bradycardia and atrio-ventricular blocks. Metoprolol was associated with a significant increase in pro-arrhythmia precisely because an increased incidence of severe bradycardias. Of all antiarrhythmics, quinidine at higher doses appeared to be the drug with more withdrawals because of adverse events, compared to controls and to other antiarrhythmics, and flecainide seemed to be the most pro-arrhythmic. Amiodarone compared favourably with class I drugs combined, but had a high OR for increasing withdrawals compared to placebo. Moreover, these were results at one year of follow-up, and adverse effects of amiodarone are known to increase in frequency over time (Harris 1983; Lafuente-Lafuente 2009).

Overall completeness and applicability of evidence

Finally, we intended to analyse other clinically relevant outcomes, such as the frequency of strokes or other embolisms, the frequency of use of long-term anticoagulation, or the influence of heart failure and structural heart disease in the response to treatment. Unfortunately, data on those outcomes were sparse, if reported at all. In the few trials that reported it, the frequency of stroke and heart failure was very low, perhaps because the population included was at low risk. No differences with controls were apparent, with the only exception of the ATHENA trial, where the incidence of stroke were lower in the group treated with dronedarone than in the placebo group (ATHENA 2009). The frequency of use of anticoagulants during the follow-up was not reported in any study. Separate data of patients having and not having structural heart disease were not available.

This lack of data for some important clinical outcomes is the main limitation of our study. Another limitation could be that in many studies patients were followed up until atrial fibrillation recurred and not thereafter, hence events between that point and the complete 1 year of follow up might have been missed. Also, the population included in most studies was at low risk of events - the mean age of included patients was about 60 years and most of them had a normal left ventricular ejection fraction. We do not know if our results can be extrapolated to other patient populations, especially older patients and those with reduced left ventricular ejection fraction.

Finally, it is important to remember that maintaining sinus rhythm by using long-term antiarrhythmic drugs is only one possible step of the more general "rhythm control" strategy, and should be put in the perspective of the global strategy chosen for the patient (ACC/AHA/ESC 2006; NICE 2006). Other therapies have proven to be useful to prevent or reduce recurrences of atrial fibrillation in selected patients, especially catheter ablation (Oral 2006; Terasawa 2009; Wazni 2005), and also occasional use of antiarrhythmics only for terminating recurrences (Alboni 2004). However, the effect of these therapies on other important clinical endpoints - mortality, stroke, incidence of heart failure - is still not known.

AUTHORS' CONCLUSIONS

Implications for practice

Various antiarrhythmic drugs are moderately effective in maintaining sinus rhythm after conversion of atrial fibrillation: disopyramide and quinidine in class IA; flecainide and propafenone in class IC; metoprolol and probably other beta-blockers in class II; and amiodarone, dofetilide, dronedarone and sotalol in class III. However, all antiarrhythmics show evidence of increased adverse effects, and the majority of increased pro-arrhythmia. Moreover, there is good evidence of a small but significant increase of the risk of death with the use of class IA drugs - except possibly quinidine at low doses combined with verapamil - and the use of sotalol. Class IA drugs and sotalol should be used most carefully for this indication.

On the basis of results at one year, amiodarone showed some advantages with respect to class I and other class III drugs: it was more effective in preventing recurrences of atrial fibrillation, produced no significant pro-arrhythmia, and associated no increase in mortality. However, we do not know if those advantages persist with longer treatment, particularly as frequency of adverse effects of amiodarone increases over time.

Currently available evidence does not allow an accurate assessment of several important clinical outcomes (i.e. stroke, peripheral embolisms, or the development of heart failure). Consequently, it remains unclear whether it is worthy maintaining sinus rhythm with antiarrhythmics, or which specific groups of patients might benefit.

Implications for research

Adequate evidence exists for some outcomes (mortality, withdrawals, pro-arrhythmia and AF recurrences) for all drugs included in this review, with the exception of flecainide, where only three small trials with few patients were identified. Larger studies would be desirable on this drug, to better define its effectiveness and long-term safety, particularly as flecainide is still frequently employed for this indication.

Available evidence is limited by the lack of systematic assessment of some important clinical outcomes: stroke, heart failure, and functional measures (exercise capacity, quality of life). Trials studying antiarrhythmic drugs should measure their effects on these outcomes, in addition to the prevention of arrhythmia recurrences. Pending questions include: the effect of antiarrhythmics on those clinical outcomes, and the effect in specific subgroups of patients (specifically patients with heart failure or reduced left ventricular ejection fraction, and older patients).

Finally, new antiarrhythmic drugs or other procedures, more effective in preventing atrial fibrillation recurrence and/or associating less adverse effects in long-term treatment, would be desirable.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

A-COMET-I 2006

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Symptomatic AF in the previous 6 months. Type: recent-onset 28%, persistent 72% (mean duration: NS). N = 446 Male: 78%. Age (mean, SD): 65, +/-10 Structural heart disease: 70%. LAD: NS. LVEF: NS
Interventions	Azimilide 250 mg/d vs placebo Method of AF cardioversion: both pharmacological and electrical, % NS Warfarin discretionary
Outcomes	At 6 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described

A-COMET-II 2006

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Symptomatic AF, persistent for more than 48 hours, less than 6 months duration. N = 658 Male: 66%. Age (mean, SD): 62, +/-9 Structural heart disease: 73%. LAD: enlarged in 72%. LVEF: reduced (< 40%) in 10% of patients
Interventions	Azimilide 125 mg/d vs Sotalol 320 mg/d vs Placebo Method of AF cardioversion: 6% pharmacological, 94% electrical. Warfarin discretionary

A-COMET-II 2006 (*Continued*)

Outcomes	At 6 months: Mortality Pro-arrhythmia Adverse effects AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Sequentially numbered drug containers

A-STAR 2006

Methods	RCT Double-blind Loss to follow-up reported: no	
Participants	Sympromatic AF in the previous 6 months. Type: paroxysmal or recent-onset 95%, persistent 5% (mean duration: NS). N = 431. Male: 62%. Age (mean, SD): 62, +/-10. Structural heart disease: 69%. LAD: NS. LVEF: NS.	
Interventions	Azimilide 125 mg/d vs Placebo. Method of AF cardioversion: 100% spontaneous or pharmacological. Warfarin discretionary.	
Outcomes	At 6 months: Mortality Adverse effects Pro-arrhythmia AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described

AFFIRM Substudy 2003

Methods	RCT Open-label Loss to follow-up reported: yes
Participants	AF likely to be recurrent and to cause illness or death. Type: paroxysmal or recent-onset 29%, persistent 71% (mean duration: NS). N = 410. Male: 63%. Age (mean, SD): 69, +/-8 Structural heart disease: 85%. LAD: enlarged in 71%. LVEF: 55%
Interventions	Amiodarone 200 mg/d vs class I drugs vs Sotalol 240 mg/d Method of AF cardioversion: both pharmacological and electrical, % NS Warfarin discretionary
Outcomes	At 3.8 years: Mortality At 12 months: Pro-arrhythmia Adverse effects AF recurrence Symptomatic recurrence
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

AFIB 1997

Methods	RCT Open-label Loss to follow-up reported: yes
Participants	Previous AF documented in the last 2 years. Type: NS. N = 1227 Male: 62%. Age (mean, SD): 63, +/-13 Structural heart disease: 67%. LAD: NS. LVEF: NS
Interventions	Bidisomide various doses (400, 800, 1200 mg/d) vs Placebo Method of AF cardioversion: pharmacological 70%, electrical 30% Warfarin discretionary
Outcomes	At 6 months: Mortality AF recurrence Symptomatic recurrence
Notes	

AFIB 1997 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Aliot 1996

Methods	RCT Open-label Loss to follow-up reported: yes
Participants	Paroxysmal AF documented any time before (70% in last 1 year). N = 97. Male: 53%. Age (mean, SD): 63, +/-12 Structural heart disease: 45%. LAD: NS. LVEF: NS
Interventions	Flecainide 100-200mg/d vs Propafenone 600 mg/d. Method of AF cardioversion: pharmacological. Warfarin discretionary.
Outcomes	At 12 months: Mortality Stroke Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

ASAP 2003

Methods	RCT Double-blind Loss to follow-up reported: no
Participants	Previous AF documented in the last 2 years. Type: NS. N = 1380 (4 sub studies) Male: 66%. Age (mean, SD): 63, +/-13 Structural heart disease: 73%. LAD: NS. LVEF: NS

ASAP 2003 (*Continued*)

Interventions	Azimilide various doses (35 to 125 mg/d) vs Placebo Method of AF cardioversion: pharmacological 65%, electrical 35% Warfarin discretionary
Outcomes	At 6 months: Mortality Pro-arrhythmia Adverse effects Time to AF recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

ATHENA 2009

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Non-permanent AF with high-risk of recurrence. Type: all types, % NS. N = 4628. Male: 53%. Age (mean, SD): 72, +/-9. Structural heart disease: 57%. LAD: NS. LVEF: reduced (<45%) in 12%
Interventions	Dronedarone 800 mg/d vs Placebo. Method of AF cardioversion: both pharmacological and electrical, % NS. Warfarin discretionary, 60% patients in both groups.
Outcomes	At 22 months: Mortality Adverse effects Pro-arrhythmia Hospitalizations due to cardiovascular events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Central allocation

Bellandi 2001

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Paroxysmal recurrent AF (47%), or persistent AF (53%, mean duration: NS). N = 194 Male: 56%. Age (mean, range): 52, 20-75 Structural heart disease: 72%. LAD: 42 mm. LVEF: 55%
Interventions	Propafenone 900 mg/d vs sotalol 240 mg/d vs placebo Method of AF cardioversion: pharmacological 89%, electrical 11% Warfarin discretionary.
Outcomes	At 12 months: Mortality Pro-arrhythmia Adverse effects AF recurrence Symptomatic recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Benditt 1999

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	AF or AFl documented in the last 3 months. Type: paroxysmal or recent-onset 77%, persistent 23% (mean duration: NS). N = 253 Male: 64%. Age (mean, range): 62, 24-86 Structural heart disease: 57%. LAD: NS (enlarged in 28%). LVEF: NS
Interventions	Sotalol various doses (80, 120, 160 mg/d) vs placebo Method of AF cardioversion: NS Warfarin discretionary
Outcomes	At 12 months: Mortality Stroke Pro-arrhythmia Adverse effects AF recurrence Symptomatic recurrence

Benditt 1999 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Byrne-Quinn 1970

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Persistent AF (mean duration: 12 months). N = 74 Male: 53%. Age (mean, range): 54, 30-70 Structural heart disease: 80%. LAD: NS. LVEF: NS
Interventions	Quinidine 1.2 g/d vs placebo Method of AF cardioversion: electrical Warfarin discretionary
Outcomes	At 12 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Carunchio 1995

Methods	RCT Open-label Loss to follow-up reported: yes
Participants	Recurrent AF (type: NS) with > 3 episodes in previous 1 year. NS. N = 66 Male: 50%. Age (mean, range): 48, 30-69 Structural heart disease: 65%. LAD: 36 mm. LVEF: NS, all > 40%

Carunchio 1995 (*Continued*)

Interventions	Flecainide 200 mg/d vs sotalol 240 mg/d vs placebo. Method of AF cardioversion: pharmacological 67%, electrical 33% Warfarin discretionary	
Outcomes	At 12 months: Mortality Stroke Pro-arrhythmia Adverse effects AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Channer 2004

Methods	RCT Double-blind Loss to follow-up reported: no	
Participants	Persistent AF (mean duration: 6 months) N = 99 Male: 78%. Age (mean, SD): 67, +/-10 Structural heart disease: NS. LAD: 44 mm. LVEF: 58%	
Interventions	Amiodarone 200 mg/d vs placebo. Method of AF cardioversion: pharmacological 20%, electrical 80% Warfarin mandatory	
Outcomes	At 12 months: Mortality Pro-arrhythmia Adverse effects AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

DAFNE 2003

Methods	RCT Double-blind Loss to follow-up reported: no
Participants	Persistent AF (mean duration: 3 months) N = 199 Male: 70%. Age (mean): 63 Structural heart disease: NS. LAD: 45 mm. LVEF: 55%
Interventions	Dronedarone various doses (800, 1200, 1600 mg/d) vs placebo Method of AF cardioversion: pharmacological 15%, electrical 85% Warfarin discretionary
Outcomes	At 6 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

DAPHNE 2008

Methods	RCT Single-blind Loss to follow-up reported: yes
Participants	Bradychardia-tachycardia sinus node disease with history of several episodes of AF/AFl and needing a pacemaker. AF type: 100% paroxysmal. N = 135. Male: 49,6%. Age (mean, SD): 73, +/-7. Structural heart disease: 71%. LAD: 43 mm. LVEF: 56%.
Interventions	Sotalol 167 mg/d (mean) vs beta-blockers (atenolol or metoprolol). Method of AF cardioversion: 100% spontaneous. Warfarin discretionary.
Outcomes	At 19 months: Adverse effects AF recurrence
Notes	

DAPHNE 2008 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described

DIAMOND 2001

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Persistent AF (mean duration: NS) in patients with heart failure or recent myocardial infarction and reduced LVEF. N = 506 Male: 77%. Age (mean, range): 72, 36-92 Structural heart disease: 100%. LAD: NS. LVEF: NS, all < 35%
Interventions	Dofetilide 500 mcg/d vs placebo Method of AF cardioversion: pharmacological 44%, electrical 15% Warfarin discretionary
Outcomes	At 12 and 24 months: Mortality Pro-arrhythmia AF recurrence
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Dogan 2004

Methods	RCT Single-blind Loss to follow-up reported: yes
Participants	AF of duration 3 hours to 3 months: recent-onset 71%, persistent 29% (mean duration: 0.5 months). N = 110 Male: 45%. Age (mean, SD): 61, +/-12 Structural heart disease: 79%. LAD: 44 mm. LVEF: 64%

Dogan 2004 (*Continued*)

Interventions	Propafenone 450 mg/d vs placebo Method of AF cardioversion: spontaneous 42%, pharmacological 31%, electrical 27% Warfarin discretionary	
Outcomes	At 15 months: Mortality Pro-arrhythmia Adverse effects AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

DYONISOS 2010

Methods	RCT. Double-blind. Loss to follow-up reported: yes.	
Participants	Documented AF for more than 72 hours. Type: 5% paroxysmal, 22% recent-onset, 63% persistent (mean duration: 1.5 months). N = 504. Male: 71%. Age (mean, SD): 64, +/-10. Structural heart disease: 29%. LAD: NS. LVEF: NS.	
Interventions	Amiodarone 200 mg/d vs Dronedarone 800 mg/d. Method of AF cardioversion: both pharmacological and electrical, % NS. Warfarin required.	
Outcomes	At 12 months: Mortality Adverse effects Pro-arrhythmia AF recurrence Heart failure	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

DYONISOS 2010 (*Continued*)

Allocation concealment (selection bias)	Low risk	Central allocation

EMERALD 2000

Methods	RCT. Double-blind. Loss to follow-up reported: yes.
Participants	Persistent AF (1 week to 1 year, mean duration < 6 months). N = 535. Male: 70%. Age (mean, SD): 64, NS. Structural heart disease: NS. LAD: NS. LVEF: NS.
Interventions	Dofetilide 250, 500 or 1000 mcg/d (3 different groups) vs Sotalol 160 mg/d vs Placebo. Method of AF cardioversion: 10% pharmacological, 90% electrical. Warfarin discretionary.
Outcomes	At 12 months: Mortality Adverse effects Pro-arrhythmia AF recurrence
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described

EURIDIS ADONIS 2007

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	AF or AFl documented in the previous 3 months. Proportions of paroxysmal and persistent AF not reported. N = 1244. Male: 69%. Age (Mean, SD): 63, +/-11 Structural heart disease: 41%. LAD: 42.5 mm. LVEF: 58%
Interventions	Dronedarone 800 mg/d vs placebo Method of AF cardioversion: any (frequencies of use not reported) Warfarin discretionary
Outcomes	At 12 months: Mortality Stroke

EURIDIS ADONIS 2007 (*Continued*)

	Pro-arrhythmia Adverse effects AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

FAPIS 1996

Methods	RCT Open-label Loss to follow-up reported: yes	
Participants	Paroxysmal recurrent AF with > 2 episodes in the last 4 months. N = 200 Male: 54%. Age (mean, SD): 57, +/-10 Structural heart disease: 0%. LAD: 35 mm. LVEF: 61%	
Interventions	Flecainide 200 mg/d vs propafenone 520 mg/d Method of AF cardioversion: pharmacological Warfarin discretionary	
Outcomes	At 12 months: Mortality Pro-arrhythmia Adverse effects AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

GEFACA 2001

Methods	RCT Double-blind Loss to follow-up reported: no	

GEFACA 2001 (*Continued*)

Participants	Persistent AF lasting > 2 months (mean duration: 36 months). N = 50 Male: 73%. Age (mean, SD): 62, +/-7 Structural heart disease: 94%. LAD: 48 mm. LVEF: 60%.
Interventions	Amiodarone 200 mg/d vs placebo Method of AF cardioversion: pharmacological 32%, electrical 68% Warfarin discretionary
Outcomes	At 16 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Hillestad 1971

Methods	RCT Open-label Loss to follow-up reported: no
Participants	Persistent AF lasting 1 month to 2 years (mean duration: NS). N = 100 Male: 46%. Age (mean, range): 54, 22-77 Structural heart disease: 92%. LAD: NS. LVEF: NS
Interventions	Quinidine 0.8-1.2 g/d vs No treatment Method of AF cardioversion: electrical Warfarin mandatory
Outcomes	At 12 months: Mortality Stroke Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Hillestad 1971 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Hohnloser 1995

Methods	RCT Open-label Loss to follow-up reported: yes
Participants	Persistent AF between 2 days and 6 months (mean duration: 1,5 months). N = 50 Male: 36%. Age (mean, SD): 62, +/-11 Structural heart disease: 86%. LAD: 50 mm. LVEF: 51%
Interventions	Quinidine 1 g/d vs sotalol 240-320 mg/d Method of AF cardioversion: pharmacological 40%, electrical 60% Warfarin discretionary
Outcomes	At 6 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Juul-Moller 1990

Methods	RCT Open-label Loss to follow-up reported: yes
Participants	Persistent AF between 2 months and 1 year (mean duration: 5 months). N = 183 Male: 81%. Age (mean, SD): 59, +/-9 Structural heart disease: NS. LAD: 42 mm. LVEF: NS
Interventions	Quinidine 1,2 g/d vs Sotalol 160-320 mg/d Method of AF cardioversion: electrical Warfarin discretionary

Juul-Moller 1990 (*Continued*)

Outcomes	At 6 months: Mortality Stroke Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kalusche 1994

Methods	RCT Open-label Loss to follow-up reported: yes
Participants	AF lasting from 2 weeks to 2 years. Type: paroxysmal 32%, persistent 68% (mean duration: NS). N = 82 Male: 68%. Age (mean, SD): 61, +/-5 Structural heart disease: 68%. LAD: 45 mm. LVEF: 30%
Interventions	Quinidine 1 g/d vs Sotalol 240-400 mg/d Method of AF cardioversion: pharmacological 47%, electrical 53% Warfarin discretionary
Outcomes	At 12 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Karlson 1998

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Persistent AF between 6 weeks and 1 year (mean duration: 5 months). N = 92 Male: 71%. Age (mean, range): 60, 31-72 Structural heart disease: 60%. LAD: NS. LVEF: NS
Interventions	Disopyramide 500 mg/d vs placebo Method of AF cardioversion: electrical Warfarin discretionary
Outcomes	At 12 months: Mortality Stroke Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kochiadakis 2000

Methods	RCT Single-blind Loss to follow-up reported: no
Participants	Any documented symptomatic previous or persistent AF. Type: paroxysmal or recent-onset 64%, persistent 34% (mean duration: 10 months). N = 186 Male: 52%. Age (mean, SD): 63, +/-9 Structural heart disease: 35%. LAD: 44 mm. LVEF: 53%
Interventions	Amiodarone 200 mg/d vs sotalol 320 mg/d vs placebo Method of AF cardioversion: both pharmacological and electrical, % NS Warfarin discretionary
Outcomes	At 12 and 24 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Kochiadakis 2000 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kochiadakis 2004a

Methods	RCT Single-blind Loss to follow-up reported: no
Participants	Any documented symptomatic previous or persistent AF. Type: paroxysmal or recent-onset 63%, persistent 37% (mean duration: 8 months). N = 146 Male: 49%. Age (mean, SD): 63, +/-9 Structural heart disease: 38%. LAD: 43 mm. LVEF: 53%
Interventions	Amiodarone 200 mg/d vs propafenone 450 mg/d Method of AF cardioversion: both pharmacological and electrical, % NS Warfarin discretionary
Outcomes	At 12 and 24 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kochiadakis 2004b

Methods	RCT Single-blind Loss to follow-up reported: no
Participants	Any documented symptomatic previous or persistent AF. Type: paroxysmal or recent-onset 59%, persistent 41% (mean duration: 8 months). N = 254 Male: 50%. Age (mean, SD): 63, +/-10 Structural heart disease: 41%. LAD: 44 mm. LVEF: 53%

Kochiadakis 2004b (*Continued*)

Interventions	Propafenone 450 mg/d vs sotalol 300 mg/d vs placebo Method of AF cardioversion: both pharmacological and electrical, % NS Warfarin discretionary
Outcomes	At 12 and 24 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Kuhlkamp 2000

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Persistent AF lasting 2 days to 1 year (mean duration: 3 months). N = 394 Male: 70%. Age (mean, range): 60, 24-86 Structural heart disease: 36%. LAD: 42 mm. LVEF: 64%
Interventions	Metoprolol 100 mg/d vs placebo Method of AF cardioversion: pharmacological 18%, electrical 82% Warfarin discretionary
Outcomes	At 6 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Lloyd 1984

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Persistent AF lasting 1 month to 3 years (mean duration: NS). N = 82 Male: 38. Age (mean, range): 46, 15-79 Structural heart disease: 94%. LAD: NS. LVEF: NS
Interventions	Disopyramide 450 mg/d vs quinidine 1.4 g/d vs placebo Method of AF cardioversion: electrical Warfarin discretionary
Outcomes	At 6 months: Mortality Stroke Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Naccarelli 1996

Methods	RCT. Open-label. Loss to follow-up reported: no.
Participants	Any documented symptomatic AF. Type: paroxysmal 74%, persistent 26% (mean duration: 36 months). N = 239 Male: 38. Age (mean): 58 Structural heart disease: 83%. LAD: NS. LVEF: NS
Interventions	Flecainide 200-300 mg/d vs Quinidine 1-1,5 g/d Method of AF cardioversion: pharmacological Warfarin discretionary
Outcomes	At 12 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Naccarelli 1996 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Nergardh 2007

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Persistent AF of less than 1 year (mean duration: 5 months). N = 168. Male: 71%. Age (mean, SD): 67, +/-11. Structural heart disease: NS. LAD: 45 mm. LVEF: 49%.
Interventions	Metoprolol 170 mg/d (mean) vs Placebo. Method of AF cardioversion: 100% electrical. Warfarin discretionary.
Outcomes	At 6 months: Mortality Adverse effects Pro-arrhythmia AF recurrence
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Sequentially numbered drug containers

Niu 2006

Methods	RCT. Open-label. Loss to follow-up reported: yes.
Participants	Any type of AF. Type: 41% paroxysmal, 59% persistent (mean duration: NS). N = 102. Male: 56%. Age (mean, SD): 56, +/-11. Structural heart disease: NS (coronary disease 33%, hypertension 25%). LAD: NS. LVEF: NS

Niu 2006 (*Continued*)

Interventions	Amiodarone 200 mg/d vs Sotalol 40-80 mg/d. Method of AF cardioversion: pharmacological. Warfarin discretionary.	
Outcomes	At 12 months: Mortality Adverse effects AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described

Okishige 2000

Methods	RCT Single-blind Loss to follow-up reported: no	
Participants	Persistent AF lasting > 6 months (mean duration: 22 months). N = 62 Male: 92%. Age (mean, SD): 51, +/-17 Structural heart disease: 61%. LAD: 41 mm. LVEF: 61%	
Interventions	Pilsicainide 150 mg/d vs placebo Method of AF cardioversion: pharmacological 21%, electrical 79% Warfarin discretionary	
Outcomes	At 12 months: Mortality Pro-arrhythmia AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

PAFAC 2004

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Persistent AF lasting > 7 days (mean duration: 15 months). N = 848 Male: 66%. Age (mean, SD): 63, +/-9 Structural heart disease: NS. LAD: 45 mm. LVEF: 60%
Interventions	Quinidine 0,480 g/d (+ verapamil) vs sotalol 320 mg/d vs placebo Method of AF cardioversion: both pharmacological and electrical, % NS Warfarin discretionary
Outcomes	At 12 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

PITAGORA 2008

Methods	RCT. Open-label. Loss to follow-up reported: yes.
Participants	Recurrent symptomatic AF in patients with sinus node disease and an indication for pacemaker. Excluded those with underlying coronary disease or reduced LVEF. Type of AF: 53% paroxysmal, 47% persistent (mean duration: NS). N = 176. Male: 81%. Age (mean, SD): 72, +/-8. Structural heart disease: NS%. LAD: 47 mm. LVEF: 56%.
Interventions	Amiodarone 190 mg/d vs Class IC (Flecainide 170 mg/d or Propafenone 530 mg/d) vs Sotalol 140 mg/d. Method of AF cardioversion: NS. Warfarin discretionary.
Outcomes	At 21 months: Mortality Adverse effects Pro-arrhythmia Stroke

PITAGORA 2008 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described

Plewan 2001

Methods	RCT Open-label Loss to follow-up reported: yes
Participants	Persistent AF (mean duration: 9 months). N = 128 Male: 62%. Age (mean, SD): 59, +/-10 Structural heart disease: 72%. LAD: 48 mm. LVEF: 41%
Interventions	Sotalol 160 mg/d vs bisoprolol 5 mg/d Method of AF cardioversion: electrical Warfarin discretionary
Outcomes	At 8 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

PRODIS 1996

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Persistent AF (mean duration: 5 months). N = 56 Male: 68%. Age (mean, SD): 60, +/-11 Structural heart disease: 65%. LAD: 46 mm. LVEF: NS

PRODIS 1996 (*Continued*)

Interventions	Disopyramide 750 mg/d vs propafenone 900 mg/d Method of AF cardioversion: electrical Warfarin discretionary	
Outcomes	At 6 months: Mortality Pro-arrhythmia Adverse effects AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

RAFT 2003

Methods	RCT Double-blind Loss to follow-up reported: no	
Participants	Previous symptomatic AF documented in the last year. Type: NS. N = 523 Male: 59%. Age (mean, range): 63, 22-89 Structural heart disease: 48%. LAD: NS. LVEF: NS	
Interventions	Propafenone at various doses (450, 650, 850 mg/d) vs placebo. Method of AF cardioversion: pharmacological 79%, electrical 21% Warfarin discretionary	
Outcomes	At 9 months: Mortality Pro-arrhythmia Adverse effects AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Reimold 1993

Methods	RCT Open-label Loss to follow-up reported: yes
Participants	Any symptomatic AF or AFl. Type: paroxysmal 47%, persistent 53% (mean duration: 36 months). N = 100 Male: 64%. Age (mean, SD): 61, +/-12 Structural heart disease: 81%. LAD: 46 mm. LVEF: 59%
Interventions	Propafenone 675 mg/d vs Sotalol 320 mg/d Method of AF cardioversion: both pharmacological and electrical, % NS Warfarin discretionary
Outcomes	At 12 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Richiardi 1992

Methods	RCT Open-label Loss to follow-up reported: yes
Participants	Paroxysmal AF having > 3 episodes in the last 3 months. N = 200 Male: 54%. Age (mean, range): 57, 29-75 Structural heart disease: 48%. LAD: 45 mm. LVEF: NS
Interventions	Propafenone 900 mg/d vs Quinidine 1 g/d Method of AF cardioversion: pharmacological 88%, electrical 12% Warfarin discretionary
Outcomes	At 12 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Richiardi 1992 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

SAFE-T 2005

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Persistent AF lasting 3 days to 1 year (mean duration: NS). N = 655. Male: 99%. Age (mean, SD): 67, +/-9 Structural heart disease: 33%. LAD: 48 mm. LVEF: 51% Type of AF: persistent, mean duration: NS
Interventions	Amiodarone 300 mg/d vs sotalol 320 mg/d vs placebo. Method of AF cardioversion: pharmacological 20%, electrical 80%
Outcomes	At 12 months: Mortality Pro-arrhythmia AF recurrence
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

SAFIRE-D 2000

Methods	RCT Double-blind Loss to follow-up reported: no
Participants	Persistent AF or AFl lasting 2 weeks to 6 months (mean duration: NS). N = 250 Male: 84%. Age (mean, range): 67, 30-88 Structural heart disease: 67%. LAD: NS. LVEF: NS
Interventions	Dofetilide various doses (250, 500, 1000 mcg/d) vs placebo Method of AF cardioversion: pharmacological 15%, electrical 85% Warfarin discretionary

SAFIRE-D 2000 (*Continued*)

Outcomes	At 12 months: Mortality Pro-arrhythmia Adverse effects AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Singh 1991

Methods	RCT Double-blind Loss to follow-up reported: yes	
Participants	Persistent AF or AFl lasting 2 weeks to 1 year (mean duration: 3 months). N = 34 Male: 71%. Age (mean, SD): 60, +/-14 Structural heart disease: NS. LAD: 44 mm. LVEF: NS	
Interventions	Sotalol 80 - 320 mg/d vs placebo Method of AF cardioversion: pharmacological 17%, electrical 83% Warfarin discretionary	
Outcomes	At 6 months: Mortality Pro-arrhythmia Adverse effects AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

SMART 2002

Methods	RCT Double-blind Loss to follow-up reported: no
Participants	Symptomatic paroxysmal AF having > 1 episode monthly (59%) or persistent AF lasting < 1 month (41%). N = 94 Male: 72%. Age (mean, SD): 60, +/-12 Structural heart disease: NS. LAD: NS. LVEF: NS
Interventions	Aprindine 40 mg/d vs placebo Method of AF cardioversion: pharmacological 50%, electrical 50% Warfarin discretionary
Outcomes	At 6 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

SOCESP 1999

Methods	RCT Open-label Loss to follow-up reported: yes
Participants	AF lasting < 6 months. Type: recent-onset 61%, persistent 39% (mean duration: NS). N = 121. Male: 59%. Age (mean, SD): 54, +/-13 Structural heart disease: 54%. LAD: 39 mm. LVEF: 68%
Interventions	Quinidine 700 mg/d vs sotalol 240 mg/d Method of AF cardioversion: both pharmacological and electrical, % NS Warfarin discretionary
Outcomes	At 6 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

SOCESP 1999 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Sodermark 1975

Methods	RCT Open-label Loss to follow-up reported: yes
Participants	Persistent AF or AFl lasting < 3 years (mean duration: 3-6 months). N = 185 Male: 78%. Age (mean, range): 58, 24-78 Structural heart disease: 94%. LAD: NS. LVEF: NS
Interventions	Quinidine 1.2 - 1.8 g/d vs no treatment Method of AF cardioversion: pharmacological 49%, electrical 51% Warfarin discretionary
Outcomes	At 12 months: Mortality Stroke Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

SOPAT 2004

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Paroxysmal AF documented in the last 1 month (mean duration: NS). N = 1033 Male: 63%. Age (mean, SD): 60, +/-11 Structural heart disease: NS. LAD: 39 mm. LVEF: 61%
Interventions	Quinidine 0,320 or 0,480 g/d (+ verapamil) vs sotalol 320 mg/d vs placebo Method of AF cardioversion: both pharmacological and electrical, % NS

SOPAT 2004 (*Continued*)

	Warfarin discretionary	
Outcomes	At 12 months: Mortality Stroke Pro-arrhythmia Adverse effects AF recurrence Symptomatic recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Steinbeck 1988

Methods	RCT Open-label Loss to follow-up reported: yes	
Participants	Paroxysmal symptomatic AF of any duration (mean duration: 6 years). N = 45 Male: 58%. Age (mean): 59 Structural heart disease: 73%. LAD: NS. LVEF: NS	
Interventions	Quinidine 1 g/d (+ digoxine) vs flecainide 200-300 mg/d (+ digoxine) vs digoxine alone Method of AF cardioversion: pharmacological Warfarin discretionary	
Outcomes	At 12 months: Mortality Pro-arrhythmia Adverse effects AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Stroobandt 1997

Methods	RCT Double-blind Loss to follow-up reported: yes
Participants	Recent-onset AF (46%) or persistent AF lasting > 2 weeks (54%, mean duration: NS). N = 102 Male: 73%. Age (mean, range): 62, 27-84 Structural heart disease: 71%. LAD: 39 mm. LVEF: NS
Interventions	Propafenone 450 mg/d vs placebo Method of AF cardioversion: pharmacological 34%, electrical 66% Warfarin discretionary
Outcomes	At 6 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

SVA-4 2008

Methods	RCT Not blinded, open label. Loss to follow-up reported: yes
Participants	Sympromatic AF/AFl. All ypes, % NS. N = 422. Male: 63%. Age (mean, SD): 61, NS. Structural heart disease: 48%. LAD: NS. LVEF: NS.
Interventions	Azimilide 125 mg/d vs Placebo. Method of AF cardioversion: spontaneous or electrical, % NS. Warfarin discretionary.
Outcomes	At 6 months: Mortality Adverse effects Pro-arrhythmia AF recurrence
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described

Van Gelder 1989

Methods	RCT Open-label Loss to follow-up reported: yes
Participants	Any persistent AF or AFl (mean duration: 12 months). N = 73. Male: 55%. Age (mean, SD): 60, +/-11 Structural heart disease: 82%. LAD: 44 mm. LVEF: NS
Interventions	Flecainide 200-300 mg/d vs no treatment Method of AF cardioversion: electrical Warfarin mandatory?
Outcomes	At 12 months: Mortality Pro-arrhythmia Adverse effects AF recurrence
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Villani 1992

Methods	RCT Open-label Loss to follow-up reported: yes
Participants	Symptomatic recent-onset AF lasting > 1 hour, being at least the second episode. N = 76 Male: 49%. Age (mean, range): 65, 37-85 Structural heart disease: 86%. LAD: 38 mm. LVEF: NS
Interventions	Amiodarone 200 mg/d vs disopyramide 500 mg/d Method of AF cardioversion: pharmacological 74%, electrical 26% Warfarin discretionary

Villani 1992 (*Continued*)

Outcomes	At 14 months: Mortality Adverse effects AF recurrence Symptomatic recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Vitolo 1981

Methods	RCT Open-label Loss to follow-up reported: no	
Participants	Any persistent AF (mean duration: NS). N = 54 Male: 37%. Age (mean, SD): 53, +/-11 Structural heart disease: 100%. LAD: NS. LVEF: NS	
Interventions	Amiodarone 400 mg/d vs Quinidine 1,2 g/d Method of AF cardioversion: electrical Warfarin discretionary	
Outcomes	At 6 months: Mortality Pro-arrhythmia Adverse effects AF recurrence	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	B - Unclear

AF = atrial fibrillation; AFl = atrial flutter; LAD = mean left atrium diameter; LVEF = mean left ventricule ejection fraction; mg/d = milligrams per day; N = number of patients included in the study; NS = not stated; RCT = randomised controlled trial; SD = standard deviation.

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

Study	Reason for exclusion
Aberg 1968	Non-controlled study: all patients were initially treated with quinidine for 1 year, then allocated to procainamide alone or procainamide plus quinidine and followed for only 3 months
AF-CHF 2002	Rate versus rhythm control comparison. Patients in control group (rate control) were in persistent atrial fibrillation not reverted to sinus rhythm. Use of long term oral anticoagulants was significantly different between rate and rhythm control groups
AFFIRM 2002	Rate versus rhythm control comparison. Patients in persistent atrial fibrillation at inclusion, not reverted to sinus rhythm. Multiple different antiarrhythmics used in intervention group (rhythm-control), not analysed separately. Warfarin mandatory in control group (rate control) but discretionary in antiarrhythmics group and actual use was very different
Anderson 1994	Crossover study. Follow-up < 6 months (4 months).
Antman 1990	Non-controlled trial.
Aros 1978	Inadequate comparison: quinidine was compared to a combination of quinidine and amiodarone. Probably not truly randomised. All patients had underwent cardiac surgery.
Babuty 1999	Comparison of drugs not relevant: flecainide versus cibenzoline, but the effectiveness of cibenzoline is not known. Included patients having atrial tachyarrhythmias of various types, not only atrial fibrillation
Beck 1978	Acute pharmacological conversion of atrial fibrillation only, no long-term therapy with antiarrhythmics
Berns 1987	Non-controlled trial.
Blevins 1987	Non-controlled trial.
Blomstrom 1984	Non-controlled trial.
Boissel 1981	Follow-up < 6 months (3 months). Some patients followed for 1 year but they had not been randomised
Brodsky 1987	Non-controlled trial.
CHF-STAF 1998	Recruited patients with heart failure, only 15% had atrial fibrillation, not reverted to sinus rhythm, not analysed separately
Chun 1995	Non-controlled trial.
Clementy 1992	Non-controlled trial.

(*Continued*)

Connolly 1989	Crossover study. Follow-up < 6 months (4 months).
CTAF 2000	Initially included, but useable data could not be extracted: amiodarone was compared against the sequential use of propafenone and sotalol, and separate data of each drug were not available
Cuan-Perez 1971	Non-randomised, retrospective study.
ERAFT 2002	Follow-up < 6 months (3 months).
Faivre 1970	Non-randomised trial, retrospective control series.
Fernandez 1998	Acute pharmacological conversion of atrial fibrillation only, no long-term therapy with antiarrhythmics
Frances 1985	Comparison of drugs not relevant: quinidine versus cibenzoline, but the effectiveness of cibenzoline is not known
Gold 1986	Non-controlled trial.
Gosselink 1992	Non-controlled trial.
Graboys 1983	Non-controlled trial.
GUSTO 2002	Randomised trial but allocation to antiarrhythmics was not randomised. Multiple different antiarrhythmics used, mainly for acute cardioversion, only 19% of patients received long-term treatment with an antiarrhythmics
Hammill 1988	Non-controlled trial.
Hartel 1970	Quasi-randomised: allocation by year of birth. Follow-up < 6 months (3 months).
Hartel 1974	Follow-up < 6 months (3 months).
Hopson 1996	Non-controlled trial.
Horowitz 1985	Non-controlled trial.
HOT-CAFE 2003	Rate versus rhythm control comparison. Patients in control group in persistent atrial fibrillation not reverted to sinus rhythm. Variuos antiarrhythmics used sequentially in intervention group (rhythm-control), not analysed separately. Warfarin mandatory in control group (rate control) but discretionary in antiarrhythmics group
J-BAF 2009	Follow-up < 6 months (3 months only). The main endpoint of the study was the rate of cardioversion achieved rather than the maintaining of sinus rhythm. Rate of patients reverted to sinus rhythm were largely different between both study groups

(*Continued*)

J-RHYTHM 2009	Rate versus rhythm control comparison. Patients in control group (rate control) in persistent atrial fibrillation not reverted to sinus rhythm. Multiple different antiarrhythmics used in intervention group (rhythm-control), not analysed separately
Jong 2006	Inadequate comparison: two different doses of amiodarone were studied, without any control (placebo or a different drug) group
Kanoupakis 2004	Follow-up < 6 months (4 weeks).
Kennelly 1977	Non-randomised trial. Comparison of drugs not relevant: quinidine versus lidoflazine, but the effectiveness of lidoflazine is not known. Stopped prematurely due to mortality excess with lidoflazine
Kerr 1988	Non-controlled trial.
Kosior 2001	Non-controlled trial.
Kyles 1991	Non-controlled trial.
Lardoux 1996	Comparison of drugs not relevant: propafenone versus cibenzoline, but the effectiveness of cibenzoline is not known. Included patients having atrial tachyarrhythmias of various types, not only atrial fibrillation
Lau 1992	Crossover study.
Levi 1973	Acute pharmacological conversion of atrial fibrillation only, no long-term therapy with antiarrhythmics
Li 2004	Non-randomised, retrospective study.
Manios 2003	Follow-up < 6 months (6 weeks).
Martin 1986	Not truly randomised. It is not known if atrial fibrillation was reverted in all patients
Mary-Rabine 1990	Non-controlled trial.
Massacci 1991	Crossover study.
Mizutani 1995	Non-controlled trial for long term use of antiarrhythmics after conversion
Nedostup 1990	Non-randomised, retrospective study.
Opolski 1997	Non-controlled trial.
PEPS 2002	Non-controlled trial.

(*Continued*)

PIAF 2000	Rate versus rhythm control comparison. Patients in control group in persistent atrial fibrillation not reverted to sinus rhythm
Pietersen 1991	Follow-up < 6 months (3 months).
Piot 1998	Comparison of drugs not relevant: disopyramide versus cibenzoline, but the effectiveness of cibenzoline is not known
Porterfield 1989	Non-controlled trial.
PSVT 1995	Crossover study. Follow-up < 6 months (3 months).
RACE 2002	Rate versus rhythm control comparison. Patients in control group in persistent atrial fibrillation not reverted to sinus rhythm. Various antiarrhythmics used sequentially in intervention group (rhythm-control), not analysed separately. Warfarin mandatory in control group (rate control) but discretionary in antiarrhythmics group
Rasmussen 1981	Crossover study. Follow-up < 6 months (3 months).
Resnekov 1971	Non-controlled trial.
STAF 2003	Rate versus rhythm control comparison. Patients in persistent atrial fibrillation at inclusion, not reverted to sinus rhythm. Multiple different antiarrhythmics used in intervention group (rhythm-control), not analysed separately
Steeds 1999	Crossover study. Follow-up < 6 months (2 months).
Tonet 1986	Crossover study.
Touboul 1995	Comparison of drugs not relevant: quinidine versus cibenzoline, but the effectiveness of cibenzoline is not known
Van Wijk 1989	Crossover study. Follow-up < 6 months (3 months).
VEPARAF 2003	Follow-up < 6 months (3 months).
Wanless 1997	Follow-up < 6 months (4 - 8 weeks).
Zehender 1992	Follow-up < 6 months (3 months). Some patients followed longer but all were on quinidine, and there was no control group

DATA AND ANALYSES

Comparison 1. All-cause mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Individual antiarrhythmics	39	19057	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.91, 1.30]
1.1 Class Ia: Quinidine	7	1676	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.26 [0.93, 5.45]
1.2 Class Ia: Disopyramide	2	146	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.56 [0.47, 122.66]
1.3 Class Ic: Flecainide	3	149	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Class Ic: Propafenone	5	1098	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.05 [0.00, 1.02]
1.5 Class I others: aprindine, bidisomide, pilsicainide	3	1383	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.94 [0.62, 6.02]
1.6 Class II: Beta-blockers	2	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.75 [0.39, 19.56]
1.7 Class III: Amiodarone	4	673	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [0.68, 5.67]
1.8 Class III: Azimilide	5	3114	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.18 [0.98, 4.89]
1.9 Class III: Dofetilide	3	1183	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.68, 1.41]
1.10 Class III: Dronedarone	3	6071	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.67, 1.09]
1.11 Class III: Sotalol	12	3002	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.47 [1.21, 5.05]
2 Individual antiarrhythmics - ITT Worst case: missing patients counted as events	39	19226	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.99, 1.36]
2.1 Class Ia: Quinidine	7	1676	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.29 [1.05, 5.01]
2.2 Class Ia: Disopyramide	2	146	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.18 [1.21, 42.55]
2.3 Class Ic: Flecainide	4	318	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Class Ic: Propafenone	5	1098	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.48, 3.37]
2.5 Class I others: aprindine, bidisomide, pilsicainide	3	1383	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.94 [0.62, 6.02]
2.6 Class II: Beta-blockers	2	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.39, 1.47]
2.7 Class III: Amiodarone	4	673	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.49 [0.69, 3.20]
2.8 Class III: Azimilide	5	3114	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.74 [0.99, 3.06]
2.9 Class III: Dofetilide	3	1183	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.72, 1.45]
2.10 Class III: Dronedarone	3	6071	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.66, 1.08]
2.11 Class III: Sotalol	12	3002	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.14 [1.40, 3.25]
3 Quinidine: older and recent studies	7	1676	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.26 [0.93, 5.45]
3.1 Older studies, higher dose	5	442	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.17 [0.99, 10.14]
3.2 More recent studies, lower dose	2	1234	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.37, 5.51]
4 Quinidine: older and recent studies - ITT Worst case: missing patients counted as events	7	1676	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.29 [1.05, 5.01]
4.1 Older studies, higher dose	5	442	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.91 [1.12, 7.56]
4.2 More recent studies, lower dose	2	1234	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.37, 5.51]
5 Class I antiarrhythmics	18	4427	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.84 [0.95, 3.57]
5.1 Class Ia	8	1797	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.39 [1.03, 5.59]
5.2 Class Ib	2	1321	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.89 [0.59, 6.03]

5.3 Class Ic	9	1309	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.01, 1.88]
6 Class I antiarrhythmics - ITT Worst case: missing patients counted as events	18	4427	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.94 [1.15, 3.25]
6.1 Class Ia	8	1797	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.45 [1.18, 5.08]
6.2 Class Ib	2	1321	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.89 [0.59, 6.03]
6.3 Class Ic	9	1309	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [0.50, 3.42]
7 Class III antiarrhythmics	24	14043	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.85, 1.24]
7.1 Amiodarone	4	673	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.96 [0.68, 5.67]
7.2 Azimilide	5	3114	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.18 [0.98, 4.89]
7.3 Dofetilide	3	1183	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.68, 1.41]
7.4 Dronedarone	3	6071	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.67, 1.09]
7.5 Sotalol	12	3002	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.47 [1.21, 5.05]
8 Class III antiarrhythmics - ITT Worst case: missing patients counted as events	24	14043	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.95, 1.33]
8.1 Amiodarone	4	673	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.49 [0.69, 3.20]
8.2 Azimilide	5	3114	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.74 [0.99, 3.06]
8.3 Dofetilide	3	1183	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.72, 1.45]
8.4 Dronedarone	3	6071	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.67, 1.09]
8.5 Sotalol	12	3002	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.27 [1.45, 3.56]
9 Comparing antiarrhythmic drugs	28		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 Disopyramide vs other Class I drugs	2	113	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.05, 4.52]
9.2 Quinidine vs Flecainide	2	269	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Quinidine vs other Class I drugs	4	526	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.14, 7.46]
9.4 Quinidine vs Sotalol	6	1978	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.34, 1.46]
9.5 Flecainide vs Propafenone	2	297	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.96]
9.6 Amiodarone vs Class I drugs	5	643	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.59 [0.31, 1.11]
9.7 Amiodarone vs Dronedarone	1	504	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.32 [0.52, 10.32]
9.8 Amiodarone vs Sotalol	5	1113	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.77 [0.47, 1.25]
9.9 Sotalol vs Class I drugs other than quinidine	4	494	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.44, 1.99]
9.10 Sotalol vs Dofetilide	1	429	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.26 [0.00, 24.03]
9.11 Sotalol vs Other Beta-blockers	2	263	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.12 Class III vs Class I drugs	13	2875	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.49, 1.26]
10 Subgroup analysis: Persistent atrial fibrillation	20		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
10.1 Class Ia: Quinidine	5	877	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.11 [0.84, 5.32]
10.2 All class Ia antiarrhythmics	6	998	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.27 [0.94, 5.49]
10.3 All class I antiarrhythmics	8	1133	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.29 [0.96, 5.48]
10.4 Class II antiarrhythmics	2	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.75 [0.39, 19.56]
10.5 Class III: Sotalol	6	1687	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.30 [1.10, 4.80]
10.6 All class III antiarrhythmics	11	3485	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.84, 1.61]

11 Sensitivity analysis: Best quality studies	12		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
11.1 Class Ia: Quinidine	2	1234	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.37, 5.51]
11.2 All class I antiarrhythmics	5	1503	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.27, 3.63]
11.3 Class II antiarrhythmics	2	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.75 [0.39, 19.56]
11.4 Class III: Sotalol	4	1686	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.78 [1.00, 7.69]
11.5 Class III: Azimilide	1	447	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.52 [1.05, 53.77]
11.6 All class III antiarrhythmics	7	6919	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.75, 1.13]
12 Sensitivity analysis: Studies > 200 patients	17		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
12.1 Class Ia: Quinidine	2	1234	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.37, 5.51]
12.2 All class I antiarrhythmics	4	2984	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.68 [0.69, 4.05]
12.3 Class II antiarrhythmics	1	394	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.47 [0.77, 72.18]
12.4 Class III: Sotalol	7	2543	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.97 [1.03, 3.75]
12.5 Class III: Azimilide	4	2704	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.06 [0.85, 4.99]
12.6 All class III antiarrhythmics	14	12294	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.82, 1.20]

Comparison 2. Withdrawals due to adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Individual antiarrhythmics	36	16532	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.69 [1.51, 1.88]
1.1 Class Ia: Quinidine	7	1676	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.86, 1.49]
1.2 Class Ia: Disopyramide	2	146	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.85 [1.13, 13.18]
1.3 Class Ic: Flecainide	3	149	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.14 [1.94, 42.94]
1.4 Class Ic: Propafenone	5	1098	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.69 [1.09, 2.62]
1.5 Class I others: aprindine, pilsicainide	2	156	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.18, 4.48]
1.6 Class II: Beta-blockers	2	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [1.57, 7.25]
1.7 Class III: Amiodarone	3	274	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.55 [2.24, 13.72]
1.8 Class III: Azimilide	5	3114	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.35 [1.72, 3.20]
1.9 Class III: Dofetilide	2	677	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.68 [0.79, 3.59]
1.10 Class III: Dronedarone	3	6071	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.64 [1.38, 1.94]
1.11 Class III: Sotalol	11	2609	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.61 [1.25, 2.06]
2 Quinidine: older and recent studies	7	1676	Odds Ratio (M-H, Random, 95% CI)	1.90 [0.90, 4.02]
2.1 Older studies, higher dose	5	442	Odds Ratio (M-H, Random, 95% CI)	3.62 [1.71, 7.65]
2.2 More recent studies, lower dose	2	1234	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.52, 1.36]
3 Class I antiarrhythmics	17	3200	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.34 [1.07, 1.68]
3.1 Class Ia	8	1797	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.90, 1.54]
3.2 Class Ib	1	94	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.11, 3.95]
3.3 Class Ic	9	1309	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.93 [1.27, 2.93]
4 Sotalol: heterogeneity study	11	2609	Odds Ratio (M-H, Random, 95% CI)	2.25 [1.28, 3.94]
4.1 PAFAC and SOPAT trials	2	986	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.68, 1.33]
4.2 Rest of studies	9	1623	Odds Ratio (M-H, Random, 95% CI)	3.31 [2.08, 5.25]
5 Class III antiarrhythmics	22	12745	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.77 [1.56, 2.00]

5.1 Amiodarone	3	274	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.55 [2.24, 13.72]
5.2 Azimilide	5	3114	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.35 [1.72, 3.20]
5.3 Dofetilide	2	677	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.68 [0.79, 3.59]
5.4 Dronedarone	3	6071	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.64 [1.38, 1.94]
5.5 Sotalol	11	2609	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.61 [1.25, 2.06]
6 Comparing antiarrhythmic drugs	27		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 Disopyramide vs other Class I drugs	2	113	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.14, 1.03]
6.2 Quinidine vs Flecainide	2	269	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.04 [1.14, 3.64]
6.3 Quinidine vs other Class I drugs	4	526	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.25 [1.45, 3.51]
6.4 Quinidine vs Sotalol	6	1978	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.89, 1.40]
6.5 Flecainide vs Propafenone	2	297	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.32, 1.43]
6.6 Amiodarone vs Class I drugs	5	652	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.36, 0.84]
6.7 Amiodarone vs Dronedarone	1	504	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [0.89, 2.35]
6.8 Amiodarone vs Sotalol	4	618	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.73, 1.95]
6.9 Sotalol vs Class I drugs other than quinidine	4	567	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.28, 0.72]
6.10 Sotalol vs Dofetilide	1	429	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.67 [1.24, 5.76]
6.11 Sotalol vs Other Beta-blockers	2	263	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.86 [1.15, 7.11]
6.12 Class III vs Class I drugs	13	2975	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.65, 0.96]
7 Subgroup analysis: Persistent atrial fibrillation	18		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Class Ia: Quinidine	5	877	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [1.26, 2.79]
7.2 All class I antiarrhythmics	8	1133	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.13 [1.48, 3.08]
7.3 Class II antiarrhythmics	2	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [1.57, 7.25]
7.4 Class III: Sotalol	5	1294	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.86 [1.30, 2.66]
7.5 All class III antiarrhythmics	9	2319	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.03 [1.50, 2.75]
8 Sensitivity analysis: Best quality studies	11		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 Class Ia: Quinidine	2	1234	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.59, 1.10]
8.2 All class I antiarrhythmics	5	1503	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.70, 1.26]
8.3 Class II antiarrhythmics	2	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.38 [1.57, 7.25]
8.4 Class III: Sotalol	4	1686	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.33 [1.00, 1.75]
8.5 All class III antiarrhythmics	6	6413	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.55 [1.33, 1.81]
9 Sensitivity analysis: Studies > 200 patients	14		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 Class Ia: Quinidine	2	1234	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.59, 1.10]
9.2 All class I antiarrhythmics	3	1757	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.70, 1.20]
9.3 Class II antiarrhythmics	1	394	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.16 [1.43, 6.99]
9.4 Class III: Sotalol	5	1900	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [1.11, 1.89]
9.5 All class III antiarrhythmics	12	11128	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.64 [1.44, 1.87]

Comparison 3. Pro-arrhythmia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Individual antiarrhythmics	37	17695	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.23 [2.68, 3.90]
1.1 Class Ia: Quinidine	7	1676	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.10 [1.02, 4.33]
1.2 Class Ia: Disopyramide	2	146	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Class Ic: Flecainide	3	149	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.97 [1.67, 21.34]
1.4 Class Ic: Propafenone	5	1098	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [0.33, 7.02]
1.5 Class I others: aprindine, pilsicainide	2	156	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 Class II: Beta-blockers	2	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.92 [3.01, 20.82]
1.7 Class III: Amiodarone	4	673	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.65 [0.88, 8.00]
1.8 Class III: Azimilide	5	3114	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.82 [3.69, 9.19]
1.9 Class III: Dofetilide	3	1183	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.79 [1.54, 9.33]
1.10 Class III: Dronedarone	3	6071	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.48 [1.85, 3.32]
1.11 Class III: Sotalol	11	2867	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.26 [2.13, 4.98]
2 Quinidine: older and recent studies	7	1676	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.10 [1.02, 4.33]
2.1 Older studies, higher dose	5	442	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.56 [1.20, 17.33]
2.2 More recent studies, lower dose	2	1234	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [0.64, 3.60]
3 Class I antiarrhythmics	17	3200	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.46 [1.38, 4.41]
3.1 Class Ia	8	1797	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.06 [1.00, 4.26]
3.2 Class Ib	1	94	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Class Ic	9	1309	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.41 [1.28, 9.09]
4 Sotalol: heterogeneity study	11	2867	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.26 [2.13, 4.98]
4.1 PAFAC and SOPAT trials	2	986	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.56, 3.60]
4.2 Rest of studies	9	1881	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.05 [2.52, 6.51]
5 Class III antiarrhythmics	23	13908	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.21 [2.62, 3.93]
5.1 Amiodarone	4	673	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.65 [0.88, 8.00]
5.2 Azimilide	5	3114	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.82 [3.69, 9.19]
5.3 Dofetilide	3	1183	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.79 [1.54, 9.33]
5.4 Dronedarone	3	6071	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.48 [1.85, 3.32]
5.5 Sotalol	11	2867	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.26 [2.13, 4.98]
6 Comparing antiarrhythmic drugs	24		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 Disopyramide vs other Class I drugs	2	113	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.43 [0.04, 4.25]
6.2 Quinidine vs Flecainide	2	269	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.60 [0.64, 3.96]
6.3 Quinidine vs other Class I drugs	4	526	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.59 [0.71, 3.56]
6.4 Quinidine vs Sotalol	6	1978	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.60, 1.68]
6.5 Flecainide vs Propafenone	2	297	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.43 [0.10, 1.93]
6.6 Amiodarone vs Class I drugs	3	475	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.13, 0.59]
6.7 Amiodarone vs Dronedarone	1	504	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.91 [0.38, 9.56]
6.8 Amiodarone vs Sotalol	3	943	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.30, 1.20]

6.9 Sotalol vs Class I drugs other than quinidine	4	567	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.77 [0.44, 1.34]
6.10 Sotalol vs Dofetilide	1	429	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.19, 3.90]
6.11 Sotalol vs Other Beta-blockers	1	128	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.35 [0.30, 6.16]
6.12 Class III vs Class I drugs	12	2899	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.78 [0.54, 1.13]
7 Subgroup analysis: Persistent atrial fibrillation	20		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Class Ia: Quinidine	5	877	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.79 [1.08, 7.21]
7.2 All class I antiarrhythmics	8	1133	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.48 [1.50, 8.08]
7.3 Class II antiarrhythmics	2	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.92 [3.01, 20.82]
7.4 Class III: Sotalol	6	1687	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.61 [2.17, 6.02]
7.5 All class III antiarrhythmics	11	3485	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.59 [2.33, 5.53]
8 Sensitivity analysis: Best quality studies	12		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 Class Ia: Quinidine	2	1234	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [0.64, 3.60]
8.2 All class I antiarrhythmics	5	1503	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.08 [1.07, 4.02]
8.3 Class II antiarrhythmics	2	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.92 [3.01, 20.82]
8.4 Class III: Sotalol	4	1686	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.78 [1.71, 4.53]
8.5 All class III antiarrhythmics	7	6919	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.85 [2.20, 3.70]
9 Sensitivity analysis: Studies > 200 patients	16		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
9.1 Class Ia: Quinidine	2	1234	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [0.64, 3.60]
9.2 All class I antiarrhythmics	3	1757	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [0.64, 3.60]
9.3 Class II antiarrhythmics	1	394	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.96 [2.84, 22.30]
9.4 Class III: Sotalol	6	2293	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.74 [1.75, 4.30]
9.5 All class III antiarrhythmics	14	12294	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.85 [2.30, 3.55]

Comparison 4. Atrial fibrillation recurrence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Individual antiarrhythmics	37	12865	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.48 [0.45, 0.53]
1.1 Class Ia: Quinidine	7	1624	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.40, 0.65]
1.2 Class Ia: Disopyramide	2	146	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.27, 1.01]
1.3 Class Ic: Flecainide	3	149	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.31 [0.16, 0.60]
1.4 Class Ic: Propafenone	5	1098	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.28, 0.48]
1.5 Class I others: aprindine, bidisomide, pilsicainide	3	1383	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.60, 1.07]
1.6 Class II: Beta-blockers	2	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.44, 0.88]
1.7 Class III: Amiodarone	4	673	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.19 [0.14, 0.27]
1.8 Class III: Azimilide	4	1602	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.55, 0.90]
1.9 Class III: Dofetilide	3	1183	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.23, 0.39]
1.10 Class III: Dronedarone	2	1443	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.59 [0.46, 0.75]
1.11 Class III: Sotalol	12	3002	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.43, 0.60]

2 Quinidine: old and recent studies	7	1624	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.40, 0.65]
2.1 Older studies, higher dose	5	390	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.42 [0.27, 0.65]
2.2 More recent studies, lower dose	2	1234	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.41, 0.73]
3 Class I antiarrhythmics	18	4375	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.44, 0.58]
3.1 Class Ia	8	1745	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.40, 0.64]
3.2 Class Ib	2	1321	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.63, 1.13]
3.3 Class Ic	9	1309	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.28, 0.45]
4 Class III antiarrhythmics	22	7903	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.42, 0.51]
4.1 Amiodarone	4	673	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.19 [0.14, 0.27]
4.2 Azimilide	4	1602	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.55, 0.90]
4.3 Dofetilide	3	1183	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.23, 0.39]
4.4 Dronedarone	2	1443	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.59 [0.46, 0.75]
4.5 Sotalol	12	3002	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.43, 0.60]
5 Comparing antiarrhythmic drugs	28		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 Disopyramide vs other Class I drugs	2	113	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.36, 1.60]
5.2 Quinidine vs Flecainide	2	269	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.38 [0.79, 2.41]
5.3 Quinidine vs other Class I drugs	4	526	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.90, 1.87]
5.4 Quinidine vs Sotalol	6	1978	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.76, 1.11]
5.5 Flecainide vs Propafenone	2	297	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.54, 1.40]
5.6 Amiodarone vs Class I drugs	5	643	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.26, 0.50]
5.7 Amiodarone vs Dronedarone	1	504	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.31, 0.63]
5.8 Amiodarone vs Sotalol	5	1113	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.43 [0.34, 0.54]
5.9 Sotalol vs Class I drugs other than quinidine	4	494	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.67, 1.45]
5.10 Sotalol vs Dofetilide	1	429	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.38 [0.88, 2.16]
5.11 Sotalol vs Other Beta-blockers	2	263	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.64, 1.90]
5.12 Class III vs Class I drugs	13	2875	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.76, 1.04]
6 Subgroup analysis: Persistent atrial fibrillation	20		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 Class Ia: Quinidine	5	825	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.43 [0.31, 0.60]
6.2 All class I antiarrhythmics	8	1081	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.33, 0.59]
6.3 Class II antiarrhythmics	2	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.44, 0.88]
6.4 Class III: Sotalol	6	1687	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.37, 0.58]
6.5 All class III antiarrhythmics	11	3485	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.30, 0.41]
7 Sensitivity analysis: Best quality studies	11		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7.1 Class Ia: Quinidine	2	1234	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.41, 0.73]
7.2 All class I antiarrhythmics	5	1503	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.56 [0.44, 0.72]
7.3 Class II antiarrhythmics	2	562	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.44, 0.88]
7.4 Class III: Sotalol	4	1686	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.43, 0.70]
7.5 All class III antiarrhythmics	6	2291	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.39 [0.32, 0.48]

8 Sensitivity analysis: Studies > 200 patients	15		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
8.1 Class Ia: Quinidine	2	1234	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.55 [0.41, 0.73]
8.2 All class I antiarrhythmics	4	2984	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.59 [0.49, 0.72]
8.3 Class II antiarrhythmics	1	394	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.49, 1.13]
8.4 Class III: Sotalol	6	2293	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.42, 0.62]
8.5 All class III antiarrhythmics	12	6154	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.49 [0.43, 0.55]

Analysis 1.1. Comparison 1 All-cause mortality, Outcome 1 Individual antiarrhythmics.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 1 All-cause mortality

Outcome: 1 Individual antiarrhythmics

Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia: Quinidine				
Byrne-Quinn 1970	1/32	0/42		10.10 [0.19, 527.80]
Hillestad 1971	1/48	0/52		8.03 [0.16, 406.02]
Lloyd 1984	2/28	0/25		6.89 [0.42, 113.67]
PAFAC 2004	9/377	2/88		1.05 [0.23, 4.83]
Sodermark 1975	6/110	2/75		1.95 [0.46, 8.24]
SOPAT 2004	2/518	0/251		4.42 [0.23, 85.12]
Steinbeck 1988	0/15	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1128**	**548**		**2.26 [0.93, 5.45]**
Total events: 21 (Antiarrhythmic), 4 (Control)				
Heterogeneity: Chi?? = 2.76, df = 5 (P = 0.74); I?? =0.0%				
Test for overall effect: Z = 1.81 (P = 0.071)				
2 Class Ia: Disopyramide				
Karlson 1998	2/46	0/46		7.56 [0.47, 122.66]
Lloyd 1984	0/29	0/25		0.0 [0.0, 0.0]
Subtotal (95% CI)	**75**	**71**		**7.56 [0.47, 122.66]**
Total events: 2 (Antiarrhythmic), 0 (Control)				
Heterogeneity: Chi?? = 0.0, df = 0 (P = 1.00); I?? =0.0%				
Test for overall effect: Z = 1.42 (P = 0.16)				
3 Class Ic: Flecainide				
Carunchio 1995	0/20	0/26		0.0 [0.0, 0.0]

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Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Steinbeck 1988	0/15	0/15		0.0 [0.0, 0.0]
Van Gelder 1989	0/36	0/37		0.0 [0.0, 0.0]
Subtotal (95% CI)	**71**	**78**		**0.0 [0.0, 0.0]**
Total events: 0 (Antiarrhythmic), 0 (Control)				
Heterogeneity: Chi?? = 0.0, df = 0 (P<0.00001); I?? =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
4 Class Ic: Propafenone				
Bellandi 2001	0/102	0/92		0.0 [0.0, 0.0]
Dogan 2004	0/58	1/52		0.12 [0.00, 6.11]
Kochiadakis 2004b	0/86	0/83		0.0 [0.0, 0.0]
RAFT 2003	0/397	0/126		0.0 [0.0, 0.0]
Stroobandt 1997	0/77	1/25		0.02 [0.00, 1.61]
Subtotal (95% CI)	**720**	**378**		**0.05 [0.00, 1.02]**
Total events: 0 (Antiarrhythmic), 2 (Control)				
Heterogeneity: Chi?? = 0.41, df = 1 (P = 0.52); I?? =0.0%				
Test for overall effect: Z = 1.95 (P = 0.052)				
5 Class I others: aprindine, bidisomide, pilsicainide				
AFIB 1997	9/734	3/493		1.89 [0.59, 6.03]
Okishige 2000	1/52	0/10		3.29 [0.02, 679.40]
SMART 2002	0/47	0/47		0.0 [0.0, 0.0]
Subtotal (95% CI)	**833**	**550**		**1.94 [0.62, 6.02]**
Total events: 10 (Antiarrhythmic), 3 (Control)				
Heterogeneity: Chi?? = 0.04, df = 1 (P = 0.84); I?? =0.0%				
Test for overall effect: Z = 1.15 (P = 0.25)				
6 Class II: Beta-blockers				
Kuhlkamp 2000	3/197	0/197		7.47 [0.77, 72.18]
Nergardh 2007	0/83	1/85		0.14 [0.00, 6.98]
Subtotal (95% CI)	**280**	**282**		**2.75 [0.39, 19.56]**
Total events: 3 (Antiarrhythmic), 1 (Control)				
Heterogeneity: Chi?? = 2.98, df = 1 (P = 0.08); I?? =66%				
Test for overall effect: Z = 1.01 (P = 0.31)				
7 Class III: Amiodarone				
Channer 2004	0/61	0/38		0.0 [0.0, 0.0]
GEFACA 2001	0/35	0/15		0.0 [0.0, 0.0]
Kochiadakis 2000	0/65	0/60		0.0 [0.0, 0.0]
SAFE-T 2005	13/267	3/132		1.96 [0.68, 5.67]
Subtotal (95% CI)	**428**	**245**		**1.96 [0.68, 5.67]**

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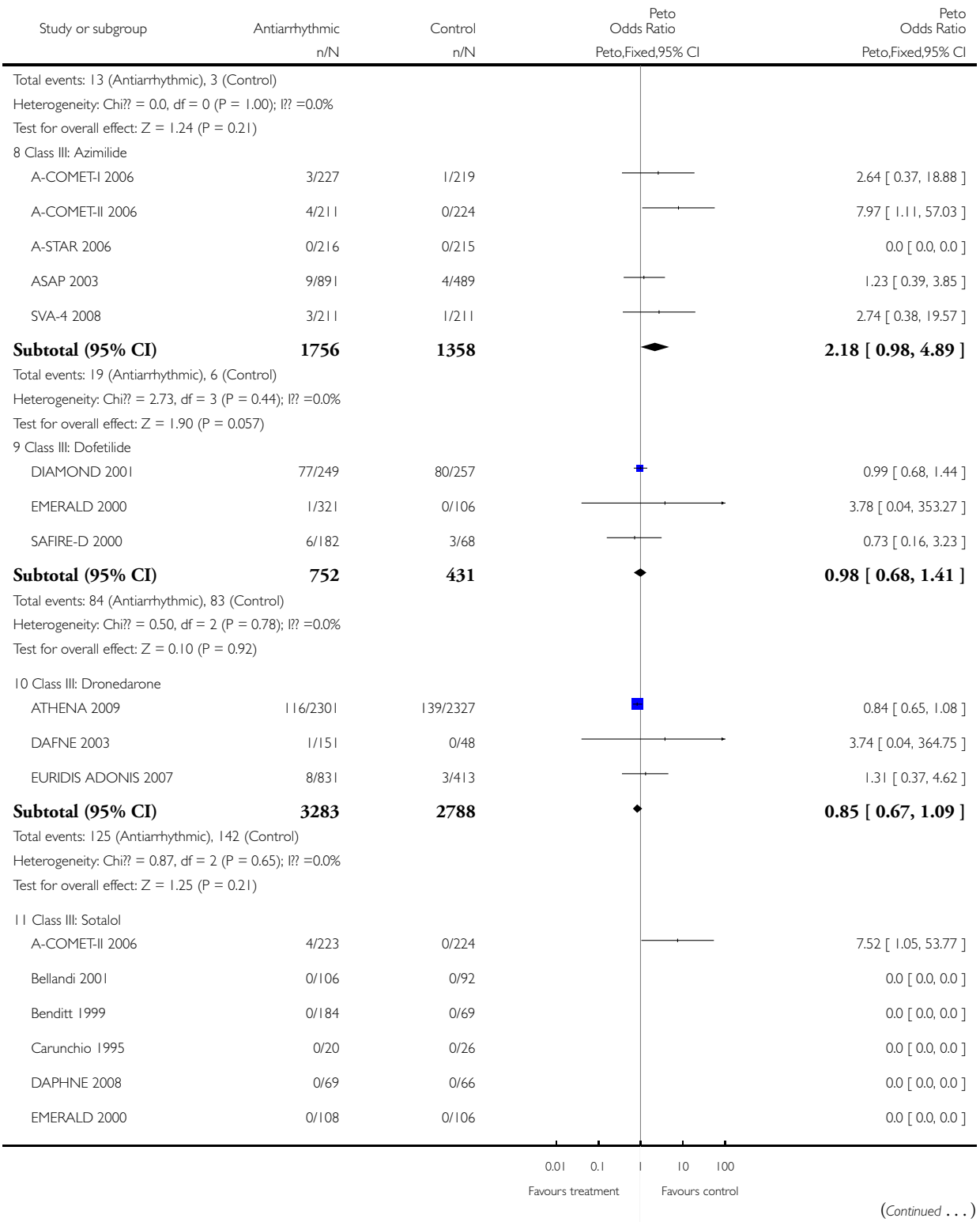

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Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Kochiadakis 2004b	0/85	0/83		0.0 [0.0, 0.0]
PAFAC 2004	13/383	2/88		1.44 [0.38, 5.37]
Plewan 2001	0/64	0/64		0.0 [0.0, 0.0]
SAFE-T 2005	15/261	3/132		2.21 [0.81, 6.01]
Singh 1991	0/24	0/10		0.0 [0.0, 0.0]
SOPAT 2004	2/264	0/251		7.06 [0.44, 113.29]
Subtotal (95% CI)	**1791**	**1211**		**2.47 [1.21, 5.05]**
Total events: 34 (Antiarrhythmic), 5 (Control)				
Heterogeneity: Chi?? = 2.48, df = 3 (P = 0.48); I?? =0.0%				
Test for overall effect: Z = 2.49 (P = 0.013)				
Total (95% CI)	**11117**	**7940**		**1.09 [0.91, 1.30]**
Total events: 311 (Antiarrhythmic), 249 (Control)				
Heterogeneity: Chi?? = 36.22, df = 27 (P = 0.11); I?? =25%				
Test for overall effect: Z = 0.92 (P = 0.36)				
Test for subgroup differences: Chi?? = 23.46, df = 9 (P = 0.01), I?? =62%				

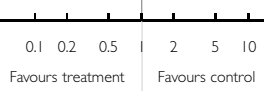
Analysis 1.2. Comparison 1 All-cause mortality, Outcome 2 Individual antiarrhythmics - ITT Worst case: missing patients counted as events.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 1 All-cause mortality

Outcome: 2 Individual antiarrhythmics - ITT Worst case: missing patients counted as events

Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia: Quinidine				
Byrne-Quinn 1970	3/32	2/42		2.06 [0.33, 12.71]
Hillestad 1971	1/48	0/52		8.03 [0.16, 406.02]
Lloyd 1984	4/28	0/25		7.45 [0.99, 56.32]
PAFAC 2004	9/377	2/88		1.05 [0.23, 4.83]
Sodermark 1975	6/110	2/75		1.95 [0.46, 8.24]
SOPAT 2004	2/518	0/251		4.42 [0.23, 85.12]
Steinbeck 1988	0/15	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1128**	**548**		**2.29 [1.05, 5.01]**
Total events: 25 (Antiarrhythmic), 6 (Control)				
Heterogeneity: Chi?? = 2.95, df = 5 (P = 0.71); I?? =0.0%				
Test for overall effect: Z = 2.08 (P = 0.037)				
2 Class Ia: Disopyramide				
Karlson 1998	2/46	0/46		7.56 [0.47, 122.66]
Lloyd 1984	3/29	0/25		6.92 [0.68, 70.01]
Subtotal (95% CI)	**75**	**71**		**7.18 [1.21, 42.55]**
Total events: 5 (Antiarrhythmic), 0 (Control)				
Heterogeneity: Chi?? = 0.00, df = 1 (P = 0.96); I?? =0.0%				
Test for overall effect: Z = 2.17 (P = 0.030)				
3 Class Ic: Flecainide				
Carunchio 1995	0/20	0/26		0.0 [0.0, 0.0]
Kochiadakis 2004b	0/86	0/83		0.0 [0.0, 0.0]
Steinbeck 1988	0/15	0/15		0.0 [0.0, 0.0]
Van Gelder 1989	0/36	0/37		0.0 [0.0, 0.0]
Subtotal (95% CI)	**157**	**161**		**0.0 [0.0, 0.0]**
Total events: 0 (Antiarrhythmic), 0 (Control)				
Heterogeneity: Chi?? = 0.0, df = 0 (P<0.00001); I?? =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
4 Class Ic: Propafenone				



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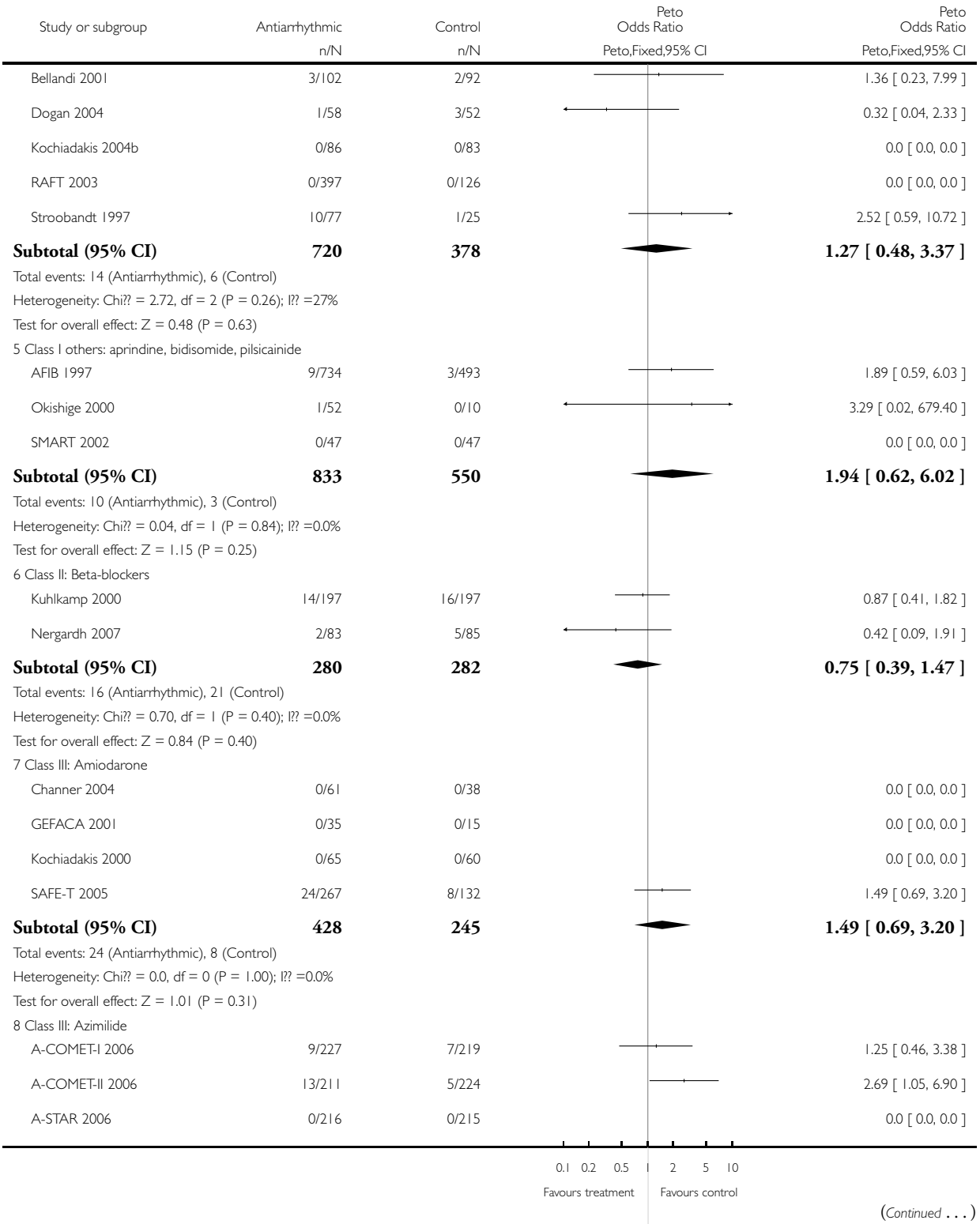

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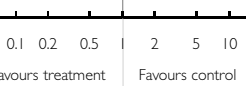
Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
ASAP 2003	9/891	4/489		1.23 [0.39, 3.85]
SVA-4 2008	3/211	1/211		2.74 [0.38, 19.57]
Subtotal (95% CI)	**1756**	**1358**		**1.74 [0.99, 3.06]**
Total events: 34 (Antiarrhythmic), 17 (Control)				
Heterogeneity: Chi?? = 1.80, df = 3 (P = 0.61); I?? =0.0%				
Test for overall effect: Z = 1.93 (P = 0.053)				
9 Class III: Dofetilide				
DIAMOND 2001	77/249	80/257		0.99 [0.68, 1.44]
EMERALD 2000	12/321	2/106		1.79 [0.52, 6.13]
SAFIRE-D 2000	6/182	3/68		0.73 [0.16, 3.23]
Subtotal (95% CI)	**752**	**431**		**1.02 [0.72, 1.45]**
Total events: 95 (Antiarrhythmic), 85 (Control)				
Heterogeneity: Chi?? = 1.02, df = 2 (P = 0.60); I?? =0.0%				
Test for overall effect: Z = 0.12 (P = 0.91)				
10 Class III: Dronedarone				
ATHENA 2009	116/2301	141/2327		0.82 [0.64, 1.06]
DAFNE 2003	1/151	0/48		3.74 [0.04, 364.75]
EURIDIS ADONIS 2007	10/831	4/413		1.23 [0.40, 3.78]
Subtotal (95% CI)	**3283**	**2788**		**0.84 [0.66, 1.08]**
Total events: 127 (Antiarrhythmic), 145 (Control)				
Heterogeneity: Chi?? = 0.89, df = 2 (P = 0.64); I?? =0.0%				
Test for overall effect: Z = 1.36 (P = 0.17)				
11 Class III: Sotalol				
A-COMET-II 2006	11/223	5/224		2.18 [0.81, 5.92]
Bellandi 2001	6/106	2/92		2.45 [0.59, 10.07]
Benditt 1999	12/184	3/69		1.47 [0.46, 4.75]
Carunchio 1995	0/20	0/26		0.0 [0.0, 0.0]
DAPHNE 2008	3/69	3/66		0.95 [0.19, 4.88]
EMERALD 2000	5/108	2/106		2.37 [0.53, 10.65]
Kochiadakis 2004b	0/85	0/83		0.0 [0.0, 0.0]
PAFAC 2004	13/383	2/88		1.44 [0.38, 5.37]
Plewan 2001	3/64	2/64		1.51 [0.25, 8.97]
SAFE-T 2005	27/261	3/132		3.13 [1.43, 6.88]
Singh 1991	0/24	0/10		0.0 [0.0, 0.0]
SOPAT 2004	2/264	0/251		7.06 [0.44, 113.29]



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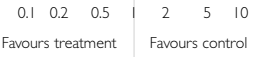
Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Subtotal (95% CI)	**1791**	**1211**		**2.14 [1.40, 3.25]**
Total events: 82 (Antiarrhythmic), 22 (Control)				
Heterogeneity: Chi?? = 3.49, df = 8 (P = 0.90); I?? =0.0%				
Test for overall effect: Z = 3.55 (P = 0.00039)				
Total (95% CI)	**11203**	**8023**		**1.16 [0.99, 1.36]**
Total events: 432 (Antiarrhythmic), 313 (Control)				
Heterogeneity: Chi?? = 40.56, df = 34 (P = 0.20); I?? =16%				
Test for overall effect: Z = 1.88 (P = 0.059)				
Test for subgroup differences: Chi?? = 26.94, df = 9 (P = 0.00), I?? =67%				



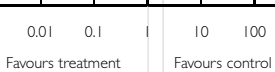
Analysis 1.3. Comparison 1 All-cause mortality, Outcome 3 Quinidine: older and recent studies.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 1 All-cause mortality

Outcome: 3 Quinidine: older and recent studies

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Older studies, higher dose				
Byrne-Quinn 1970	1/32	0/42		10.10 [0.19, 527.80]
Hillestad 1971	1/48	0/52		8.03 [0.16, 406.02]
Lloyd 1984	2/28	0/25		6.89 [0.42, 113.67]
Sodermark 1975	6/110	2/75		1.95 [0.46, 8.24]
Steinbeck 1988	0/15	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**233**	**209**		**3.17 [0.99, 10.14]**
Total events: 10 (Treatment), 2 (Control)				
Heterogeneity: Chi?? = 1.27, df = 3 (P = 0.74); I?? =0.0%				
Test for overall effect: Z = 1.94 (P = 0.052)				
2 More recent studies, lower dose				
PAFAC 2004	9/377	2/88		1.05 [0.23, 4.83]



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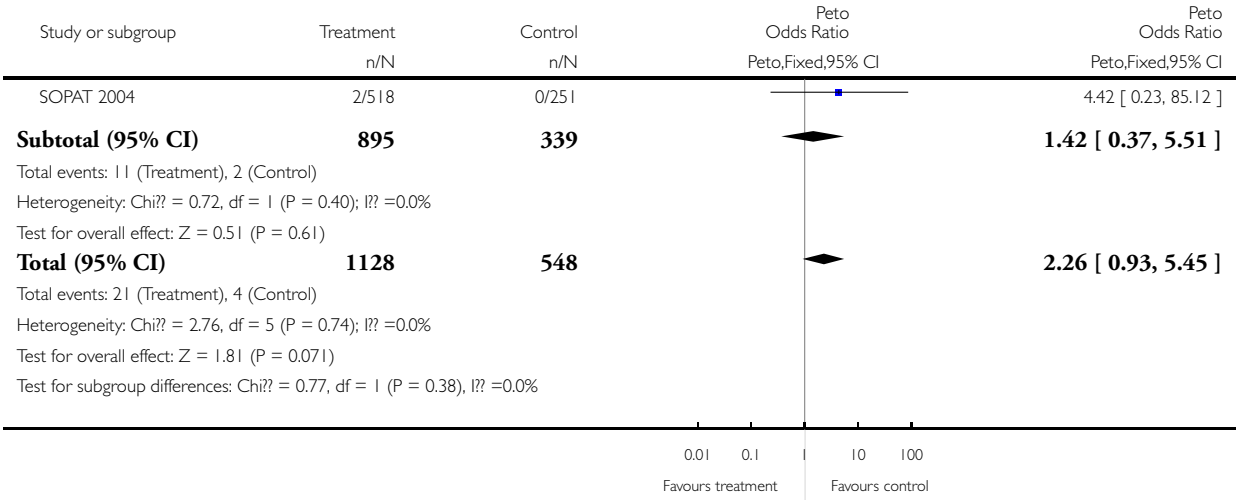
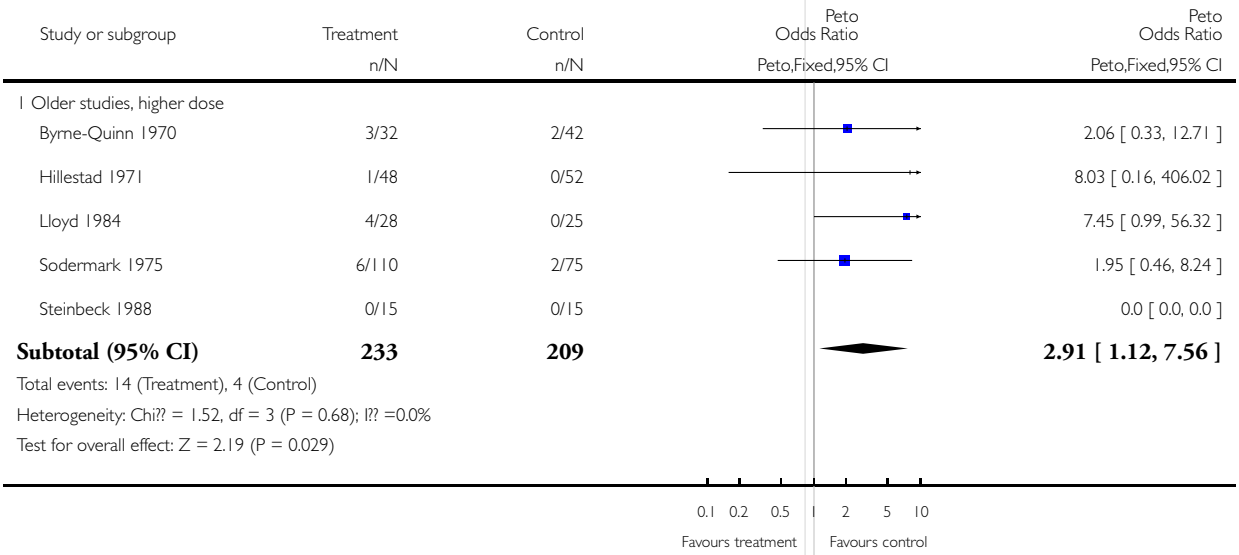


Analysis 1.4. Comparison 1 All-cause mortality, Outcome 4 Quinidine: older and recent studies - ITT Worst case: missing patients counted as events.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 1 All-cause mortality

Outcome: 4 Quinidine: older and recent studies - ITT Worst case: missing patients counted as events



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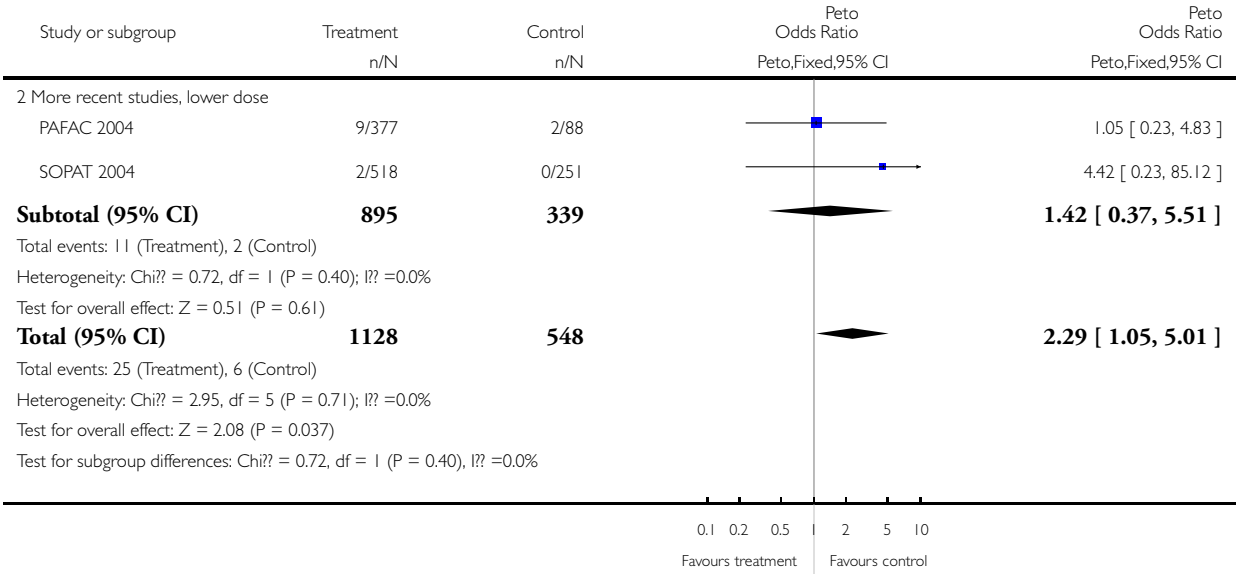
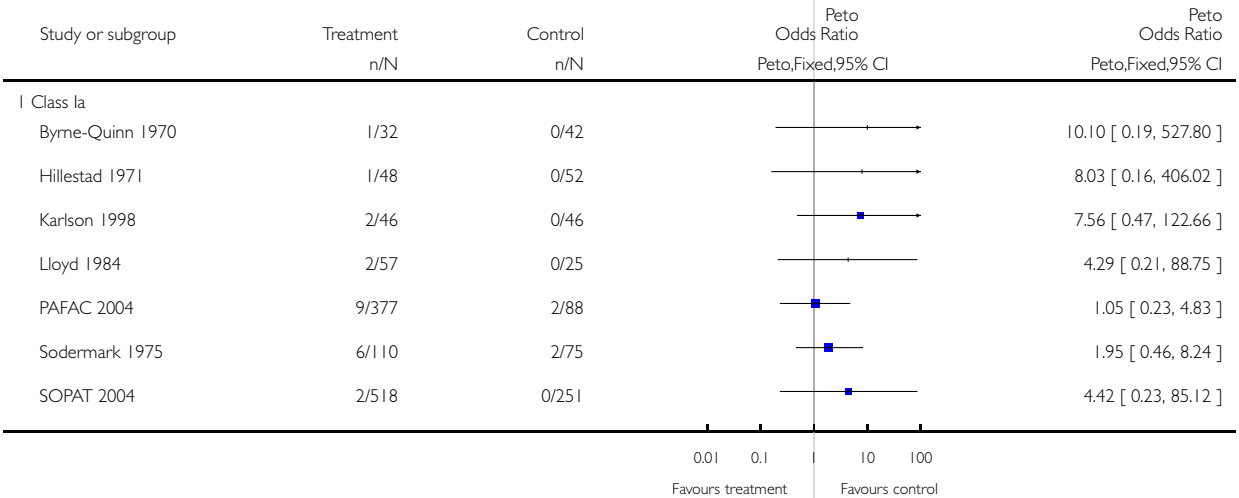


Analysis 1.5. Comparison 1 All-cause mortality, Outcome 5 Class I antiarrhythmics.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 1 All-cause mortality

Outcome: 5 Class I antiarrhythmics



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Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Steinbeck 1988	0/15	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1203**	**594**		**2.39 [1.03, 5.59]**
Total events: 23 (Treatment), 4 (Control)				
Heterogeneity: Chi?? = 3.03, df = 6 (P = 0.80); I?? =0.0%				
Test for overall effect: Z = 2.02 (P = 0.043)				
2 Class Ib				
AFIB 1997	9/734	3/493		1.89 [0.59, 6.03]
SMART 2002	0/47	0/47		0.0 [0.0, 0.0]
Subtotal (95% CI)	**781**	**540**		**1.89 [0.59, 6.03]**
Total events: 9 (Treatment), 3 (Control)				
Heterogeneity: Chi?? = 0.0, df = 0 (P = 1.00); I?? =0.0%				
Test for overall effect: Z = 1.08 (P = 0.28)				
3 Class Ic				
Bellandi 2001	0/102	0/92		0.0 [0.0, 0.0]
Carunchio 1995	0/20	0/26		0.0 [0.0, 0.0]
Dogan 2004	0/58	1/52		0.12 [0.00, 6.11]
Kochiadakis 2004b	0/86	0/83		0.0 [0.0, 0.0]
Okishige 2000	1/52	0/10		3.29 [0.02, 679.40]
RAFT 2003	0/397	0/126		0.0 [0.0, 0.0]
Steinbeck 1988	0/15	0/15		0.0 [0.0, 0.0]
Stroobandt 1997	0/77	1/25		0.02 [0.00, 1.61]
Van Gelder 1989	0/36	0/37		0.0 [0.0, 0.0]
Subtotal (95% CI)	**843**	**466**		**0.14 [0.01, 1.88]**
Total events: 1 (Treatment), 2 (Control)				
Heterogeneity: Chi?? = 2.18, df = 2 (P = 0.34); I?? =8%				
Test for overall effect: Z = 1.49 (P = 0.14)				
Total (95% CI)	**2827**	**1600**		**1.84 [0.95, 3.57]**
Total events: 33 (Treatment), 9 (Control)				
Heterogeneity: Chi?? = 9.37, df = 10 (P = 0.50); I?? =0.0%				
Test for overall effect: Z = 1.81 (P = 0.070)				
Test for subgroup differences: Chi?? = 4.16, df = 2 (P = 0.13), I?? =52%				

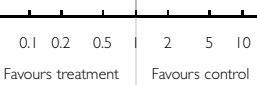
Analysis 1.6. Comparison 1 All-cause mortality, Outcome 6 Class I antiarrhythmics - ITT Worst case: missing patients counted as events.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 1 All-cause mortality

Outcome: 6 Class I antiarrhythmics - ITT Worst case: missing patients counted as events

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia				
Byrne-Quinn 1970	3/32	2/42		2.06 [0.33, 12.71]
Hillestad 1971	1/48	0/52		8.03 [0.16, 406.02]
Karlson 1998	2/46	0/46		7.56 [0.47, 122.66]
Lloyd 1984	7/57	0/25		4.73 [0.89, 25.18]
PAFAC 2004	9/377	2/88		1.05 [0.23, 4.83]
Sodermark 1975	6/110	2/75		1.95 [0.46, 8.24]
SOPAT 2004	2/518	0/251		4.42 [0.23, 85.12]
Steinbeck 1988	0/15	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1203**	**594**		**2.45 [1.18, 5.08]**
Total events: 30 (Treatment), 6 (Control)				
Heterogeneity: Chi?? = 3.04, df = 6 (P = 0.80); I?? =0.0%				
Test for overall effect: Z = 2.41 (P = 0.016)				
2 Class Ib				
AFIB 1997	9/734	3/493		1.89 [0.59, 6.03]
SMART 2002	0/47	0/47		0.0 [0.0, 0.0]
Subtotal (95% CI)	**781**	**540**		**1.89 [0.59, 6.03]**
Total events: 9 (Treatment), 3 (Control)				
Heterogeneity: Chi?? = 0.0, df = 0 (P = 1.00); I?? =0.0%				
Test for overall effect: Z = 1.08 (P = 0.28)				
3 Class Ic				
Bellandi 2001	3/102	2/92		1.36 [0.23, 7.99]
Carunchio 1995	0/20	0/26		0.0 [0.0, 0.0]
Dogan 2004	1/58	3/52		0.32 [0.04, 2.33]
Kochiadakis 2004b	0/86	0/83		0.0 [0.0, 0.0]
Okishige 2000	1/52	0/10		3.29 [0.02, 679.40]
RAFT 2003	0/397	0/126		0.0 [0.0, 0.0]
Steinbeck 1988	0/15	0/15		0.0 [0.0, 0.0]



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Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Stroobandt 1997	10/77	1/25		2.52 [0.59, 10.72]
Van Gelder 1989	0/36	0/37		0.0 [0.0, 0.0]
Subtotal (95% CI)	**843**	**466**		**1.31 [0.50, 3.42]**
Total events: 15 (Treatment), 6 (Control)				
Heterogeneity: Chi?? = 2.84, df = 3 (P = 0.42); I?? =0.0%				
Test for overall effect: Z = 0.55 (P = 0.58)				
Total (95% CI)	**2827**	**1600**		**1.94 [1.15, 3.25]**
Total events: 54 (Treatment), 15 (Control)				
Heterogeneity: Chi?? = 6.92, df = 11 (P = 0.81); I?? =0.0%				
Test for overall effect: Z = 2.49 (P = 0.013)				
Test for subgroup differences: Chi?? = 1.04, df = 2 (P = 0.60), I?? =0.0%				

Analysis 1.7. Comparison 1 All-cause mortality, Outcome 7 Class III antiarrhythmics.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 1 All-cause mortality

Outcome: 7 Class III antiarrhythmics

Study or subgroup	Antiarrhythmic n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Amiodarone				
Channer 2004	0/61	0/38		0.0 [0.0, 0.0]
GEFACA 2001	0/35	0/15		0.0 [0.0, 0.0]
Kochiadakis 2000	0/65	0/60		0.0 [0.0, 0.0]
SAFE-T 2005	13/267	3/132		1.96 [0.68, 5.67]
Subtotal (95% CI)	**428**	**245**		**1.96 [0.68, 5.67]**
Total events: 13 (Antiarrhythmic), 3 (Placebo)				
Heterogeneity: Chi?? = 0.0, df = 0 (P = 1.00); I?? =0.0%				
Test for overall effect: Z = 1.24 (P = 0.21)				
2 Azimilide				

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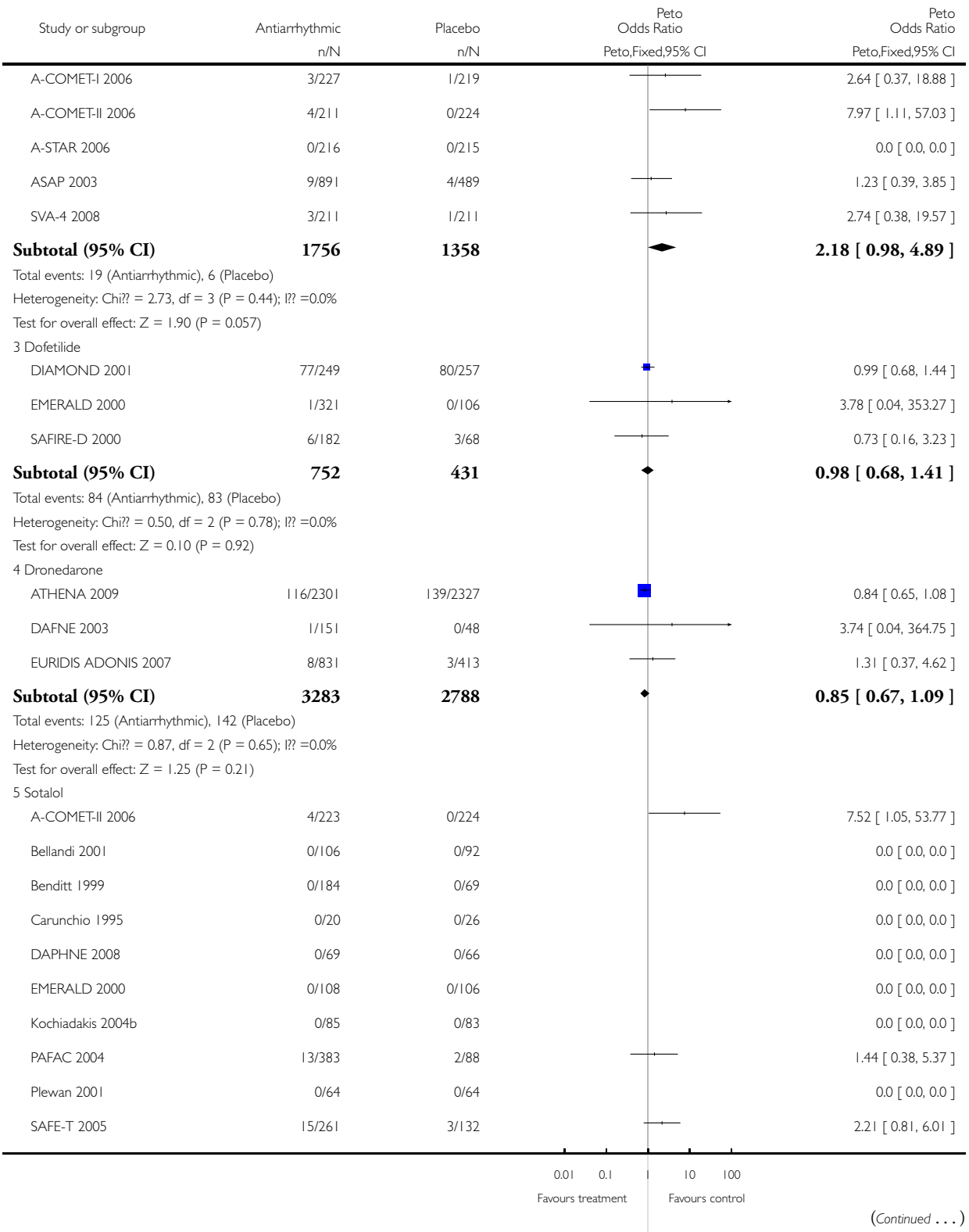

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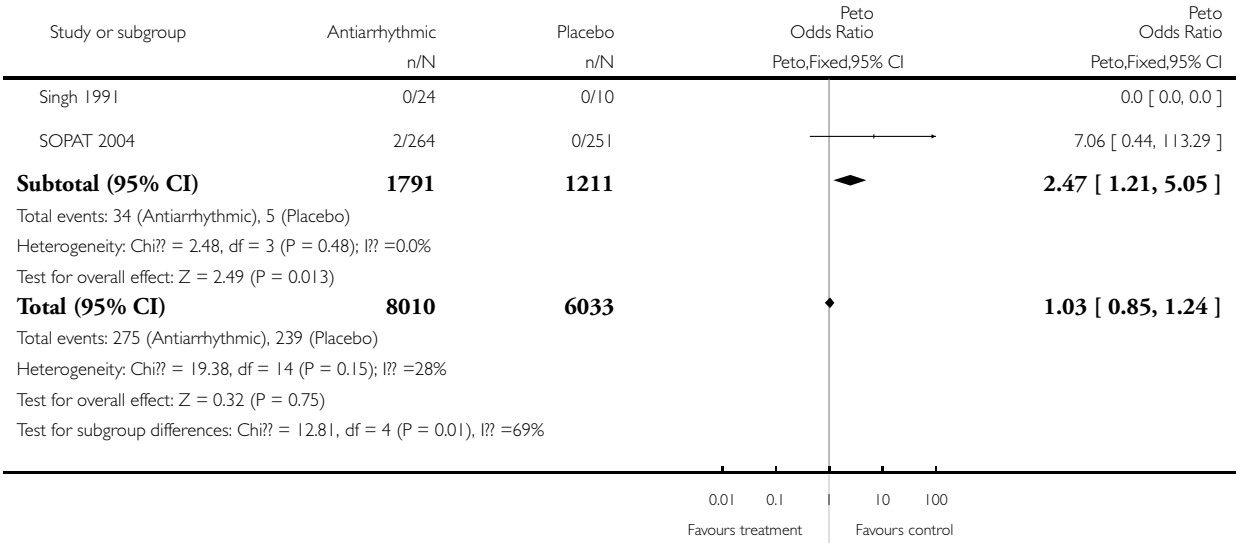
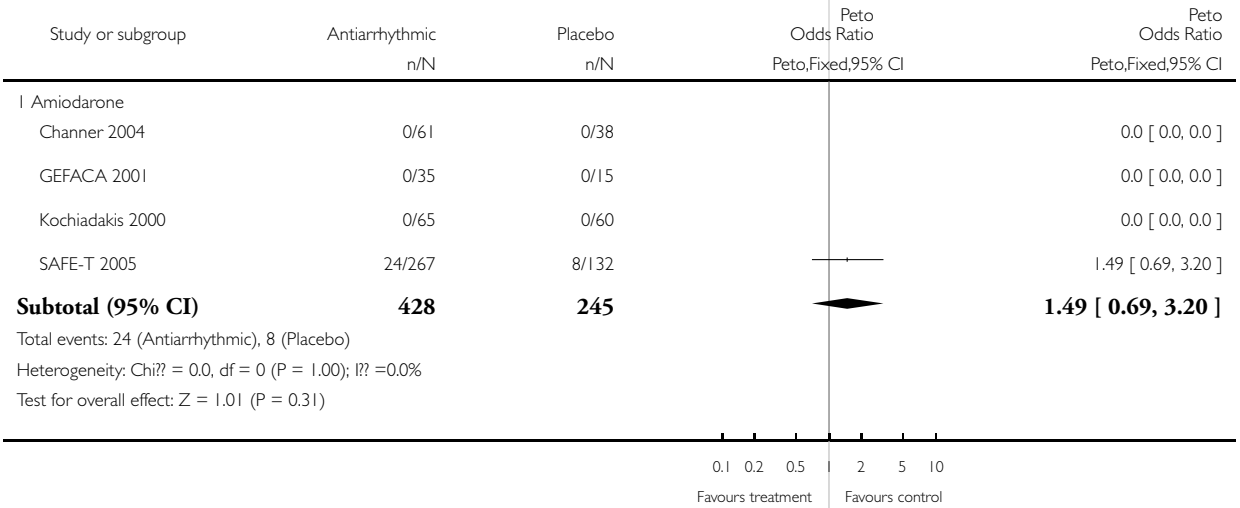


Analysis 1.8. Comparison 1 All-cause mortality, Outcome 8 Class III antiarrhythmics - ITT Worst case: missing patients counted as events.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 1 All-cause mortality

Outcome: 8 Class III antiarrhythmics - ITT Worst case: missing patients counted as events



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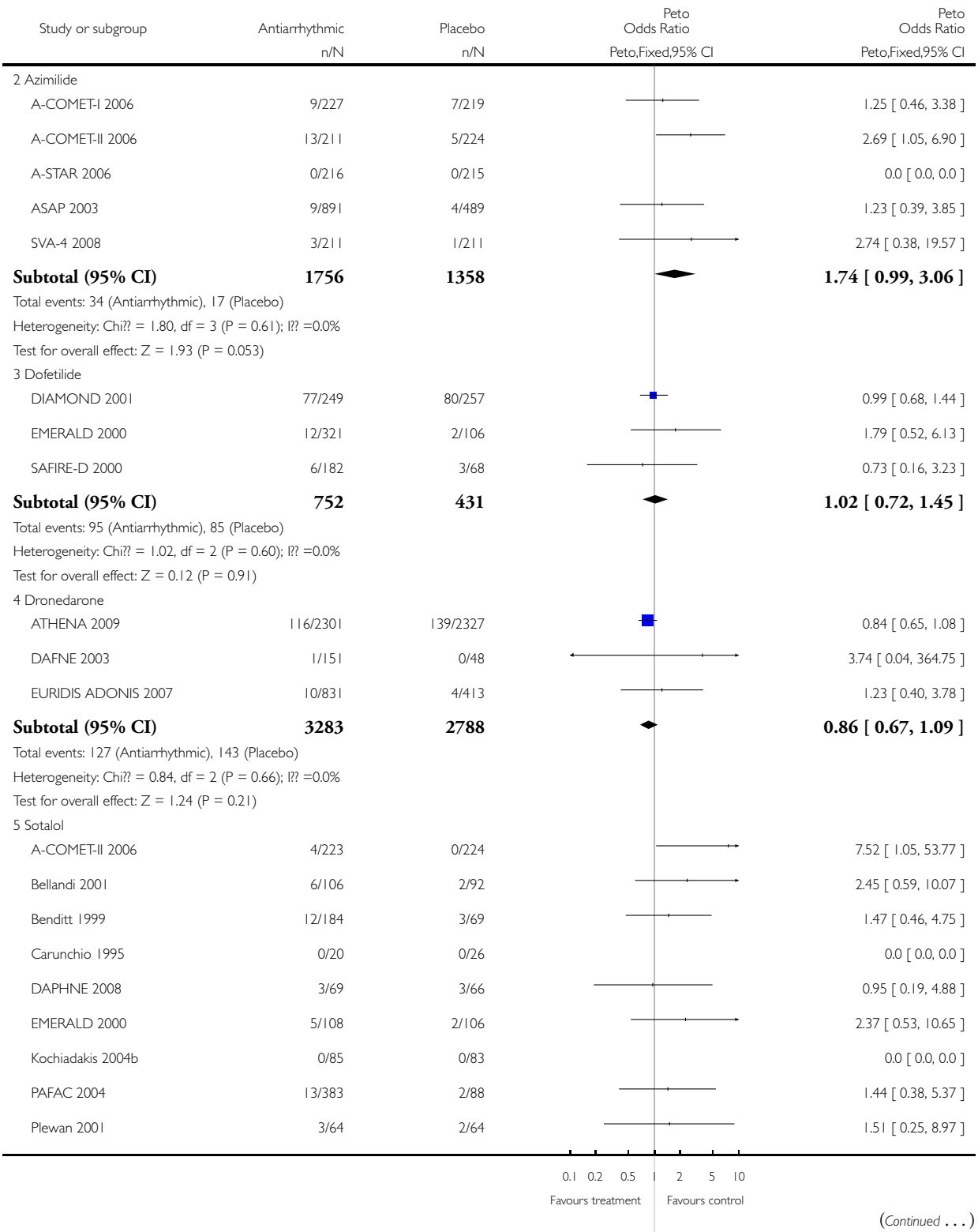

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Study or subgroup	Antiarrhythmic n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
SAFE-T 2005	27/261	3/132		3.13 [1.43, 6.88]
Singh 1991	0/24	0/10		0.0 [0.0, 0.0]
SOPAT 2004	2/264	0/251		7.06 [0.44, 113.29]
Subtotal (95% CI)	**1791**	**1211**		**2.27 [1.45, 3.56]**
Total events: 75 (Antiarrhythmic), 17 (Placebo)				
Heterogeneity: Chi?? = 4.99, df = 8 (P = 0.76); I?? =0.0%				
Test for overall effect: Z = 3.57 (P = 0.00035)				
Total (95% CI)	**8010**	**6033**		**1.13 [0.95, 1.33]**
Total events: 355 (Antiarrhythmic), 270 (Placebo)				
Heterogeneity: Chi?? = 25.90, df = 19 (P = 0.13); I?? =27%				
Test for overall effect: Z = 1.36 (P = 0.17)				
Test for subgroup differences: Chi?? = 17.23, df = 4 (P = 0.00), I?? =77%				

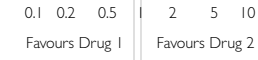
Analysis 1.9. Comparison 1 All-cause mortality, Outcome 9 Comparing antiarrhythmic drugs.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 1 All-cause mortality

Outcome: 9 Comparing antiarrhythmic drugs

Study or subgroup	Antiarrhythmic 1 n/N	Antiarrhythmic 2 n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Disopyramide vs other Class I drugs				
Lloyd 1984	0/29	2/28		0.13 [0.01, 2.06]
PRODIS 1996	1/31	0/25		6.09 [0.12, 313.90]
Subtotal (95% CI)	**60**	**53**		**0.46 [0.05, 4.52]**
Total events: 1 (Antiarrhythmic 1), 2 (Antiarrhythmic 2)				
Heterogeneity: Chi?? = 2.47, df = 1 (P = 0.12); I?? =60%				
Test for overall effect: Z = 0.66 (P = 0.51)				
2 Quinidine vs Flecainide				
Naccarelli 1996	0/117	0/122		0.0 [0.0, 0.0]



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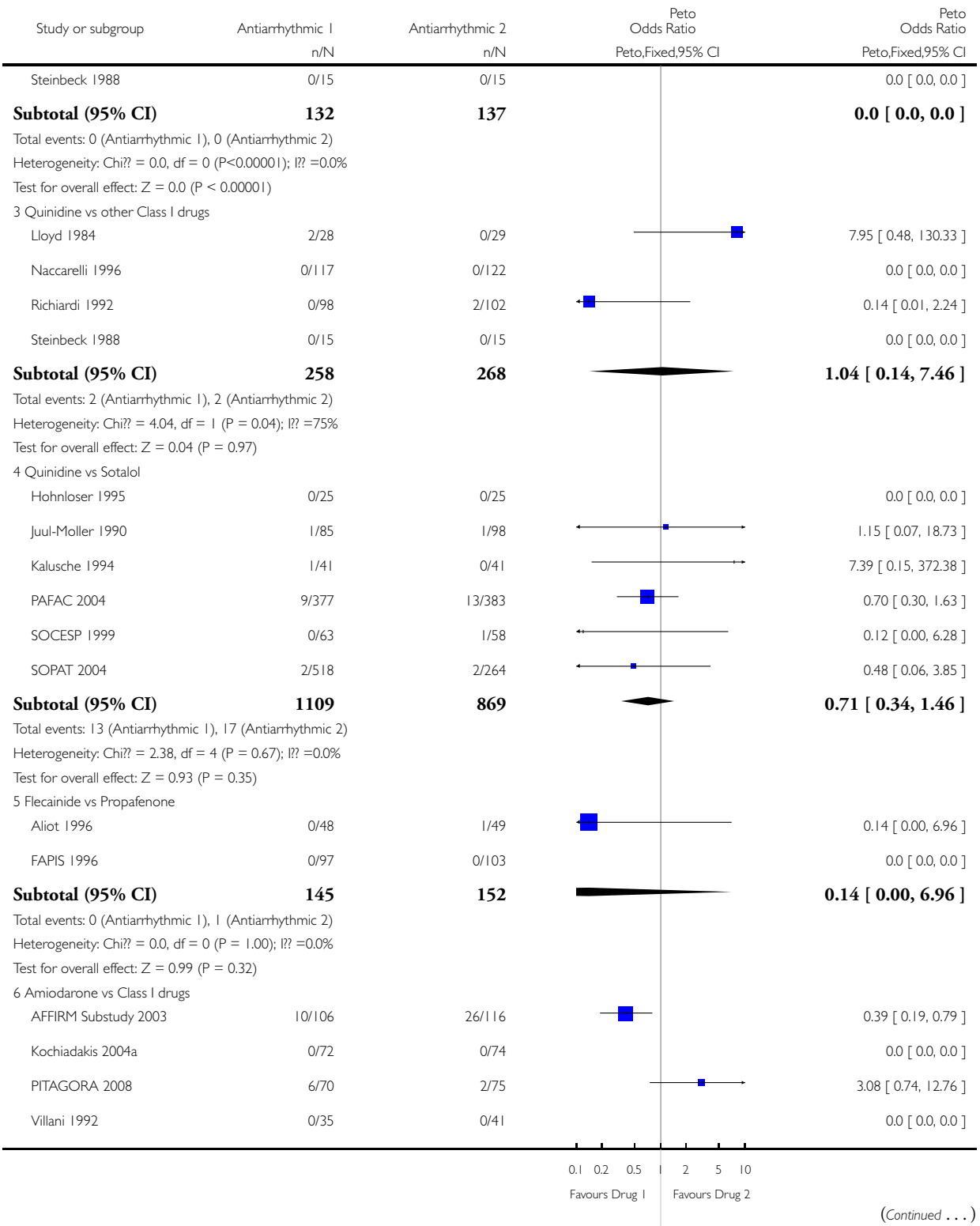

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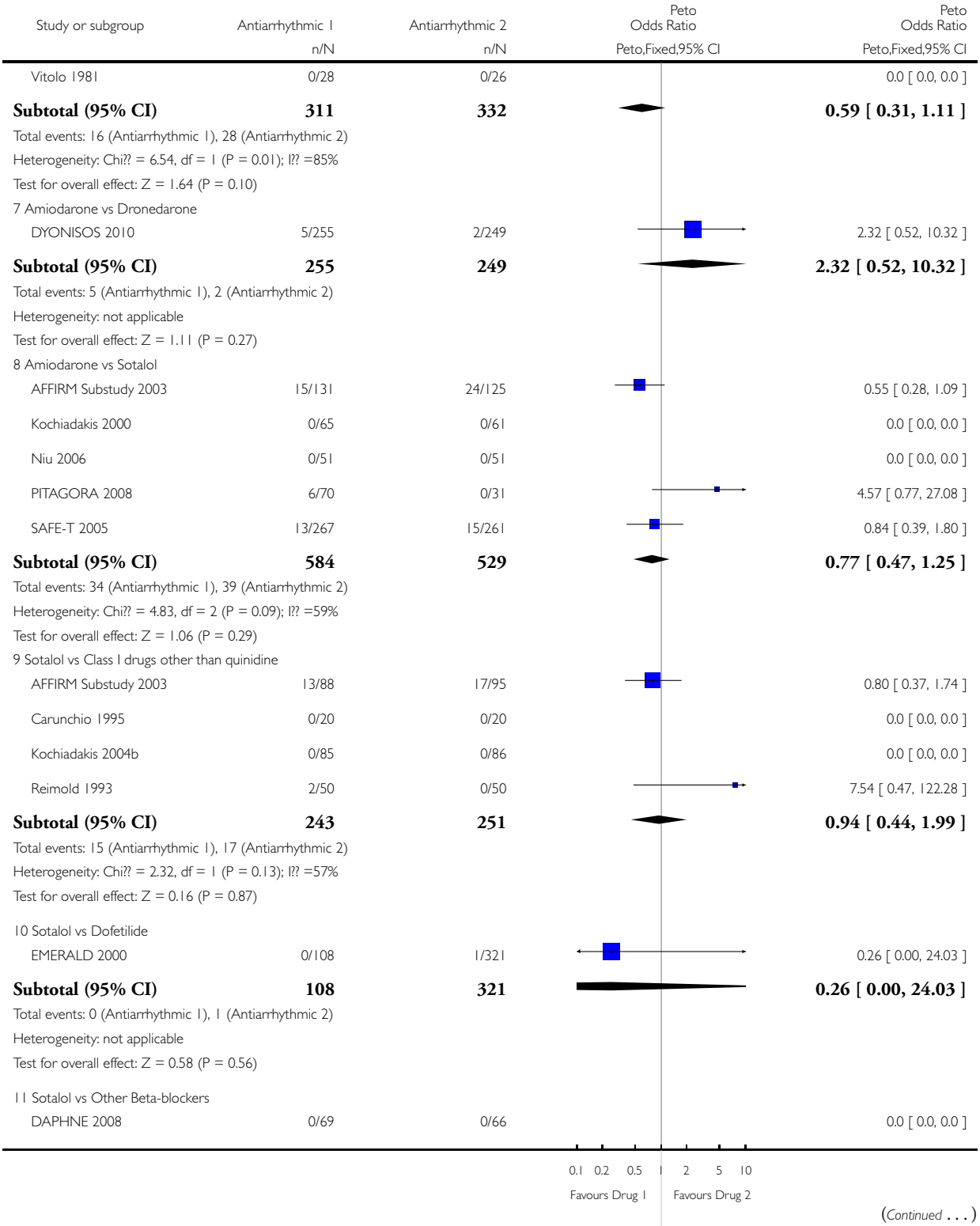

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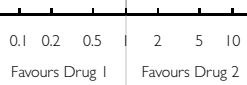
Study or subgroup	Antiarrhythmic 1 n/N	Antiarrhythmic 2 n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Plewan 2001	0/64	0/64		0.0 [0.0, 0.0]
Subtotal (95% CI)	**133**	**130**		**0.0 [0.0, 0.0]**
Total events: 0 (Antiarrhythmic 1), 0 (Antiarrhythmic 2)				
Heterogeneity: Chi?? = 0.0, df = 0 (P<0.00001); I?? =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
12 Class III vs Class I drugs				
AFFIRM Substudy 2003	23/194	26/116		0.45 [0.24, 0.85]
Carunchio 1995	0/20	0/20		0.0 [0.0, 0.0]
Hohnloser 1995	0/25	0/25		0.0 [0.0, 0.0]
Juul-Moller 1990	1/98	1/85		0.87 [0.05, 14.05]
Kalusche 1994	0/41	1/41		0.14 [0.00, 6.82]
Kochiadakis 2004a	0/72	0/74		0.0 [0.0, 0.0]
Kochiadakis 2004b	0/85	0/86		0.0 [0.0, 0.0]
PAFAC 2004	13/383	9/377		1.43 [0.61, 3.34]
Reimold 1993	2/50	0/50		7.54 [0.47, 122.28]
SOCESP 1999	1/58	0/63		8.05 [0.16, 407.27]
SOPAT 2004	2/264	2/518		2.07 [0.26, 16.53]
Villani 1992	0/35	0/41		0.0 [0.0, 0.0]
Vitolo 1981	0/28	0/26		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1353**	**1522**		**0.79 [0.49, 1.26]**
Total events: 42 (Antiarrhythmic 1), 39 (Antiarrhythmic 2)				
Heterogeneity: Chi?? = 10.35, df = 6 (P = 0.11); I?? =42%				
Test for overall effect: Z = 0.99 (P = 0.32)				
Test for subgroup differences: Chi?? = 4.38, df = 9 (P = 0.88), I?? =0.0%				



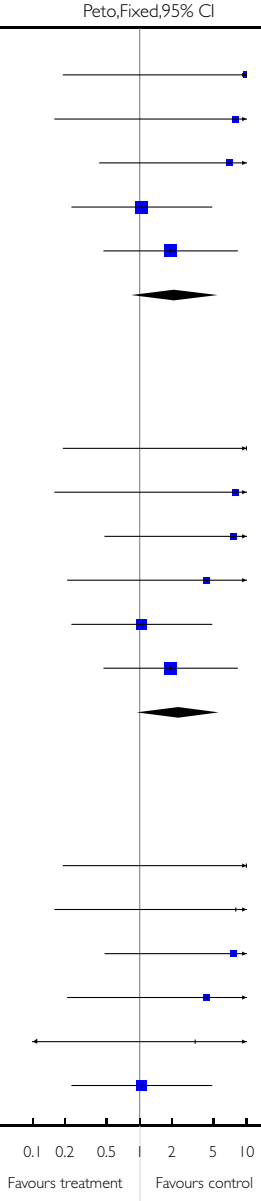
Analysis 1.10. Comparison 1 All-cause mortality, Outcome 10 Subgroup analysis: Persistent atrial fibrillation.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 1 All-cause mortality

Outcome: 10 Subgroup analysis: Persistent atrial fibrillation

Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia: Quinidine				
Byrne-Quinn 1970	1/32	0/42		10.10 [0.19, 527.80]
Hillestad 1971	1/48	0/52		8.03 [0.16, 406.02]
Lloyd 1984	2/28	0/25		6.89 [0.42, 113.67]
PAFAC 2004	9/377	2/88		1.05 [0.23, 4.83]
Sodermark 1975	6/110	2/75		1.95 [0.46, 8.24]
Subtotal (95% CI)	**595**	**282**		**2.11 [0.84, 5.32]**
Total events: 19 (Antiarrhythmic), 4 (Control)				
Heterogeneity: Chi?? = 2.55, df = 4 (P = 0.64); I?? =0.0%				
Test for overall effect: Z = 1.58 (P = 0.11)				
2 All class Ia antiarrhythmics				
Byrne-Quinn 1970	1/32	0/42		10.10 [0.19, 527.80]
Hillestad 1971	1/48	0/52		8.03 [0.16, 406.02]
Karlson 1998	2/46	0/46		7.56 [0.47, 122.66]
Lloyd 1984	2/57	0/25		4.29 [0.21, 88.75]
PAFAC 2004	9/377	2/88		1.05 [0.23, 4.83]
Sodermark 1975	6/110	2/75		1.95 [0.46, 8.24]
Subtotal (95% CI)	**670**	**328**		**2.27 [0.94, 5.49]**
Total events: 21 (Antiarrhythmic), 4 (Control)				
Heterogeneity: Chi?? = 2.85, df = 5 (P = 0.72); I?? =0.0%				
Test for overall effect: Z = 1.81 (P = 0.070)				
3 All class I antiarrhythmics				
Byrne-Quinn 1970	1/32	0/42		10.10 [0.19, 527.80]
Hillestad 1971	1/48	0/52		8.03 [0.16, 406.02]
Karlson 1998	2/46	0/46		7.56 [0.47, 122.66]
Lloyd 1984	2/57	0/25		4.29 [0.21, 88.75]
Okishige 2000	1/52	0/10		3.29 [0.02, 679.40]
PAFAC 2004	9/377	2/88		1.05 [0.23, 4.83]



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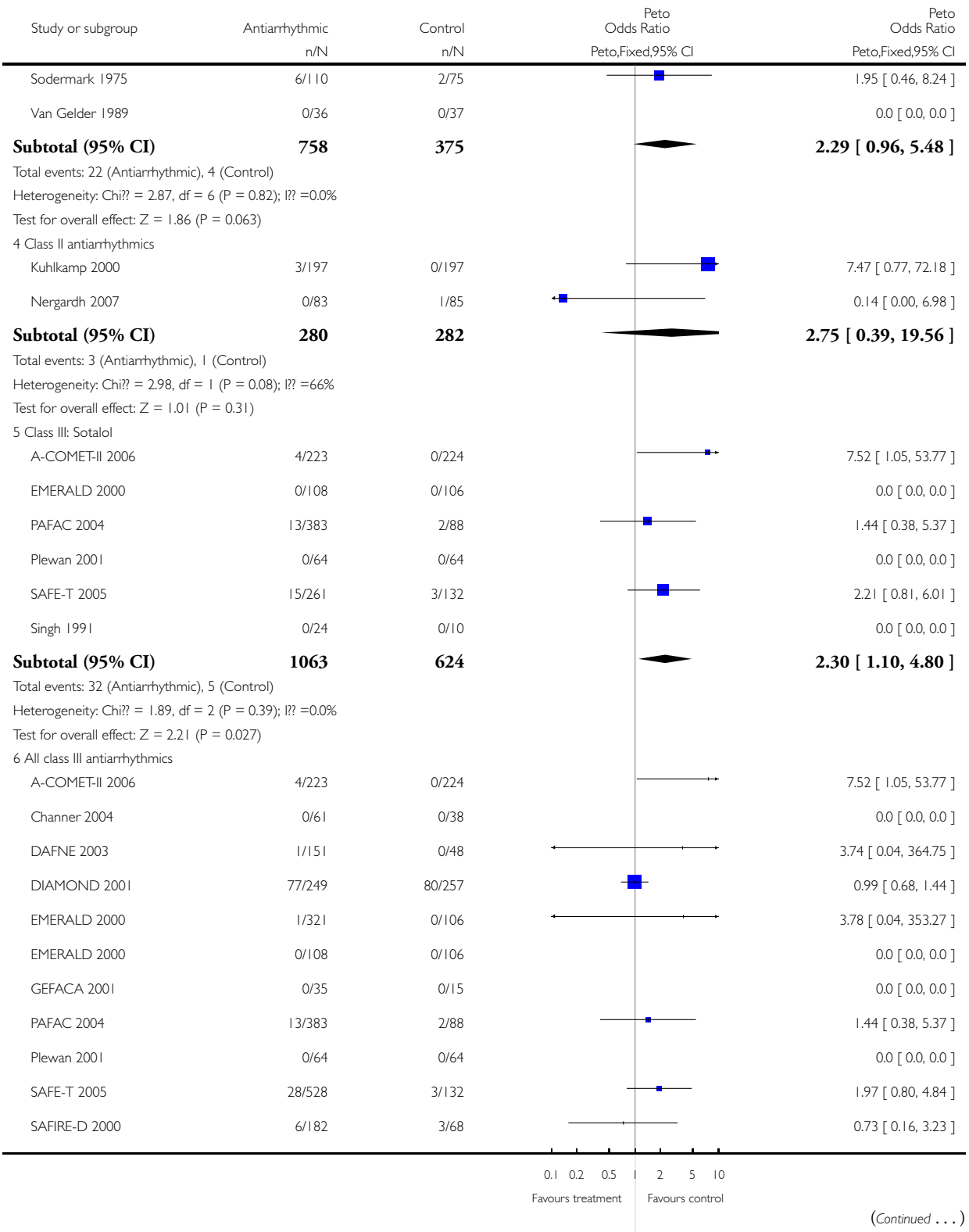

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Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Singh 1991	0/24	0/10		0.0 [0.0, 0.0]
Subtotal (95% CI)	**2329**	**1156**		**1.17 [0.84, 1.61]**
Total events: 130 (Antiarrhythmic), 88 (Control)				
Heterogeneity: Chi?? = 6.46, df = 6 (P = 0.37); I?? =7%				
Test for overall effect: Z = 0.93 (P = 0.35)				
Test for subgroup differences: Chi?? = 6.27, df = 5 (P = 0.28), I?? =20%				

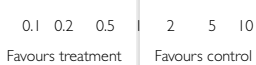
Analysis 1.11. Comparison 1 All-cause mortality, Outcome 11 Sensitivity analysis: Best quality studies.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 1 All-cause mortality

Outcome: 11 Sensitivity analysis: Best quality studies

Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia: Quinidine				
PAFAC 2004	9/377	2/88		1.05 [0.23, 4.83]
SOPAT 2004	2/518	0/251		4.42 [0.23, 85.12]
Subtotal (95% CI)	**895**	**339**		**1.42 [0.37, 5.51]**
Total events: 11 (Antiarrhythmic), 2 (Control)				
Heterogeneity: Chi?? = 0.72, df = 1 (P = 0.40); I?? =0.0%				
Test for overall effect: Z = 0.51 (P = 0.61)				
2 All class I antiarrhythmics				
PAFAC 2004	9/377	2/88		1.05 [0.23, 4.83]
SMART 2002	0/47	0/47		0.0 [0.0, 0.0]
SOPAT 2004	2/518	0/251		4.42 [0.23, 85.12]
Stroobandt 1997	0/77	1/25		0.02 [0.00, 1.61]
Van Gelder 1989	0/36	0/37		0.0 [0.0, 0.0]
Subtotal (95% CI)	**1055**	**448**		**0.99 [0.27, 3.63]**



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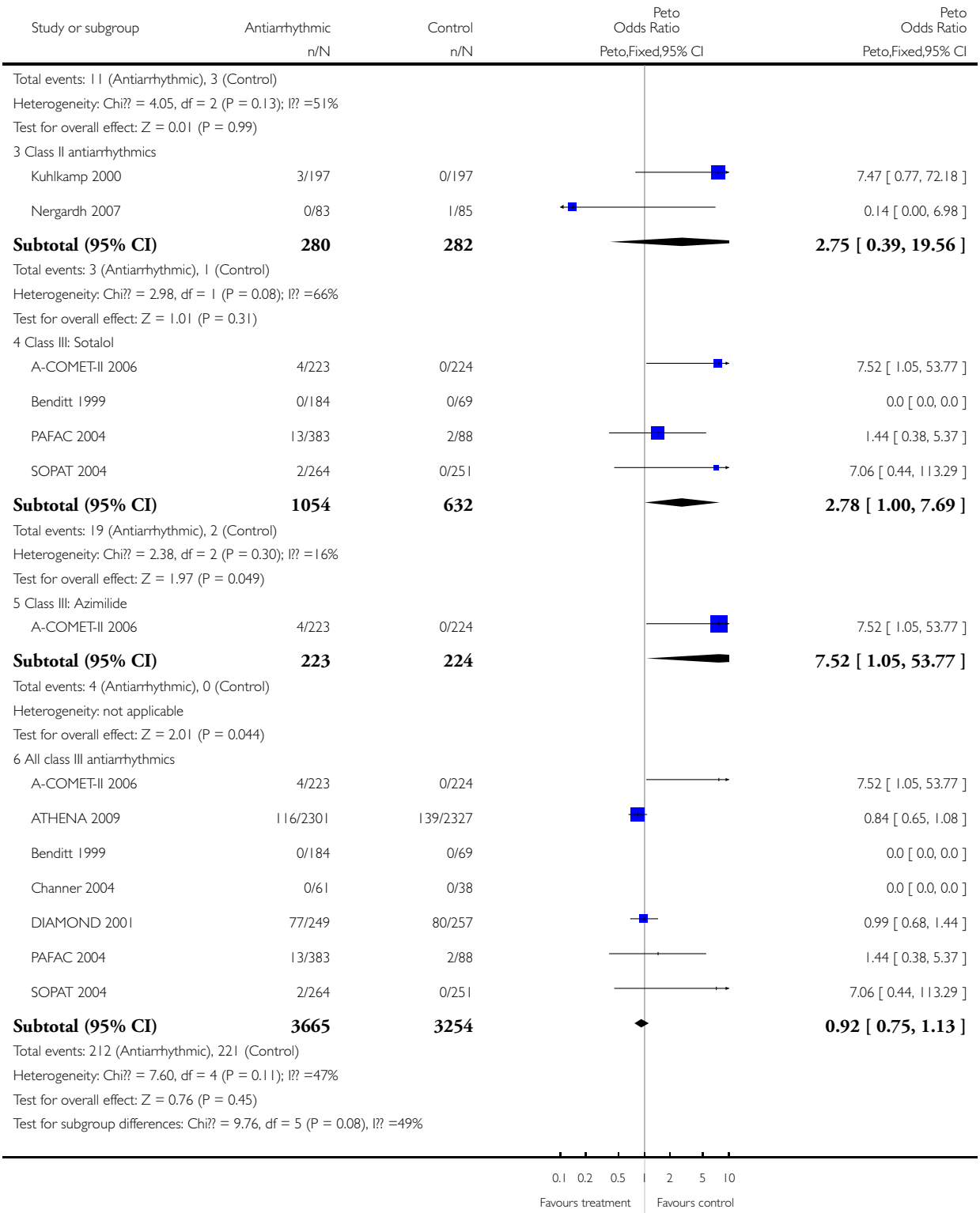
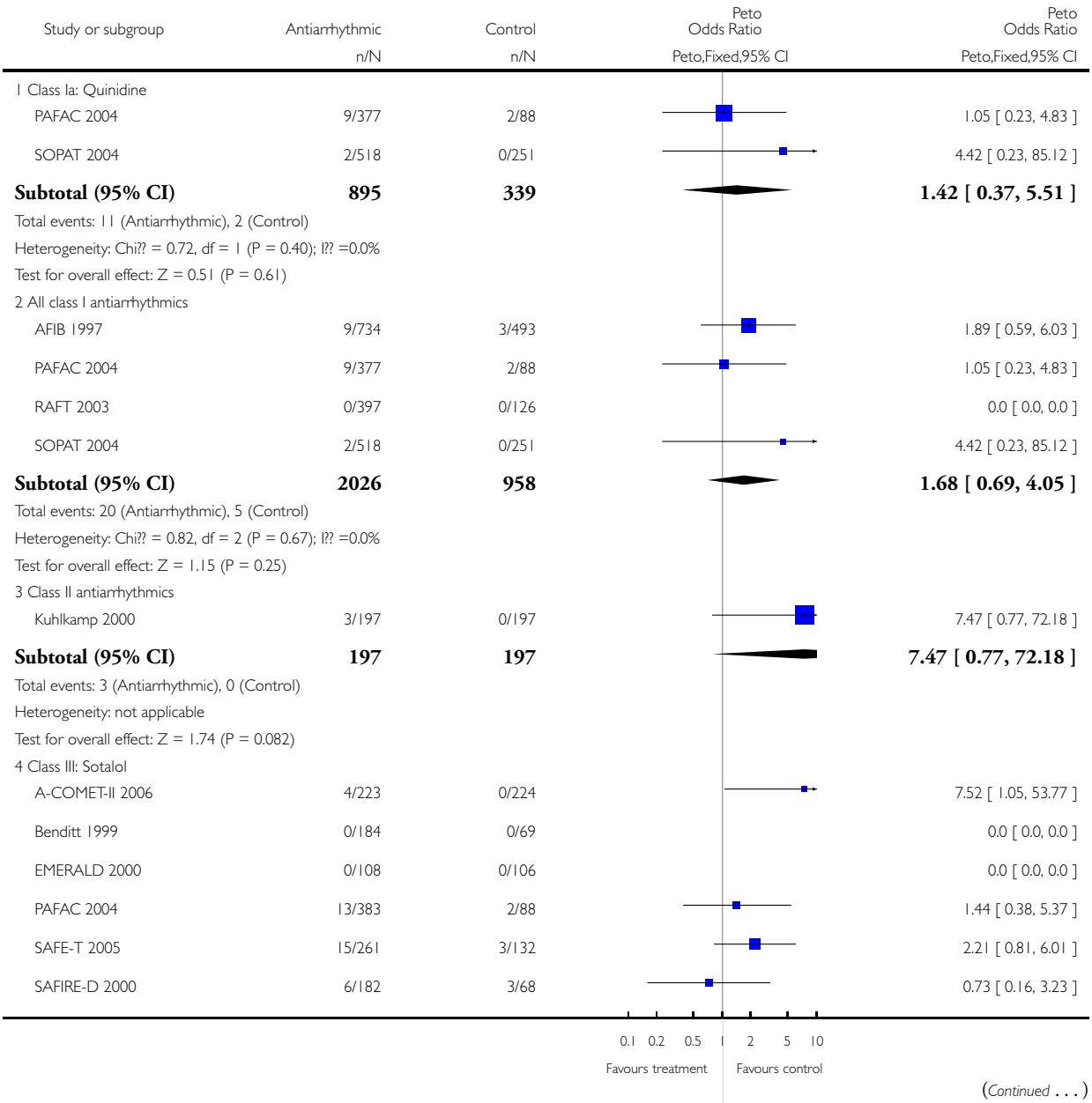


Analysis 1.12. Comparison 1 All-cause mortality, Outcome 12 Sensitivity analysis: Studies > 200 patients.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 1 All-cause mortality

Outcome: 12 Sensitivity analysis: Studies > 200 patients



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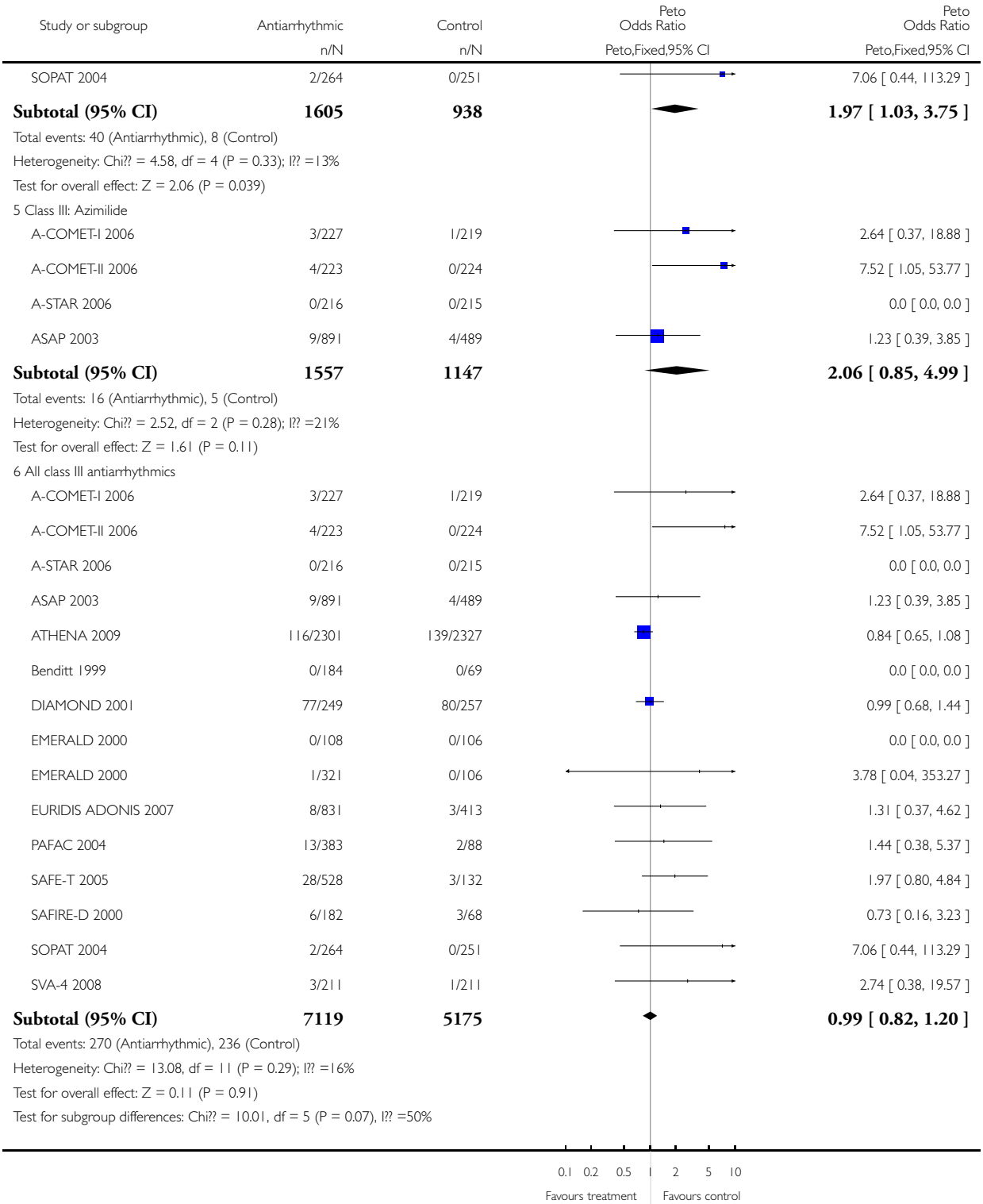
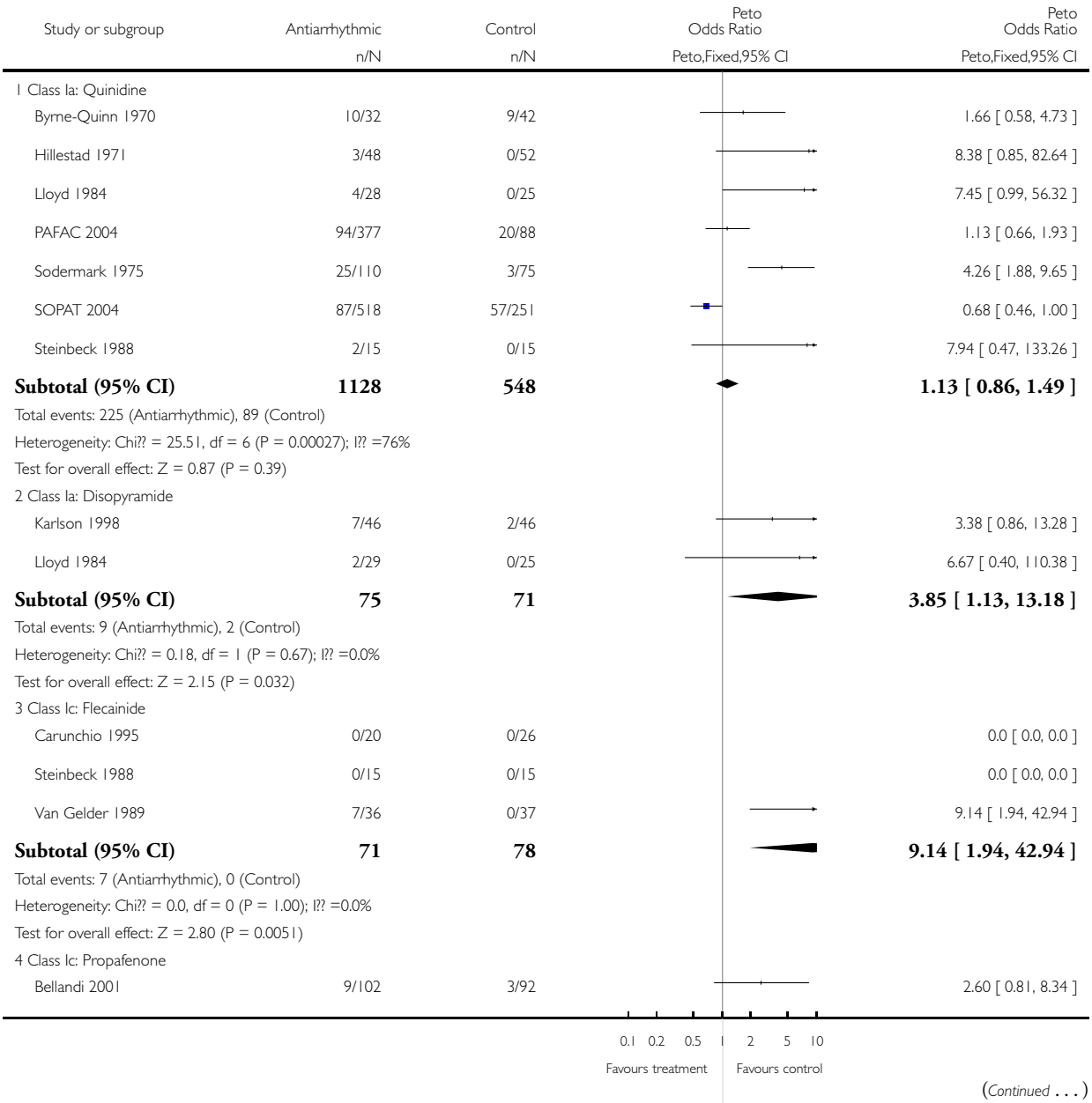


Analysis 2.1. Comparison 2 Withdrawals due to adverse effects, Outcome 1 Individual antiarrhythmics.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 2 Withdrawals due to adverse effects

Outcome: 1 Individual antiarrhythmics



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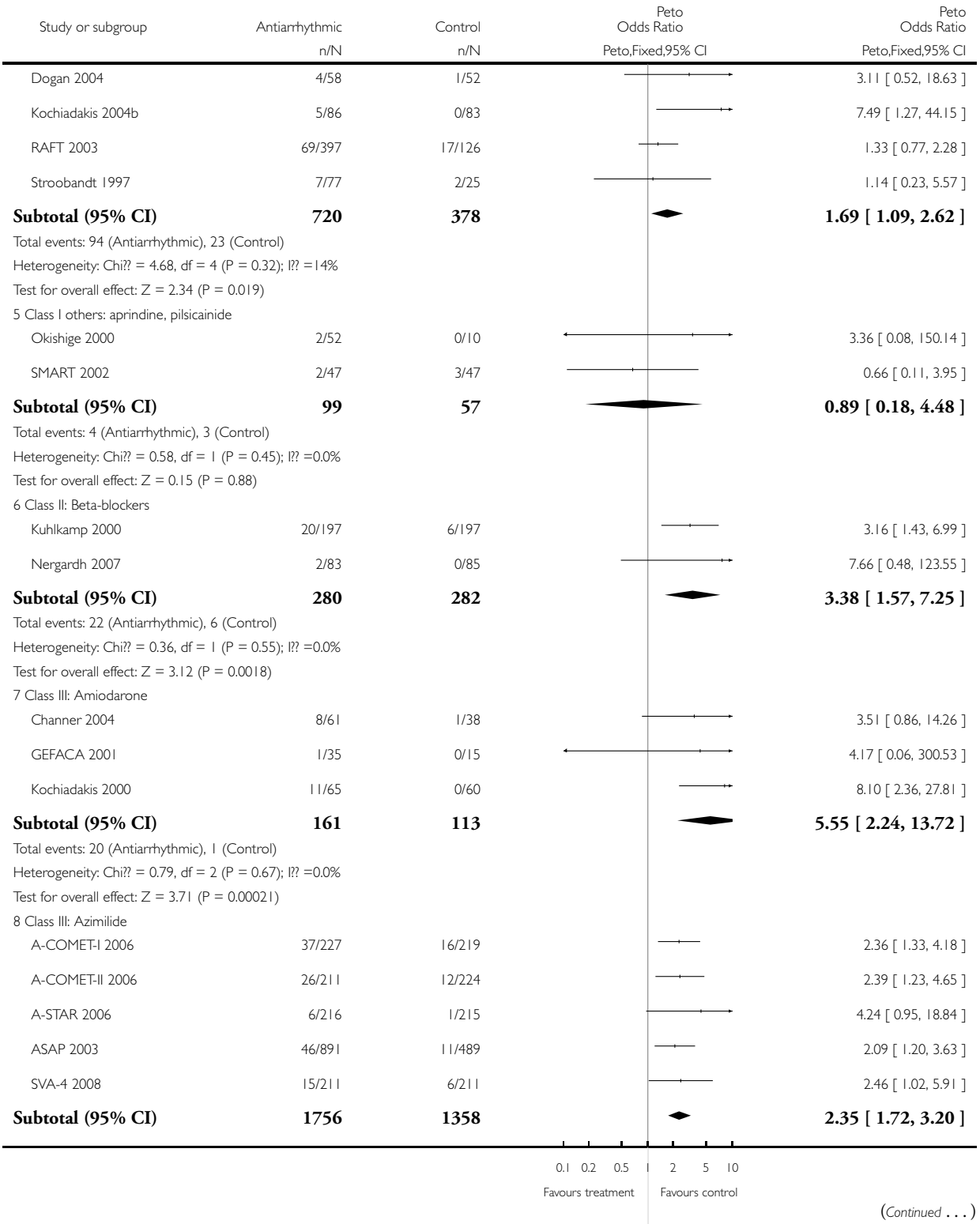

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Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 130 (Antiarrhythmic), 46 (Control)				
Heterogeneity: Chi?? = 0.79, df = 4 (P = 0.94); I?? =0.0%				
Test for overall effect: Z = 5.37 (P < 0.00001)				
9 Class III: Dofetilide				
EMERALD 2000	22/321	4/106		1.71 [0.68, 4.28]
SAFIRE-D 2000	9/182	2/68		1.61 [0.41, 6.23]
Subtotal (95% CI)	**503**	**174**		**1.68 [0.79, 3.59]**
Total events: 31 (Antiarrhythmic), 6 (Control)				
Heterogeneity: Chi?? = 0.01, df = 1 (P = 0.94); I?? =0.0%				
Test for overall effect: Z = 1.34 (P = 0.18)				
10 Class III: Dronedarone				
ATHENA 2009	290/2301	187/2327		1.64 [1.36, 1.98]
DAFNE 2003	22/151	0/48		4.37 [1.55, 12.27]
EURIDIS ADONIS 2007	80/831	29/413		1.38 [0.91, 2.10]
Subtotal (95% CI)	**3283**	**2788**		**1.64 [1.38, 1.94]**
Total events: 392 (Antiarrhythmic), 216 (Control)				
Heterogeneity: Chi?? = 4.08, df = 2 (P = 0.13); I?? =51%				
Test for overall effect: Z = 5.67 (P < 0.00001)				
11 Class III: Sotalol				
A-COMET-II 2006	31/223	12/224		2.67 [1.42, 5.00]
Bellandi 2001	7/106	3/92		2.00 [0.56, 7.14]
Benditt 1999	25/184	1/69		3.71 [1.49, 9.21]
Carunchio 1995	0/20	0/26		0.0 [0.0, 0.0]
DAPHNE 2008	11/69	2/66		4.36 [1.40, 13.63]
EMERALD 2000	16/108	4/106		3.66 [1.46, 9.17]
Kochiadakis 2004b	5/85	0/83		7.58 [1.28, 44.68]
PAFAC 2004	96/383	20/88		1.13 [0.66, 1.94]
Plewan 2001	4/64	3/64		1.35 [0.30, 6.16]
Singh 1991	3/24	0/10		4.52 [0.35, 58.58]
SOPAT 2004	53/264	57/251		0.86 [0.56, 1.30]
Subtotal (95% CI)	**1530**	**1079**		**1.61 [1.25, 2.06]**
Total events: 251 (Antiarrhythmic), 102 (Control)				
Heterogeneity: Chi?? = 25.74, df = 9 (P = 0.002); I?? =65%				
Test for overall effect: Z = 3.75 (P = 0.00018)				
Total (95% CI)	**9606**	**6926**		**1.69 [1.51, 1.88]**
Total events: 1185 (Antiarrhythmic), 494 (Control)				

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Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Heterogeneity: Chi?? = 92.13, df = 41 (P<0.00001); I?? =55%				
Test for overall effect: Z = 9.47 (P < 0.00001)				
Test for subgroup differences: Chi?? = 29.42, df = 10 (P = 0.00), I?? =66%				

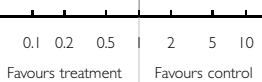
Analysis 2.2. Comparison 2 Withdrawals due to adverse effects, Outcome 2 Quinidine: older and recent studies.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 2 Withdrawals due to adverse effects

Outcome: 2 Quinidine: older and recent studies

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Older studies, higher dose					
Byrne-Quinn 1970	10/32	9/42		18.2 %	1.67 [0.58, 4.76]
Hillestad 1971	3/48	0/52		5.1 %	8.08 [0.41, 160.56]
Lloyd 1984	4/28	0/25		5.2 %	9.37 [0.48, 183.30]
Sodermark 1975	25/110	3/75		15.9 %	7.06 [2.05, 24.34]
Steinbeck 1988	2/15	0/15		4.8 %	5.74 [0.25, 130.37]
Subtotal (95% CI)	**233**	**209**		**49.2 %**	**3.62 [1.71, 7.65]**
Total events: 44 (Treatment), 12 (Control)					
Heterogeneity: Tau?? = 0.02; Chi?? = 4.10, df = 4 (P = 0.39); I?? =2%					
Test for overall effect: Z = 3.37 (P = 0.00075)					
2 More recent studies, lower dose					
PAFAC 2004	94/377	20/88		24.5 %	1.13 [0.65, 1.96]
SOPAT 2004	87/518	57/251		26.3 %	0.69 [0.47, 1.00]
Subtotal (95% CI)	**895**	**339**		**50.8 %**	**0.84 [0.52, 1.36]**
Total events: 181 (Treatment), 77 (Control)					
Heterogeneity: Tau?? = 0.07; Chi?? = 2.14, df = 1 (P = 0.14); I?? =53%					
Test for overall effect: Z = 0.69 (P = 0.49)					



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Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Total (95% CI)	**1128**	**548**		**100.0 %**	**1.90 [0.90, 4.02]**
Total events: 225 (Treatment), 89 (Control)					
Heterogeneity: Tau?? = 0.52; Chi?? = 20.33, df = 6 (P = 0.002); I?? =70%					
Test for overall effect: Z = 1.68 (P = 0.093)					
Test for subgroup differences: Chi?? = 10.32, df = 1 (P = 0.00), I?? =90%					

Analysis 2.3. Comparison 2 Withdrawals due to adverse effects, Outcome 3 Class I antiarrhythmics.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 2 Withdrawals due to adverse effects

Outcome: 3 Class I antiarrhythmics

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia				
Byrne-Quinn 1970	10/32	9/42		1.66 [0.58, 4.73]
Hillestad 1971	3/48	0/52		8.38 [0.85, 82.64]
Karlson 1998	7/46	2/46		3.38 [0.86, 13.28]
Lloyd 1984	6/57	0/25		4.63 [0.77, 27.87]
PAFAC 2004	94/377	20/88		1.13 [0.66, 1.93]
Sodermark 1975	25/110	3/75		4.26 [1.88, 9.65]
SOPAT 2004	87/518	57/251		0.68 [0.46, 1.00]
Steinbeck 1988	2/15	0/15		7.94 [0.47, 133.26]
Subtotal (95% CI)	**1203**	**594**		**1.18 [0.90, 1.54]**
Total events: 234 (Treatment), 91 (Control)				
Heterogeneity: Chi?? = 26.92, df = 7 (P = 0.00034); I?? =74%				
Test for overall effect: Z = 1.18 (P = 0.24)				
2 Class Ib				
SMART 2002	2/47	3/47		0.66 [0.11, 3.95]

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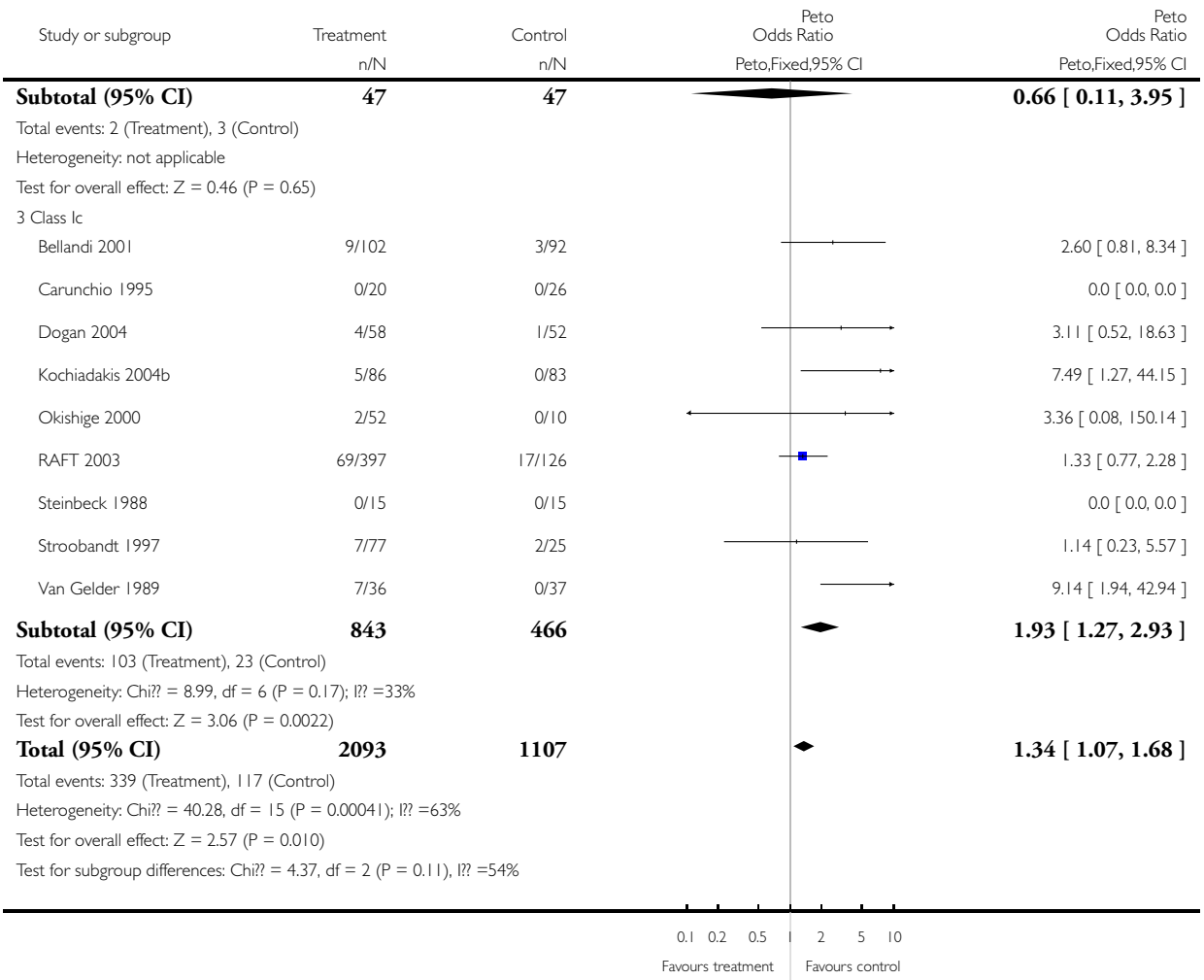
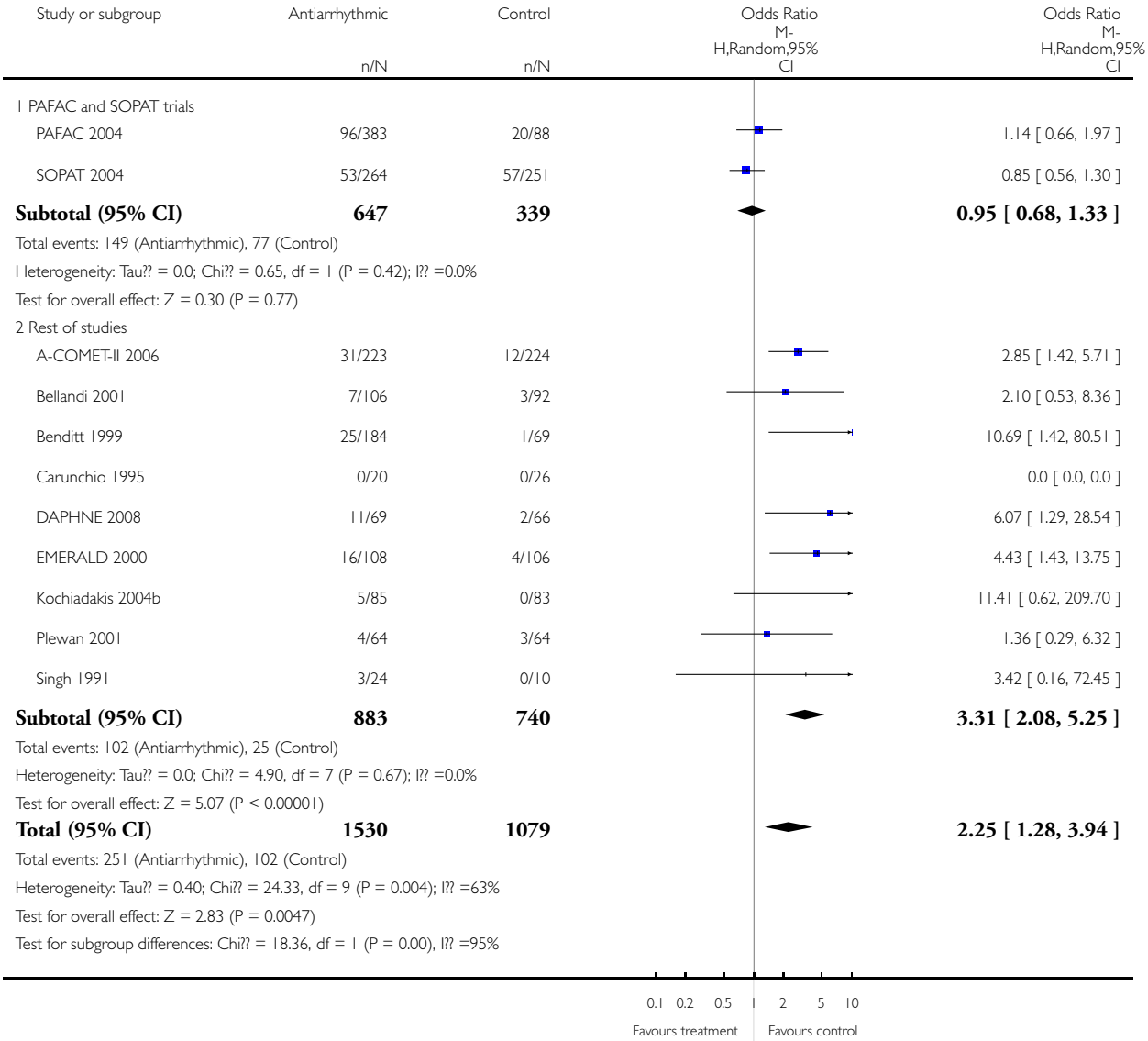


Analysis 2.4. Comparison 2 Withdrawals due to adverse effects, Outcome 4 Sotalol: heterogeneity study.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 2 Withdrawals due to adverse effects

Outcome: 4 Sotalol: heterogeneity study

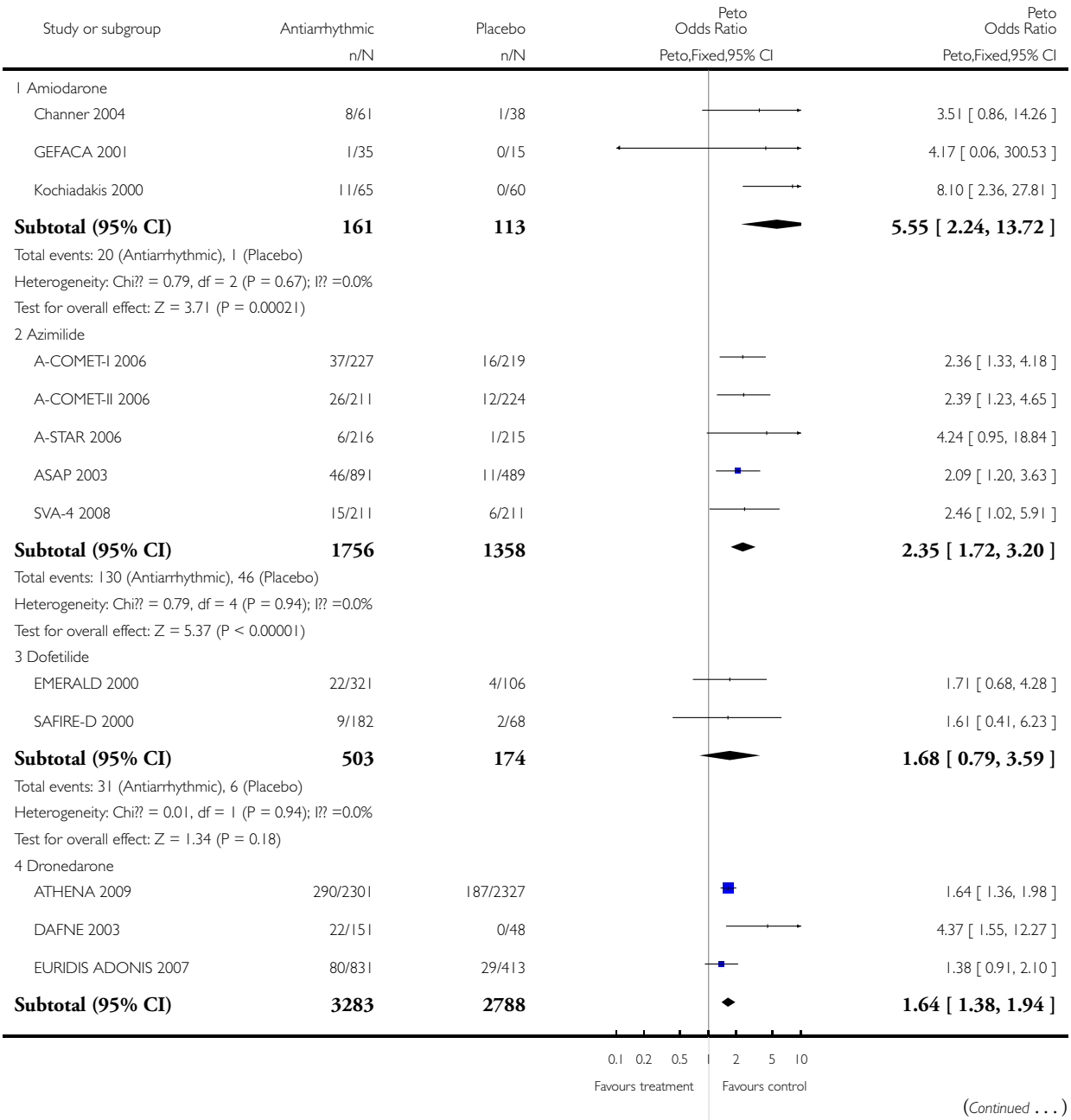


Analysis 2.5. Comparison 2 Withdrawals due to adverse effects, Outcome 5 Class III antiarrhythmics.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 2 Withdrawals due to adverse effects

Outcome: 5 Class III antiarrhythmics



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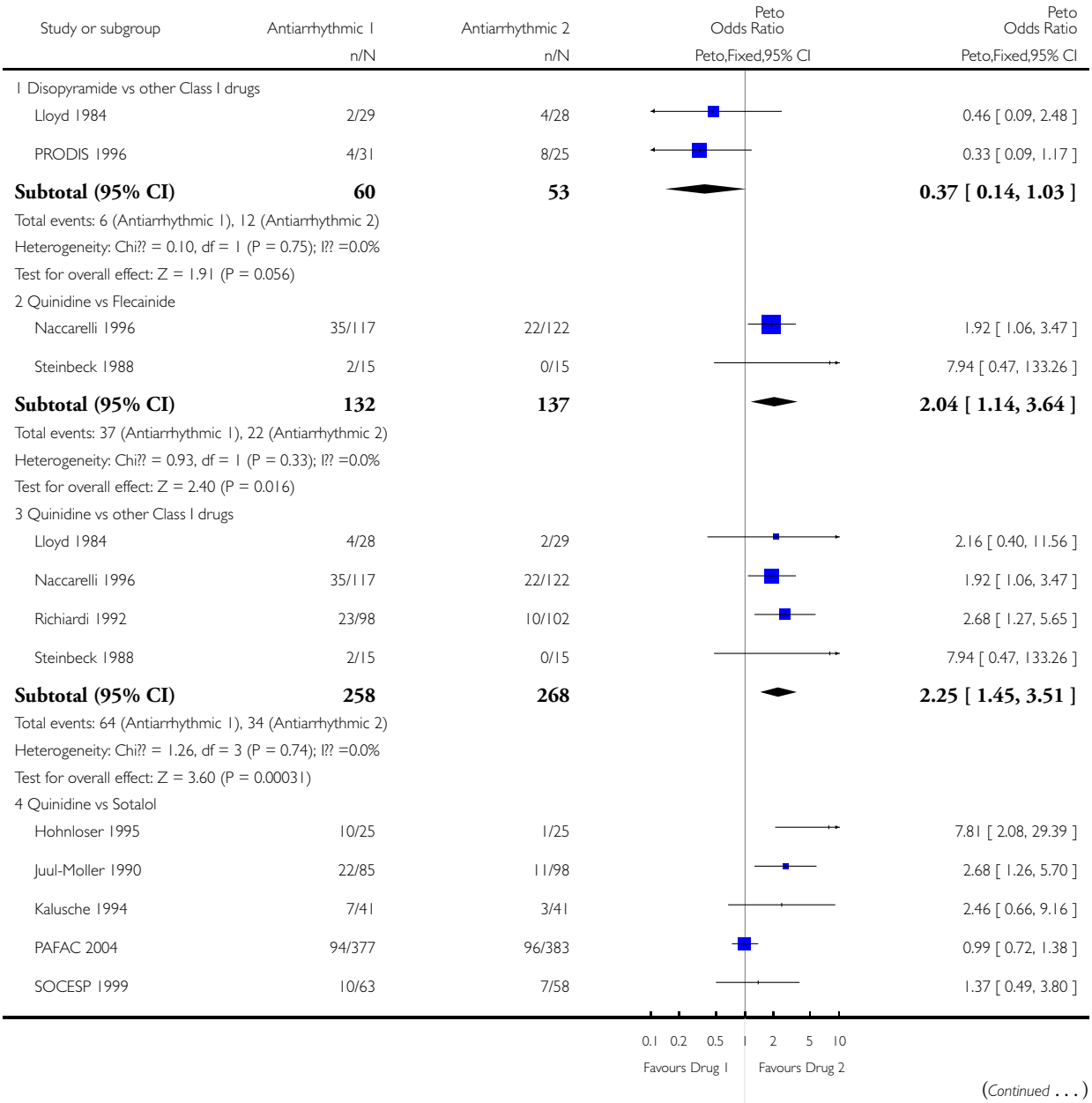
Study or subgroup	Antiarrhythmic n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 392 (Antiarrhythmic), 216 (Placebo)				
Heterogeneity: Chi?? = 4.08, df = 2 (P = 0.13); I?? =51%				
Test for overall effect: Z = 5.67 (P < 0.00001)				
5 Sotalol				
A-COMET-II 2006	31/223	12/224		2.67 [1.42, 5.00]
Bellandi 2001	7/106	3/92		2.00 [0.56, 7.14]
Benditt 1999	25/184	1/69		3.71 [1.49, 9.21]
Carunchio 1995	0/20	0/26		0.0 [0.0, 0.0]
DAPHNE 2008	11/69	2/66		4.36 [1.40, 13.63]
EMERALD 2000	16/108	4/106		3.66 [1.46, 9.17]
Kochiadakis 2004b	5/85	0/83		7.58 [1.28, 44.68]
PAFAC 2004	96/383	20/88		1.13 [0.66, 1.94]
Plewan 2001	4/64	3/64		1.35 [0.30, 6.16]
Singh 1991	3/24	0/10		4.52 [0.35, 58.58]
SOPAT 2004	53/264	57/251		0.86 [0.56, 1.30]
Subtotal (95% CI)	**1530**	**1079**		**1.61 [1.25, 2.06]**
Total events: 251 (Antiarrhythmic), 102 (Placebo)				
Heterogeneity: Chi?? = 25.74, df = 9 (P = 0.002); I?? =65%				
Test for overall effect: Z = 3.75 (P = 0.00018)				
Total (95% CI)	**7233**	**5512**		**1.77 [1.56, 2.00]**
Total events: 824 (Antiarrhythmic), 371 (Placebo)				
Heterogeneity: Chi?? = 42.10, df = 22 (P = 0.01); I?? =48%				
Test for overall effect: Z = 8.94 (P < 0.00001)				
Test for subgroup differences: Chi?? = 10.70, df = 4 (P = 0.03), I?? =63%				

Analysis 2.6. Comparison 2 Withdrawals due to adverse effects, Outcome 6 Comparing antiarrhythmic drugs.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 2 Withdrawals due to adverse effects

Outcome: 6 Comparing antiarrhythmic drugs



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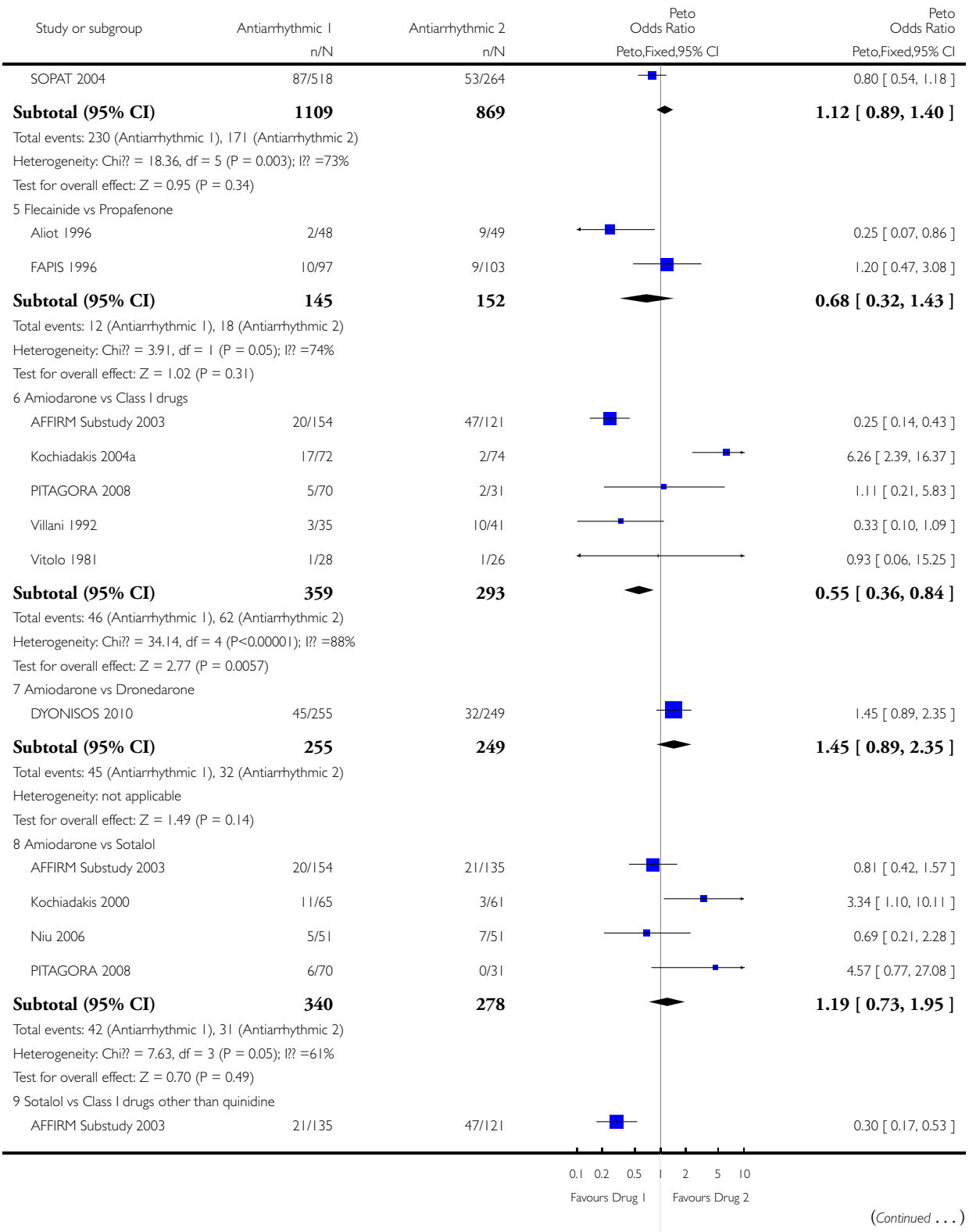

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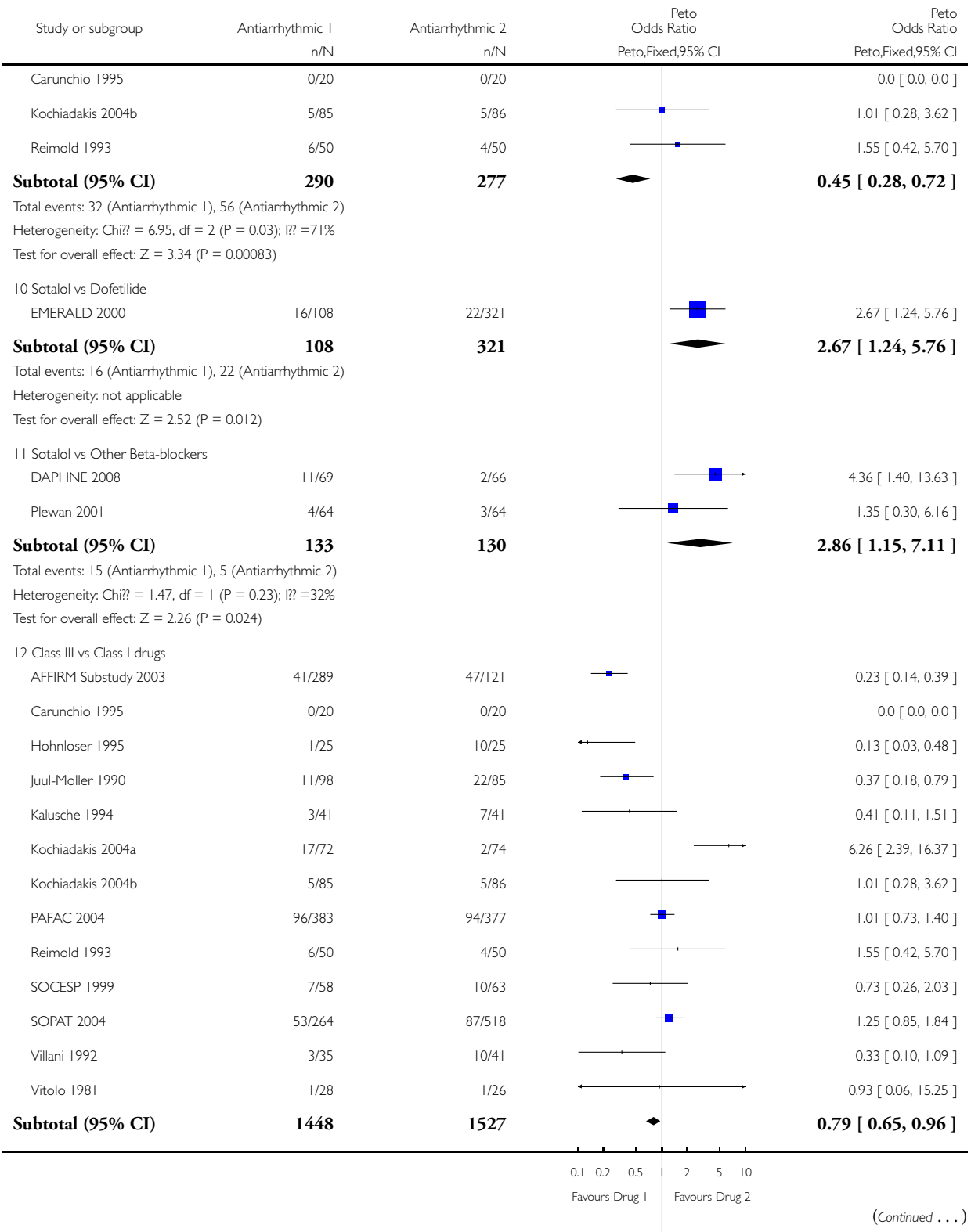

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Study or subgroup	Antiarrhythmic 1 n/N	Antiarrhythmic 2 n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 244 (Antiarrhythmic 1), 299 (Antiarrhythmic 2)				
Heterogeneity: Chi?? = 62.20, df = 11 (P<0.00001); I?? =82%				
Test for overall effect: Z = 2.34 (P = 0.019)				
Test for subgroup differences: Chi?? = 62.74, df = 11 (P = 0.00), I?? =82%				

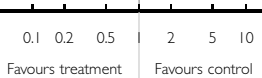
Analysis 2.7. Comparison 2 Withdrawals due to adverse effects, Outcome 7 Subgroup analysis: Persistent atrial fibrillation.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 2 Withdrawals due to adverse effects

Outcome: 7 Subgroup analysis: Persistent atrial fibrillation

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia: Quinidine					
Byrne-Quinn 1970	10/32	9/42		14.5 %	1.66 [0.58, 4.73]
Hillestad 1971	3/48	0/52		3.0 %	8.38 [0.85, 82.64]
Lloyd 1984	4/28	0/25		3.9 %	7.45 [0.99, 56.32]
PAFAC 2004	94/377	20/88		54.7 %	1.13 [0.66, 1.93]
Sodermark 1975	25/110	3/75		23.8 %	4.26 [1.88, 9.65]
Subtotal (95% CI)	**595**	**282**		**100.0 %**	**1.87 [1.26, 2.79]**
Total events: 136 (Treatment), 32 (Control)					
Heterogeneity: Chi?? = 10.81, df = 4 (P = 0.03); I?? =63%					
Test for overall effect: Z = 3.08 (P = 0.0021)					
2 All class I antiarrhythmics					
Byrne-Quinn 1970	10/32	9/42		12.4 %	1.66 [0.58, 4.73]
Hillestad 1971	3/48	0/52		2.6 %	8.38 [0.85, 82.64]
Karlson 1998	7/46	2/46		7.2 %	3.38 [0.86, 13.28]
Lloyd 1984	6/57	0/25		4.2 %	4.63 [0.77, 27.87]



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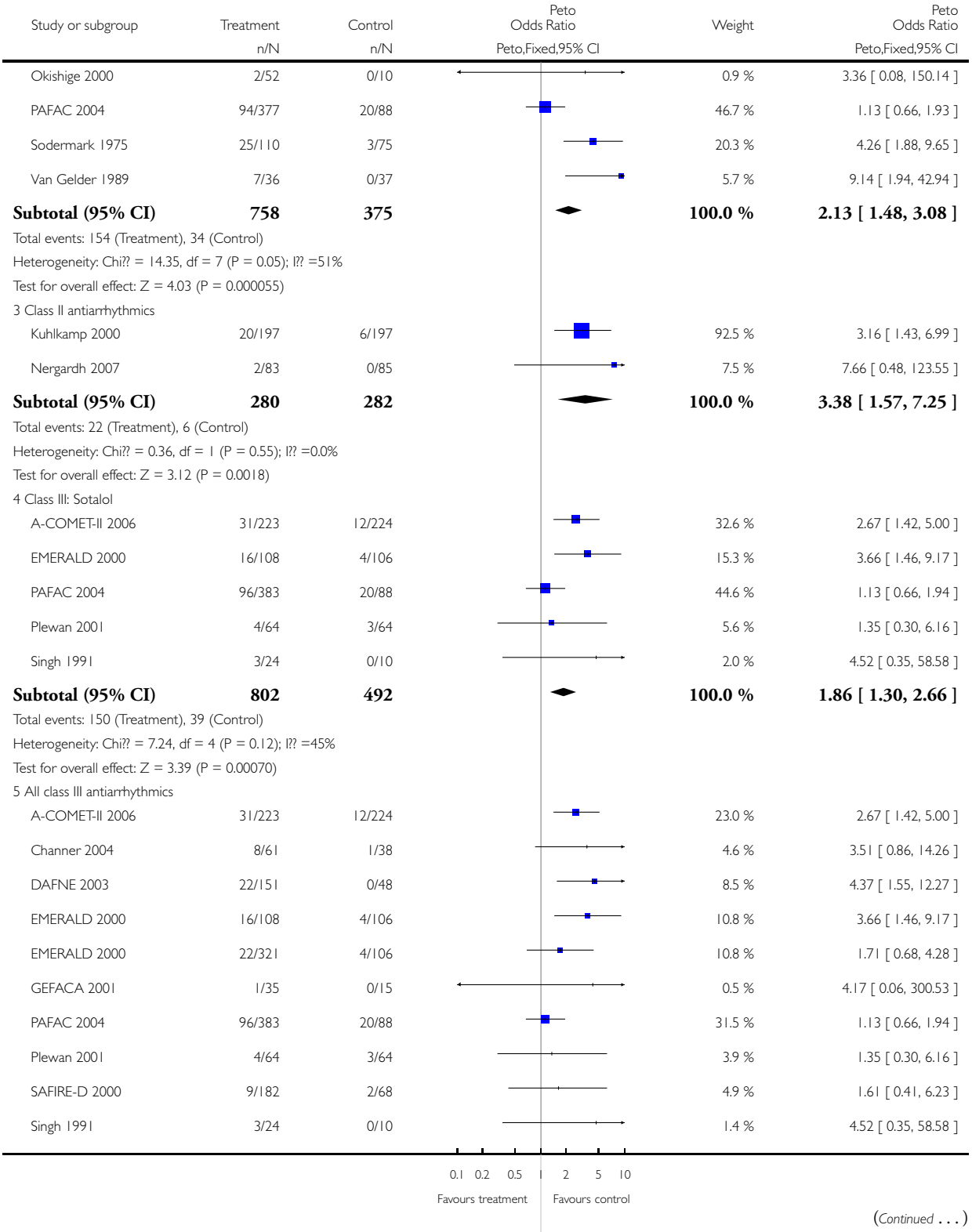

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Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Subtotal (95% CI)	**1552**	**767**		**100.0 %**	**2.03 [1.50, 2.75]**
Total events: 212 (Treatment), 46 (Control)					
Heterogeneity: Chi?? = 10.53, df = 9 (P = 0.31); I?? =14%					
Test for overall effect: Z = 4.62 (P < 0.00001)					
Test for subgroup differences: Chi?? = 2.16, df = 4 (P = 0.71), I?? =0.0%					

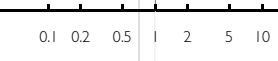
Analysis 2.8. Comparison 2 Withdrawals due to adverse effects, Outcome 8 Sensitivity analysis: Best quality studies.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 2 Withdrawals due to adverse effects

Outcome: 8 Sensitivity analysis: Best quality studies

Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia: Quinidine					
PAFAC 2004	94/377	20/88		33.9 %	1.13 [0.66, 1.93]
SOPAT 2004	87/518	57/251		66.1 %	0.68 [0.46, 1.00]
Subtotal (95% CI)	**895**	**339**		**100.0 %**	**0.81 [0.59, 1.10]**
Total events: 181 (Antiarrhythmic), 77 (Control)					
Heterogeneity: Chi?? = 2.25, df = 1 (P = 0.13); I?? =56%					
Test for overall effect: Z = 1.35 (P = 0.18)					
2 All class I antiarrhythmics					
PAFAC 2004	94/377	20/88		29.6 %	1.13 [0.66, 1.93]
SMART 2002	2/47	3/47		2.7 %	0.66 [0.11, 3.95]
SOPAT 2004	87/518	57/251		57.7 %	0.68 [0.46, 1.00]
Stroobandt 1997	17/77	2/25		6.5 %	2.51 [0.79, 7.95]
Van Gelder 1989	7/36	0/37		3.6 %	9.14 [1.94, 42.94]
Subtotal (95% CI)	**1055**	**448**		**100.0 %**	**0.94 [0.70, 1.26]**
Total events: 207 (Antiarrhythmic), 82 (Control)					



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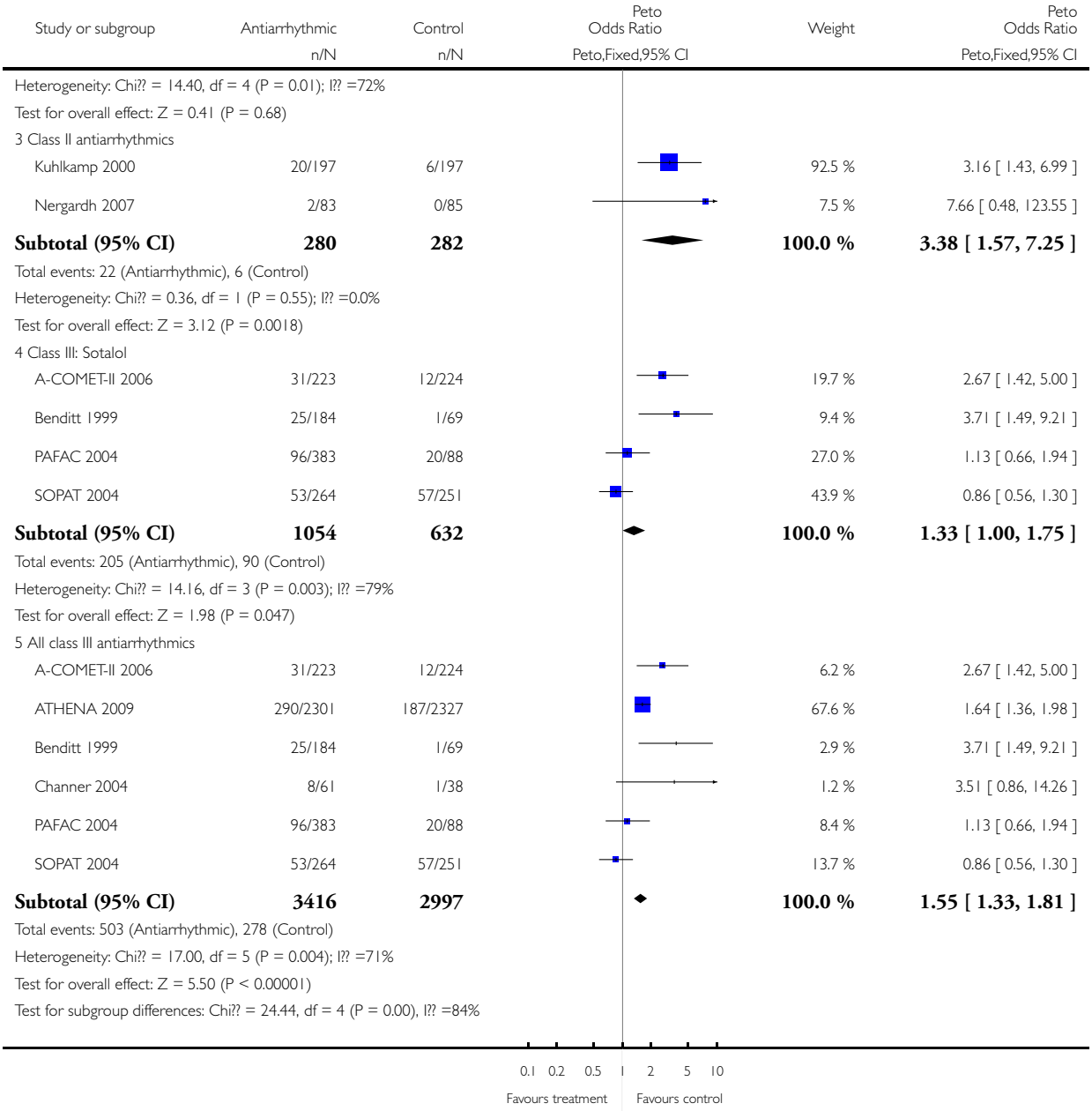


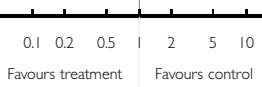
Analysis 2.9. Comparison 2 Withdrawals due to adverse effects, Outcome 9 Sensitivity analysis: Studies > 200 patients.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 2 Withdrawals due to adverse effects

Outcome: 9 Sensitivity analysis: Studies > 200 patients

Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia: Quinidine					
PAFAC 2004	94/377	20/88		33.9 %	1.13 [0.66, 1.93]
SOPAT 2004	87/518	57/251		66.1 %	0.68 [0.46, 1.00]
Subtotal (95% CI)	**895**	**339**		**100.0 %**	**0.81 [0.59, 1.10]**
Total events: 181 (Antiarrhythmic), 77 (Control)					
Heterogeneity: Chi?? = 2.25, df = 1 (P = 0.13); I?? =56%					
Test for overall effect: Z = 1.35 (P = 0.18)					
2 All class I antiarrhythmics					
PAFAC 2004	94/377	20/88		25.4 %	1.13 [0.66, 1.93]
RAFT 2003	69/397	17/126		25.2 %	1.33 [0.77, 2.28]
SOPAT 2004	87/518	57/251		49.4 %	0.68 [0.46, 1.00]
Subtotal (95% CI)	**1292**	**465**		**100.0 %**	**0.91 [0.70, 1.20]**
Total events: 250 (Antiarrhythmic), 94 (Control)					
Heterogeneity: Chi?? = 4.69, df = 2 (P = 0.10); I?? =57%					
Test for overall effect: Z = 0.65 (P = 0.51)					
3 Class II antiarrhythmics					
Kuhlkamp 2000	20/197	6/197		100.0 %	3.16 [1.43, 6.99]
Subtotal (95% CI)	**197**	**197**		**100.0 %**	**3.16 [1.43, 6.99]**
Total events: 20 (Antiarrhythmic), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.84 (P = 0.0045)					
4 Class III: Sotalol					
A-COMET-II 2006	31/223	12/224		18.1 %	2.67 [1.42, 5.00]
Benditt 1999	25/184	1/69		8.6 %	3.71 [1.49, 9.21]
EMERALD 2000	16/108	4/106		8.4 %	3.66 [1.46, 9.17]
PAFAC 2004	96/383	20/88		24.7 %	1.13 [0.66, 1.94]
SOPAT 2004	53/264	57/251		40.2 %	0.86 [0.56, 1.30]
Subtotal (95% CI)	**1162**	**738**		**100.0 %**	**1.44 [1.11, 1.89]**
Total events: 221 (Antiarrhythmic), 94 (Control)					
Heterogeneity: Chi?? = 18.46, df = 4 (P = 0.001); I?? =78%					



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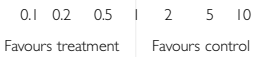
Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Test for overall effect: Z = 2.70 (P = 0.0069)					
5 All class III antiarrhythmics					
A-COMET-I 2006	37/227	16/219		5.3 %	2.36 [1.33, 4.18]
A-COMET-II 2006	31/223	12/224		4.4 %	2.67 [1.42, 5.00]
A-STAR 2006	6/216	1/215		0.8 %	4.24 [0.95, 18.84]
ASAP 2003	46/891	11/489		5.7 %	2.09 [1.20, 3.63]
ATHENA 2009	290/2301	187/2327		48.5 %	1.64 [1.36, 1.98]
Benditt 1999	25/184	1/69		2.1 %	3.71 [1.49, 9.21]
EMERALD 2000	16/108	4/106		2.1 %	3.66 [1.46, 9.17]
EMERALD 2000	22/321	4/106		2.1 %	1.71 [0.68, 4.28]
EURIDIS ADONIS 2007	80/831	29/413		10.0 %	1.38 [0.91, 2.10]
PAFAC 2004	96/383	20/88		6.0 %	1.13 [0.66, 1.94]
SAFIRE-D 2000	9/182	2/68		0.9 %	1.61 [0.41, 6.23]
SOPAT 2004	53/264	57/251		9.8 %	0.86 [0.56, 1.30]
SVA-4 2008	15/211	6/211		2.3 %	2.46 [1.02, 5.91]
Subtotal (95% CI)	**6342**	**4786**		**100.0 %**	**1.64 [1.44, 1.87]**
Total events: 726 (Antiarrhythmic), 350 (Control)					
Heterogeneity: Chi?? = 24.60, df = 12 (P = 0.02); I?? =51%					
Test for overall effect: Z = 7.37 (P < 0.00001)					
Test for subgroup differences: Chi?? = 31.13, df = 4 (P = 0.00), I?? =87%					



Analysis 3.1. Comparison 3 Pro-arrhythmia, Outcome 1 Individual antiarrhythmics.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 3 Pro-arrhythmia

Outcome: 1 Individual antiarrhythmics

Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia: Quinidine				
Byrne-Quinn 1970	1/32	0/42		10.10 [0.19, 527.80]
Hillestad 1971	1/48	0/52		8.03 [0.16, 406.02]
Lloyd 1984	1/28	0/25		6.64 [0.13, 336.66]
PAFAC 2004	17/377	2/88		1.77 [0.55, 5.70]
Sodermark 1975	3/110	0/75		5.48 [0.54, 55.57]
SOPAT 2004	8/518	3/251		1.28 [0.36, 4.55]
Steinbeck 1988	2/15	1/15		2.05 [0.20, 21.36]
Subtotal (95% CI)	**1128**	**548**		**2.10 [1.02, 4.33]**
Total events: 33 (Antiarrhythmic), 6 (Control)				
Heterogeneity: Chi?? = 2.71, df = 6 (P = 0.84); I?? =0.0%				
Test for overall effect: Z = 2.01 (P = 0.044)				
2 Class Ia: Disopyramide				
Karlson 1998	0/46	0/46		0.0 [0.0, 0.0]
Lloyd 1984	0/29	0/25		0.0 [0.0, 0.0]
Subtotal (95% CI)	**75**	**71**		**0.0 [0.0, 0.0]**
Total events: 0 (Antiarrhythmic), 0 (Control)				
Heterogeneity: Chi?? = 0.0, df = 0 (P<0.00001); I?? =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Class Ic: Flecainide				
Carunchio 1995	3/20	0/26		11.10 [1.07, 114.68]
Steinbeck 1988	1/15	1/15		1.00 [0.06, 16.79]
Van Gelder 1989	5/36	0/37		8.56 [1.41, 51.99]
Subtotal (95% CI)	**71**	**78**		**5.97 [1.67, 21.34]**
Total events: 9 (Antiarrhythmic), 1 (Control)				
Heterogeneity: Chi?? = 1.97, df = 2 (P = 0.37); I?? =0.0%				
Test for overall effect: Z = 2.75 (P = 0.0060)				
4 Class Ic: Propafenone				
Bellandi 2001	0/102	0/92		0.0 [0.0, 0.0]
Dogan 2004	1/58	0/52		6.66 [0.13, 337.76]

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Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Kochiadakis 2004b	2/86	0/83		7.22 [0.45, 116.44]
RAFT 2003	0/397	0/126		0.0 [0.0, 0.0]
Stroobandt 1997	3/77	2/25		0.42 [0.05, 3.35]
Subtotal (95% CI)	**720**	**378**		**1.52 [0.33, 7.02]**
Total events: 6 (Antiarrhythmic), 2 (Control)				
Heterogeneity: Chi?? = 3.23, df = 2 (P = 0.20); I?? =38%				
Test for overall effect: Z = 0.53 (P = 0.59)				
5 Class I others: aprindine, pilsicainide				
Okishige 2000	0/52	0/10		0.0 [0.0, 0.0]
SMART 2002	0/47	0/47		0.0 [0.0, 0.0]
Subtotal (95% CI)	**99**	**57**		**0.0 [0.0, 0.0]**
Total events: 0 (Antiarrhythmic), 0 (Control)				
Heterogeneity: Chi?? = 0.0, df = 0 (P<0.00001); I?? =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
6 Class II: Beta-blockers				
Kuhlkamp 2000	15/197	0/197		7.96 [2.84, 22.30]
Nergardh 2007	2/83	0/85		7.66 [0.48, 123.55]
Subtotal (95% CI)	**280**	**282**		**7.92 [3.01, 20.82]**
Total events: 17 (Antiarrhythmic), 0 (Control)				
Heterogeneity: Chi?? = 0.00, df = 1 (P = 0.98); I?? =0.0%				
Test for overall effect: Z = 4.20 (P = 0.000027)				
7 Class III: Amiodarone				
Channer 2004	3/61	0/38		5.24 [0.50, 55.02]
GEFACA 2001	1/35	0/15		4.17 [0.06, 300.53]
Kochiadakis 2000	2/65	0/60		6.95 [0.43, 112.62]
SAFE-T 2005	6/267	2/132		1.45 [0.33, 6.41]
Subtotal (95% CI)	**428**	**245**		**2.65 [0.88, 8.00]**
Total events: 12 (Antiarrhythmic), 2 (Control)				
Heterogeneity: Chi?? = 1.46, df = 3 (P = 0.69); I?? =0.0%				
Test for overall effect: Z = 1.73 (P = 0.084)				
8 Class III: Azimilide				
A-COMET-I 2006	19/227	1/219		6.32 [2.58, 15.48]
A-COMET-II 2006	28/211	1/224		7.82 [3.68, 16.60]
A-STAR 2006	5/216	0/215		7.49 [1.29, 43.61]
ASAP 2003	11/891	1/489		3.30 [1.01, 10.82]
SVA-4 2008	10/211	2/211		3.93 [1.25, 12.38]
Subtotal (95% CI)	**1756**	**1358**		**5.82 [3.69, 9.19]**

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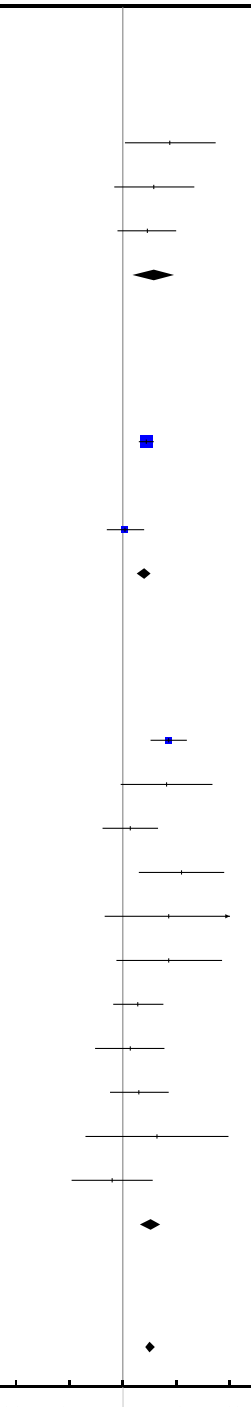
Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 73 (Antiarrhythmic), 5 (Control)				
Heterogeneity: Chi?? = 2.03, df = 4 (P = 0.73); I?? =0.0%				
Test for overall effect: Z = 7.57 (P < 0.00001)				
9 Class III: Dofetilide				
DIAMOND 2001	4/249	0/257		7.72 [1.08, 55.17]
EMERALD 2000	7/321	0/106		3.85 [0.69, 21.68]
SAFIRE-D 2000	12/182	1/68		2.82 [0.80, 9.85]
Subtotal (95% CI)	**752**	**431**		**3.79 [1.54, 9.33]**
Total events: 23 (Antiarrhythmic), 1 (Control)				
Heterogeneity: Chi?? = 0.72, df = 2 (P = 0.70); I?? =0.0%				
Test for overall effect: Z = 2.90 (P = 0.0037)				
10 Class III: Dronedarone				
ATHENA 2009	122/2301	42/2327		2.78 [2.04, 3.80]
DAFNE 2003	0/151	0/48		0.0 [0.0, 0.0]
EURIDIS ADONIS 2007	18/831	8/413		1.12 [0.49, 2.55]
Subtotal (95% CI)	**3283**	**2788**		**2.48 [1.85, 3.32]**
Total events: 140 (Antiarrhythmic), 50 (Control)				
Heterogeneity: Chi?? = 4.10, df = 1 (P = 0.04); I?? =76%				
Test for overall effect: Z = 6.11 (P < 0.00001)				
11 Class III: Sotalol				
A-COMET-II 2006	27/223	1/224		7.25 [3.38, 15.58]
Bellandi 2001	4/106	0/92		6.66 [0.92, 48.27]
Benditt 1999	11/184	3/69		1.36 [0.41, 4.56]
Carunchio 1995	5/20	0/26		12.48 [1.96, 79.58]
EMERALD 2000	2/108	0/106		7.32 [0.45, 117.84]
Kochiadakis 2004b	3/85	0/83		7.39 [0.76, 72.06]
PAFAC 2004	20/383	2/88		1.94 [0.65, 5.80]
Plewan 2001	4/64	3/64		1.35 [0.30, 6.16]
SAFE-T 2005	9/261	2/132		2.03 [0.57, 7.22]
Singh 1991	2/24	0/10		4.31 [0.20, 94.61]
SOPAT 2004	2/264	3/251		0.63 [0.11, 3.69]
Subtotal (95% CI)	**1722**	**1145**		**3.26 [2.13, 4.98]**
Total events: 89 (Antiarrhythmic), 14 (Control)				
Heterogeneity: Chi?? = 15.59, df = 10 (P = 0.11); I?? =36%				
Test for overall effect: Z = 5.47 (P < 0.00001)				
Total (95% CI)	**10314**	**7381**		**3.23 [2.68, 3.90]**



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Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 402 (Antiarrhythmic), 81 (Control)				
Heterogeneity: Chi?? = 48.09, df = 39 (P = 0.15); I?? =19%				
Test for overall effect: Z = 12.21 (P < 0.00001)				
Test for subgroup differences: Chi?? = 16.28, df = 8 (P = 0.04), I?? =51%				

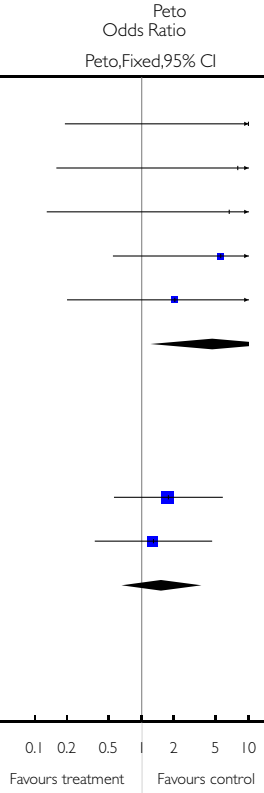
Analysis 3.2. Comparison 3 Pro-arrhythmia, Outcome 2 Quinidine: older and recent studies.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 3 Pro-arrhythmia

Outcome: 2 Quinidine: older and recent studies

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Older studies, higher dose					
Byrne-Quinn 1970	1/32	0/42		3.3 %	10.10 [0.19, 527.80]
Hillestad 1971	1/48	0/52		3.4 %	8.03 [0.16, 406.02]
Lloyd 1984	1/28	0/25		3.4 %	6.64 [0.13, 336.66]
Sodermark 1975	3/110	0/75		9.7 %	5.48 [0.54, 55.57]
Steinbeck 1988	2/15	1/15		9.5 %	2.05 [0.20, 21.36]
Subtotal (95% CI)	**233**	**209**		**29.4 %**	**4.56 [1.20, 17.33]**
Total events: 8 (Treatment), 1 (Control)					
Heterogeneity: Chi?? = 0.74, df = 4 (P = 0.95); I?? =0.0%					
Test for overall effect: Z = 2.23 (P = 0.026)					
2 More recent studies, lower dose					
PAFAC 2004	17/377	2/88		38.1 %	1.77 [0.55, 5.70]
SOPAT 2004	8/518	3/251		32.5 %	1.28 [0.36, 4.55]
Subtotal (95% CI)	**895**	**339**		**70.6 %**	**1.52 [0.64, 3.60]**
Total events: 25 (Treatment), 5 (Control)					
Heterogeneity: Chi?? = 0.13, df = 1 (P = 0.71); I?? =0.0%					
Test for overall effect: Z = 0.96 (P = 0.34)					



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Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Total (95% CI)	**1128**	**548**		**100.0 %**	**2.10 [1.02, 4.33]**
Total events: 33 (Treatment), 6 (Control)					
Heterogeneity: Chi?? = 2.71, df = 6 (P = 0.84); I?? =0.0%					
Test for overall effect: Z = 2.01 (P = 0.044)					
Test for subgroup differences: Chi?? = 1.83, df = 1 (P = 0.18), I?? =45%					

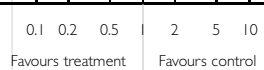
Analysis 3.3. Comparison 3 Pro-arrhythmia, Outcome 3 Class I antiarrhythmics.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 3 Pro-arrhythmia

Outcome: 3 Class I antiarrhythmics

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia				
Byrne-Quinn 1970	1/32	0/42		10.10 [0.19, 527.80]
Hillestad 1971	1/48	0/52		8.03 [0.16, 406.02]
Karlson 1998	0/46	0/46		0.0 [0.0, 0.0]
Lloyd 1984	1/57	0/25		4.21 [0.06, 297.70]
PAFAC 2004	17/377	2/88		1.77 [0.55, 5.70]
Sodermark 1975	3/110	0/75		5.48 [0.54, 55.57]
SOPAT 2004	8/518	3/251		1.28 [0.36, 4.55]
Steinbeck 1988	2/15	1/15		2.05 [0.20, 21.36]
Subtotal (95% CI)	**1203**	**594**		**2.06 [1.00, 4.26]**
Total events: 33 (Treatment), 6 (Control)				
Heterogeneity: Chi?? = 2.48, df = 6 (P = 0.87); I?? =0.0%				
Test for overall effect: Z = 1.96 (P = 0.050)				
2 Class Ib				
SMART 2002	0/47	0/47		0.0 [0.0, 0.0]



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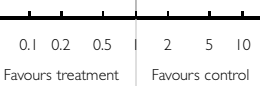
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Subtotal (95% CI)	**47**	**47**		**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 Class Ic				
Bellandi 2001	0/102	0/92		0.0 [0.0, 0.0]
Carunchio 1995	3/20	0/26		11.10 [1.07, 114.68]
Dogan 2004	1/58	0/52		6.66 [0.13, 337.76]
Kochiadakis 2004b	2/86	0/83		7.22 [0.45, 116.44]
Okishige 2000	0/52	0/10		0.0 [0.0, 0.0]
RAFT 2003	0/397	0/126		0.0 [0.0, 0.0]
Steinbeck 1988	1/15	1/15		1.00 [0.06, 16.79]
Stroobandt 1997	3/77	2/25		0.42 [0.05, 3.35]
Van Gelder 1989	5/36	0/37		8.56 [1.41, 51.99]
Subtotal (95% CI)	**843**	**466**		**3.41 [1.28, 9.09]**
Total events: 15 (Treatment), 3 (Control)				
Heterogeneity: Chi?? = 7.01, df = 5 (P = 0.22); I?? =29%				
Test for overall effect: Z = 2.45 (P = 0.014)				
Total (95% CI)	**2093**	**1107**		**2.46 [1.38, 4.41]**
Total events: 48 (Treatment), 9 (Control)				
Heterogeneity: Chi?? = 10.14, df = 12 (P = 0.60); I?? =0.0%				
Test for overall effect: Z = 3.03 (P = 0.0024)				
Test for subgroup differences: Chi?? = 0.65, df = 1 (P = 0.42), I?? =0.0%				



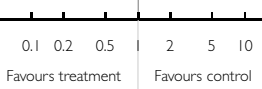
Analysis 3.4. Comparison 3 Pro-arrhythmia, Outcome 4 Sotalol: heterogeneity study.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 3 Pro-arrhythmia

Outcome: 4 Sotalol: heterogeneity study

Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 PAFAC and SOPAT trials					
PAFAC 2004	20/383	2/88		14.9 %	1.94 [0.65, 5.80]
SOPAT 2004	2/264	3/251		5.8 %	0.63 [0.11, 3.69]
Subtotal (95% CI)	**647**	**339**		**20.7 %**	**1.42 [0.56, 3.60]**
Total events: 22 (Antiarrhythmic), 5 (Control)					
Heterogeneity: Chi?? = 1.11, df = 1 (P = 0.29); I?? =10%					
Test for overall effect: Z = 0.73 (P = 0.46)					
2 Rest of studies					
A-COMET-II 2006	27/223	1/224		30.7 %	7.25 [3.38, 15.58]
Bellandi 2001	4/106	0/92		4.6 %	6.66 [0.92, 48.27]
Benditt 1999	11/184	3/69		12.3 %	1.36 [0.41, 4.56]
Carunchio 1995	5/20	0/26		5.2 %	12.48 [1.96, 79.58]
EMERALD 2000	2/108	0/106		2.3 %	7.32 [0.45, 117.84]
Kochiadakis 2004b	3/85	0/83		3.5 %	7.39 [0.76, 72.06]
Plewan 2001	4/64	3/64		7.8 %	1.35 [0.30, 6.16]
SAFE-T 2005	9/261	2/132		11.2 %	2.03 [0.57, 7.22]
Singh 1991	2/24	0/10		1.9 %	4.31 [0.20, 94.61]
Subtotal (95% CI)	**1075**	**806**		**79.3 %**	**4.05 [2.52, 6.51]**
Total events: 67 (Antiarrhythmic), 9 (Control)					
Heterogeneity: Chi?? = 10.61, df = 8 (P = 0.22); I?? =25%					
Test for overall effect: Z = 5.77 (P < 0.00001)					
Total (95% CI)	**1722**	**1145**		**100.0 %**	**3.26 [2.13, 4.98]**
Total events: 89 (Antiarrhythmic), 14 (Control)					
Heterogeneity: Chi?? = 15.59, df = 10 (P = 0.11); I?? =36%					
Test for overall effect: Z = 5.47 (P < 0.00001)					
Test for subgroup differences: Chi?? = 3.87, df = 1 (P = 0.05), I?? =74%					

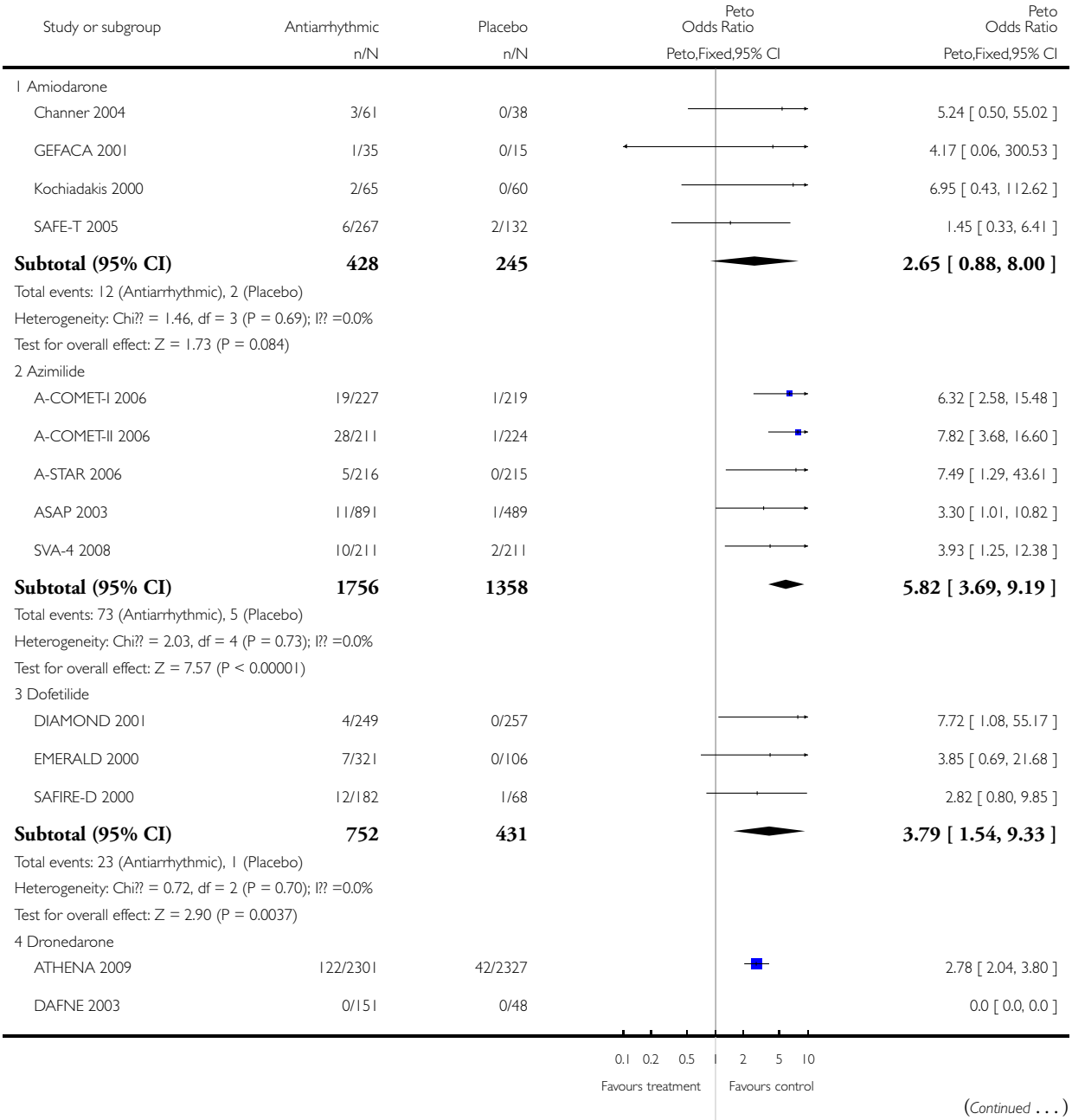


Analysis 3.5. Comparison 3 Pro-arrhythmia, Outcome 5 Class III antiarrhythmics.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 3 Pro-arrhythmia

Outcome: 5 Class III antiarrhythmics



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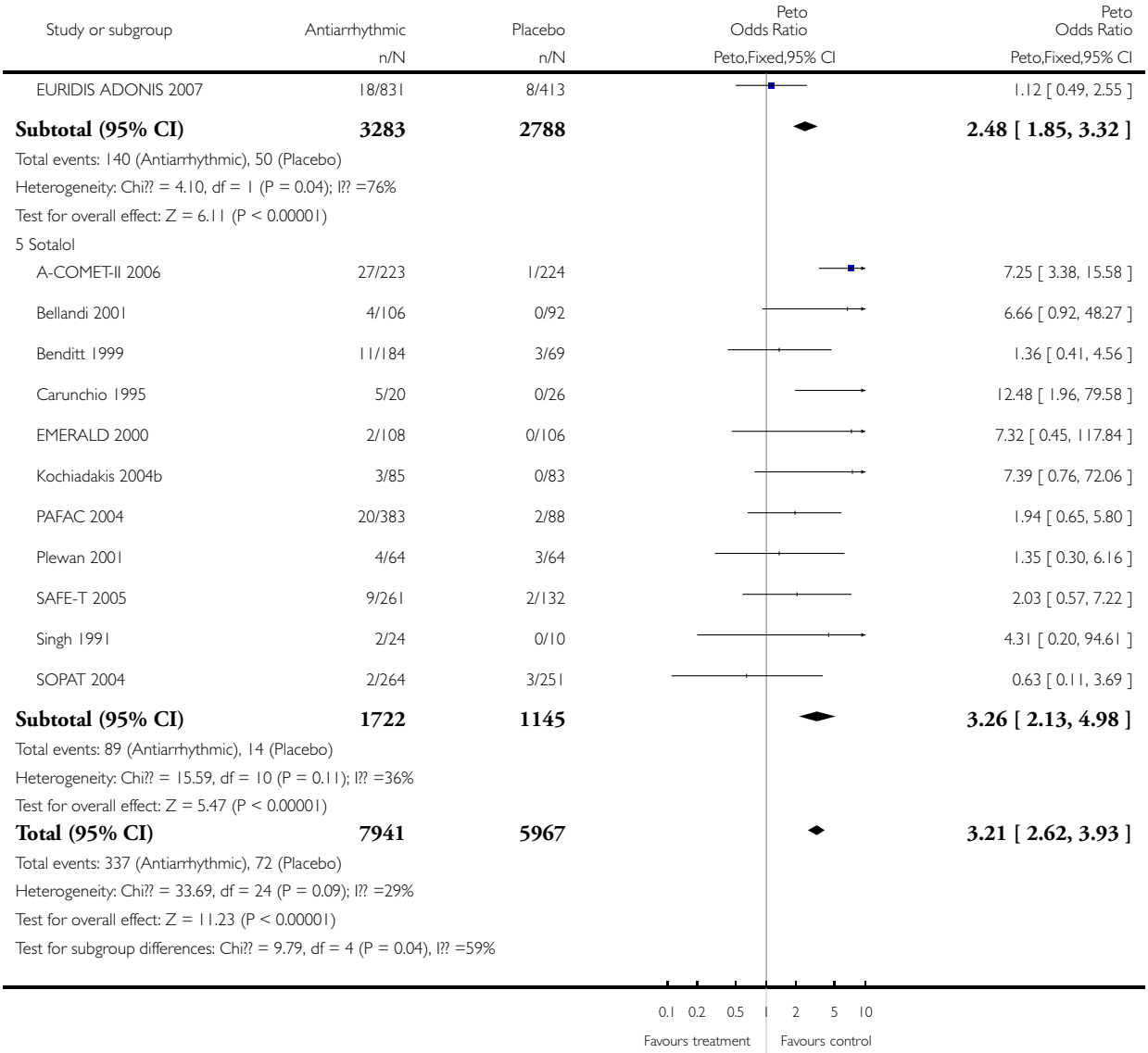
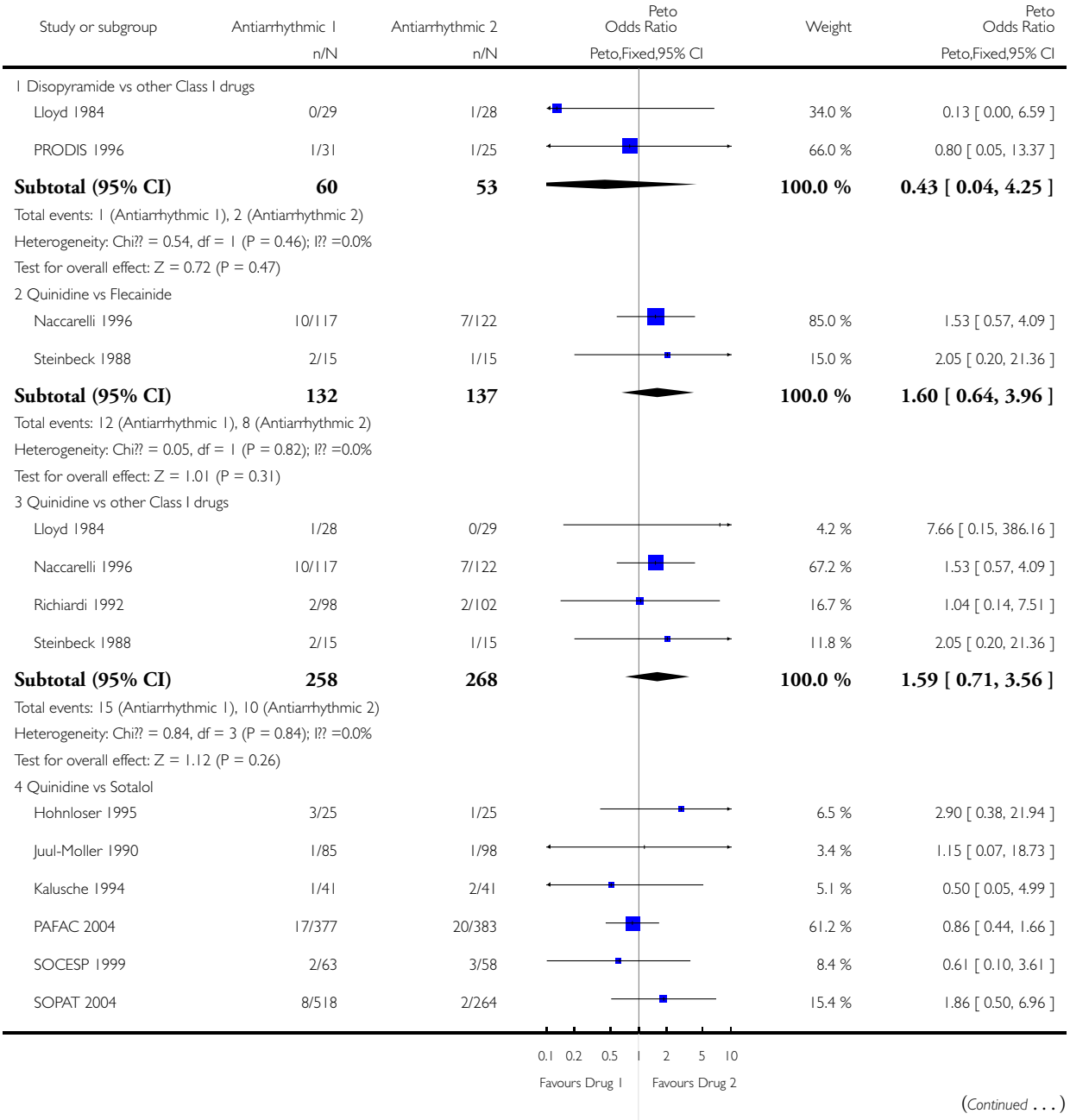


Analysis 3.6. Comparison 3 Pro-arrhythmia, Outcome 6 Comparing antiarrhythmic drugs.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 3 Pro-arrhythmia

Outcome: 6 Comparing antiarrhythmic drugs



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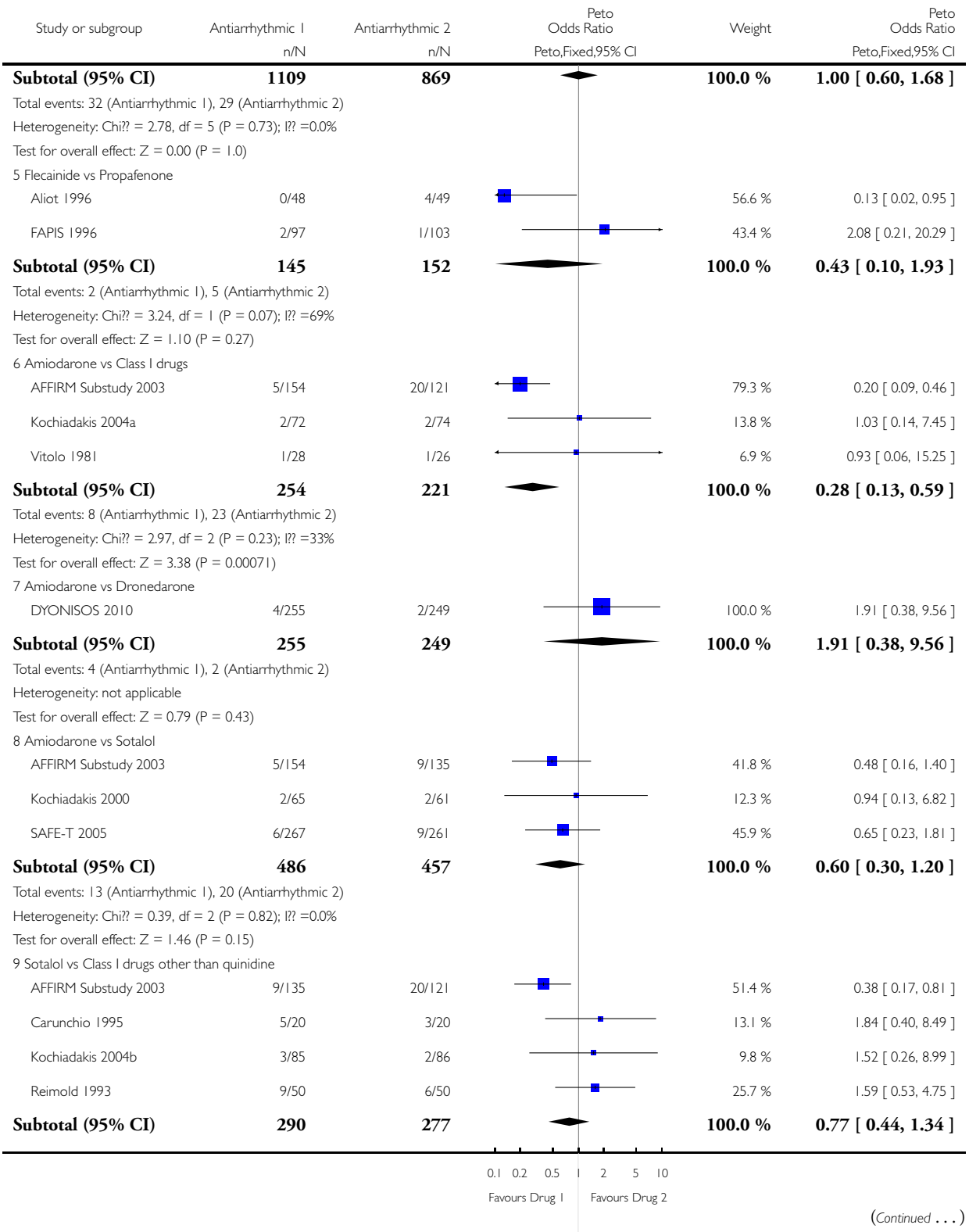

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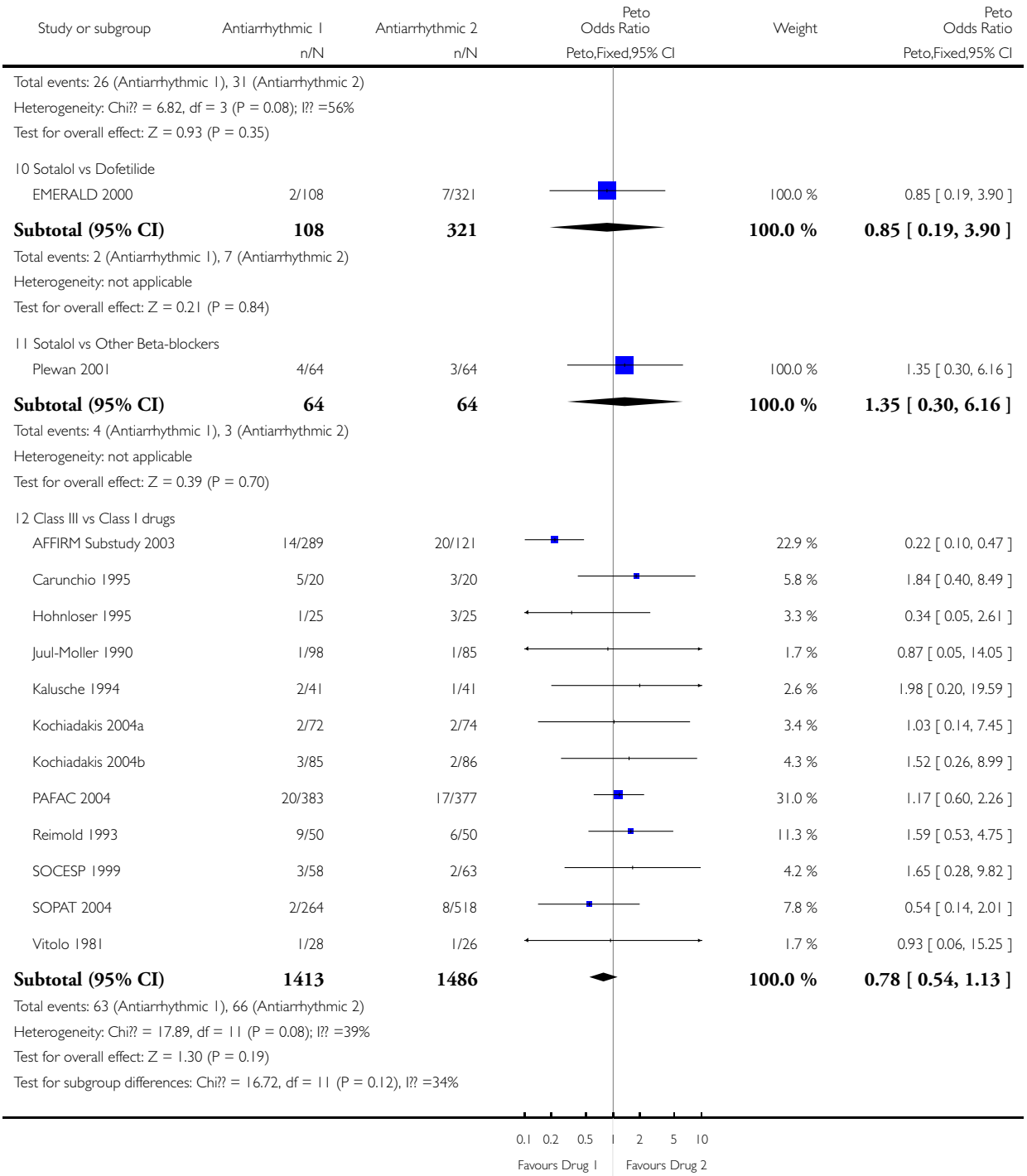
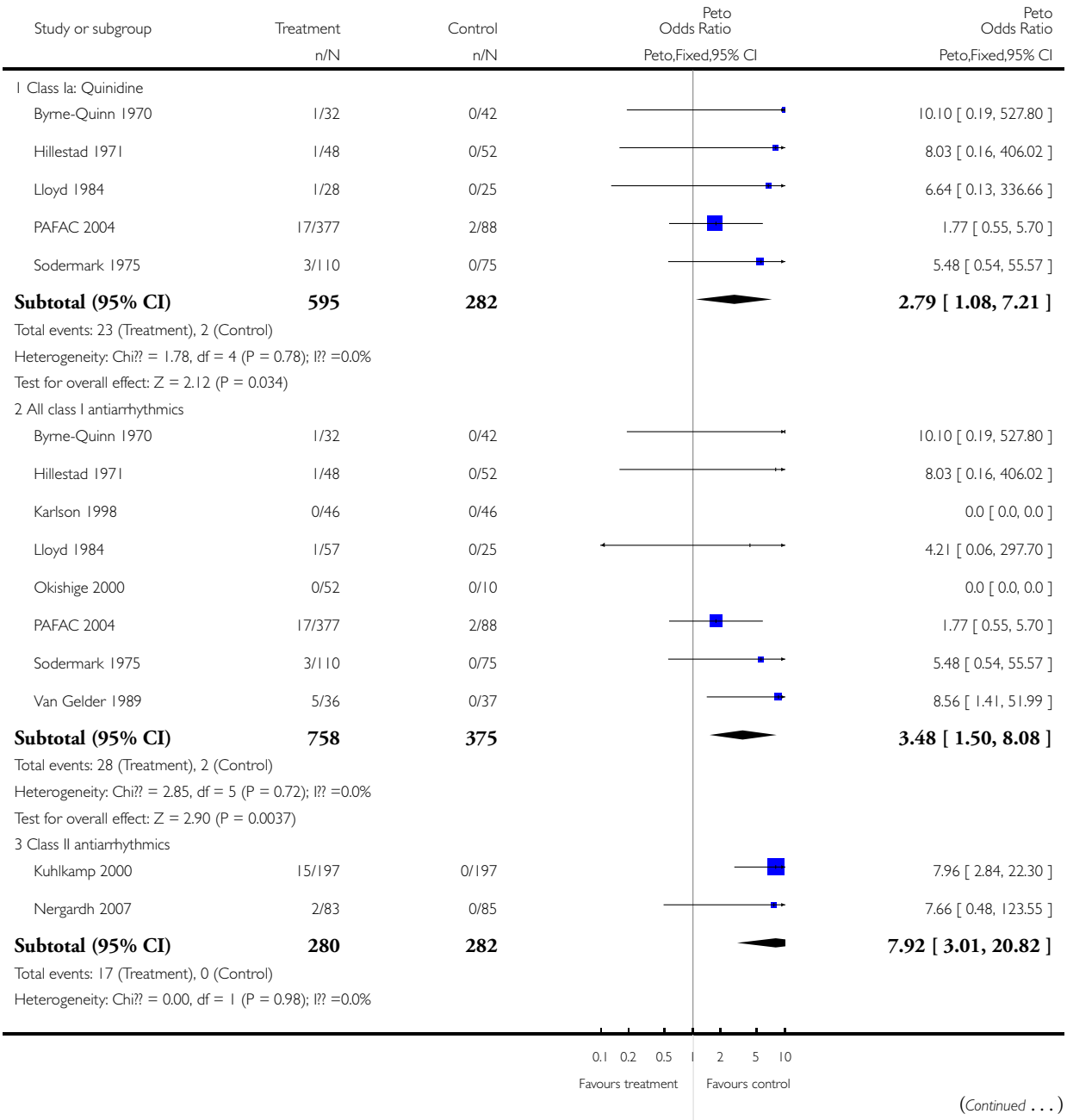


Analysis 3.7. Comparison 3 Pro-arrhythmia, Outcome 7 Subgroup analysis: Persistent atrial fibrillation.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 3 Pro-arrhythmia

Outcome: 7 Subgroup analysis: Persistent atrial fibrillation



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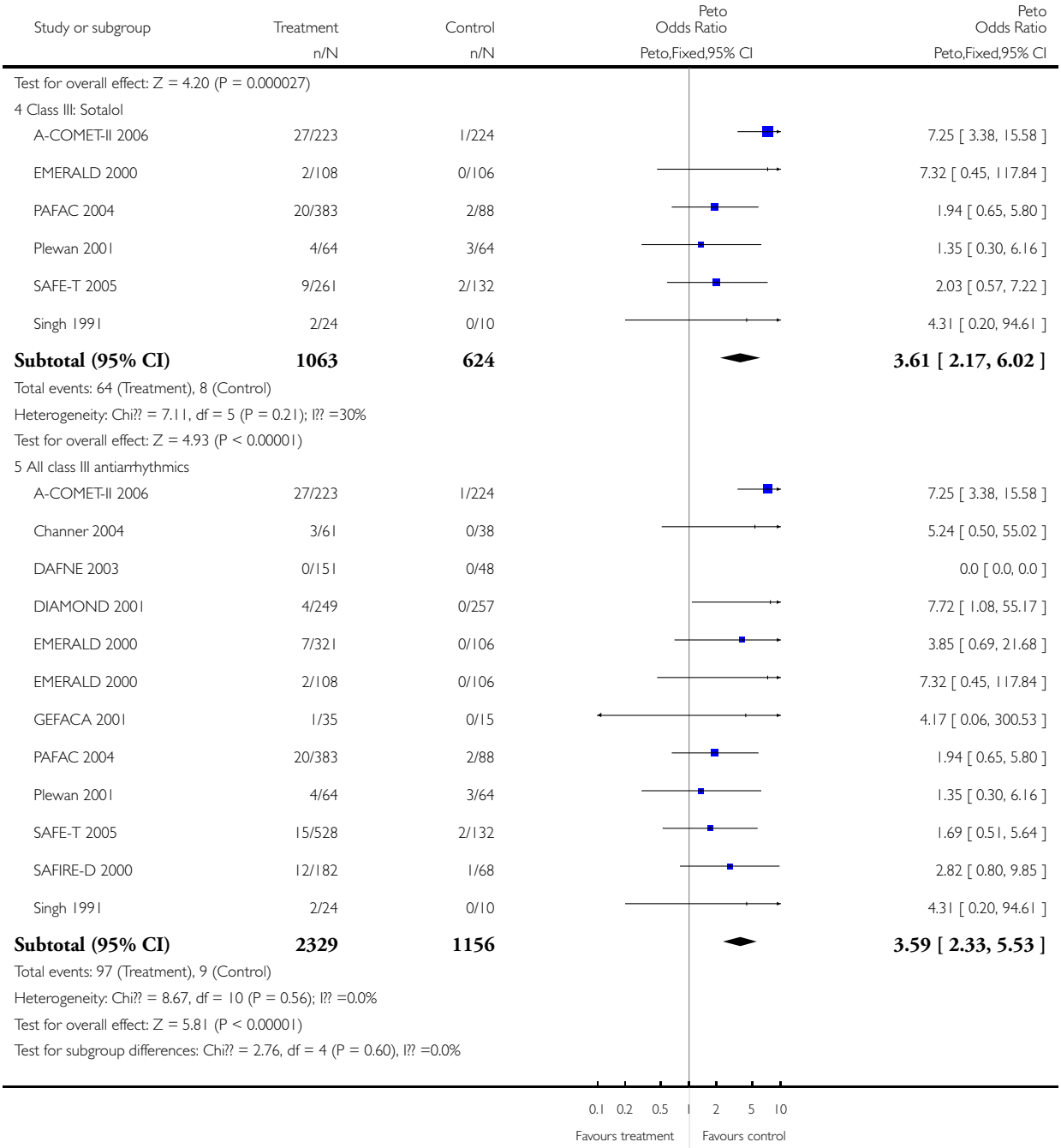
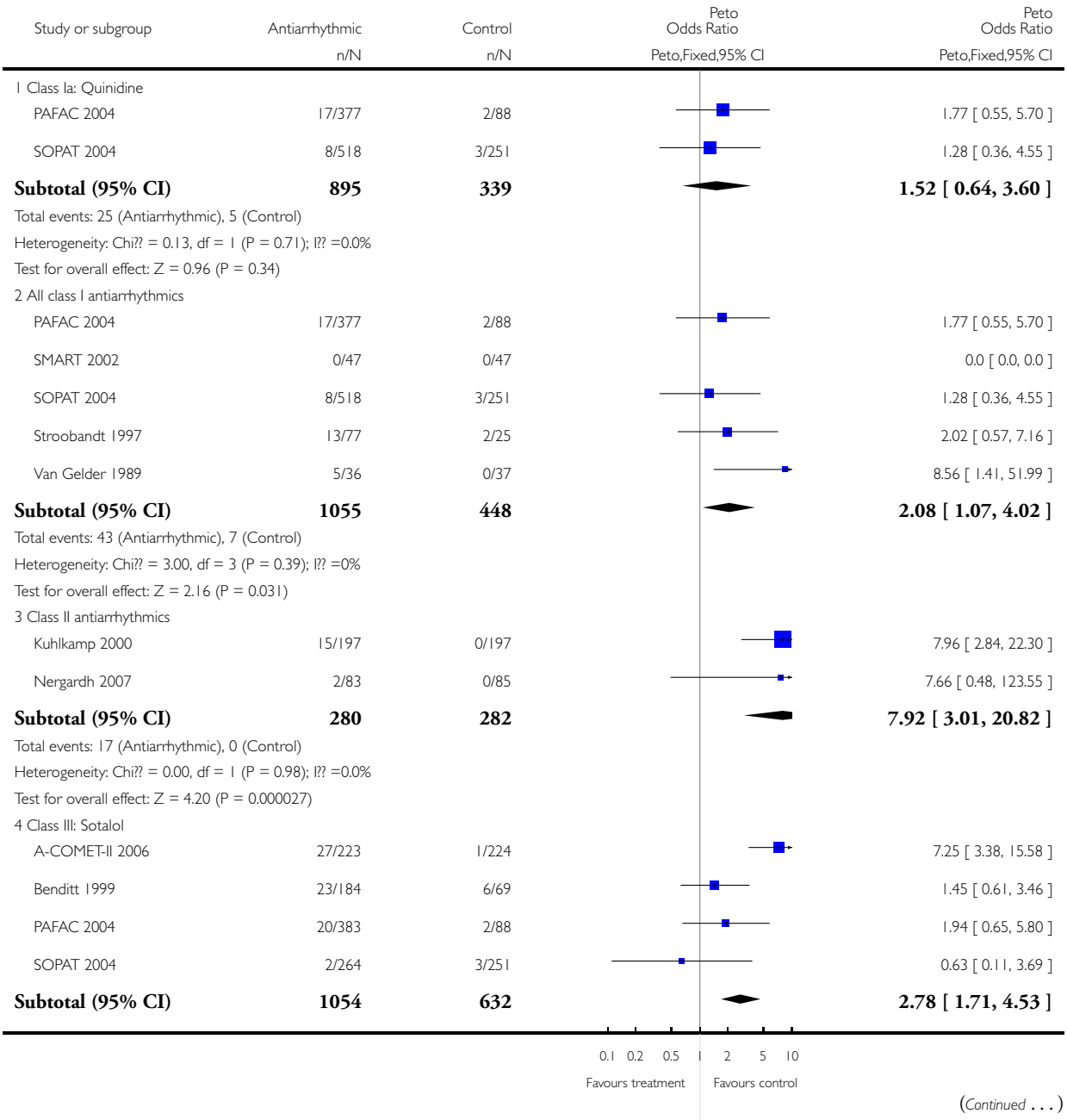


Analysis 3.8. Comparison 3 Pro-arrhythmia, Outcome 8 Sensitivity analysis: Best quality studies.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 3 Pro-arrhythmia

Outcome: 8 Sensitivity analysis: Best quality studies



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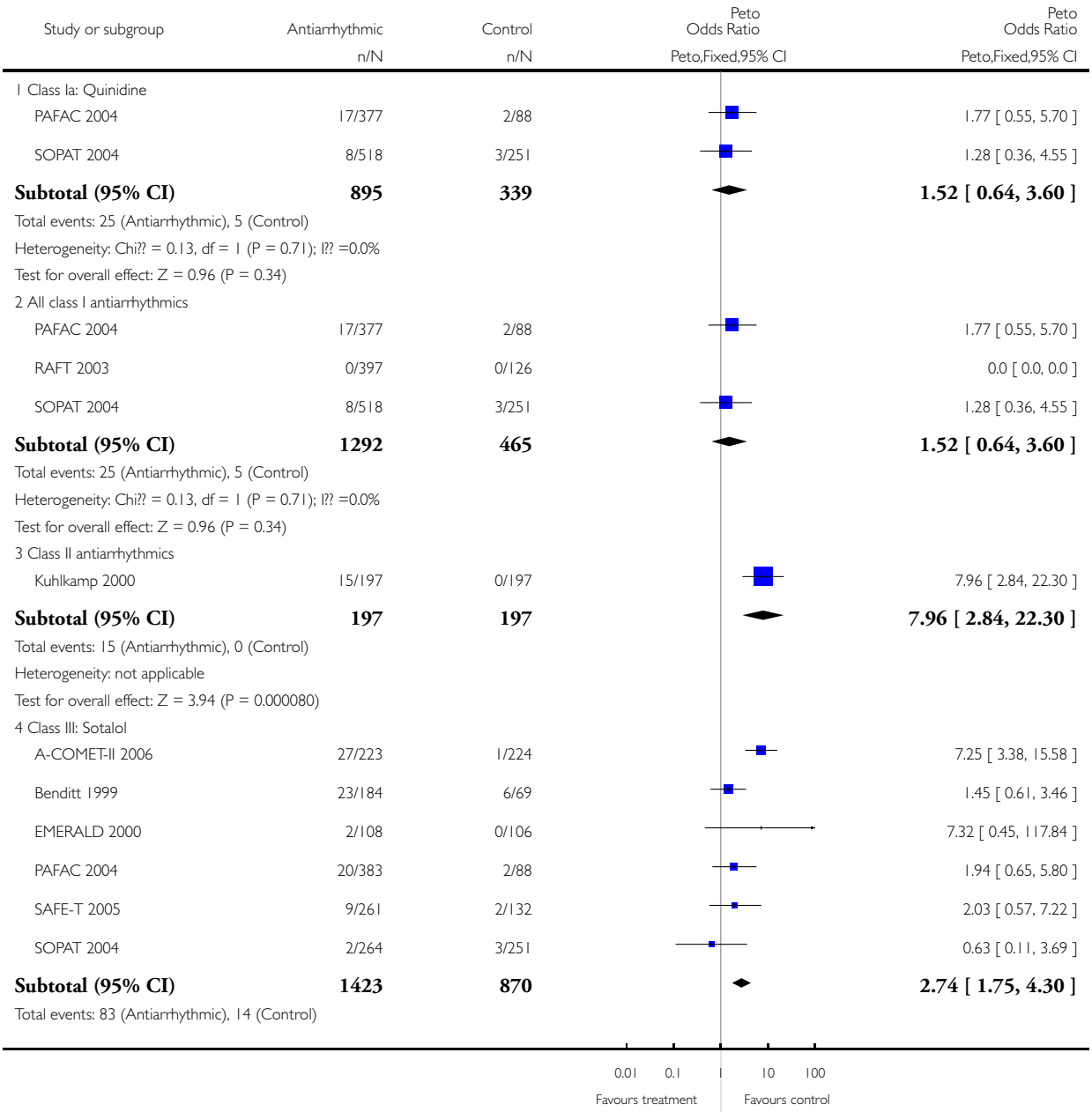
Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 72 (Antiarrhythmic), 12 (Control)				
Heterogeneity: Chi?? = 11.32, df = 3 (P = 0.01); I?? =74%				
Test for overall effect: Z = 4.11 (P = 0.000040)				
5 All class III antiarrhythmics				
A-COMET-II 2006	27/223	1/224		7.25 [3.38, 15.58]
ATHENA 2009	122/2301	42/2327		2.78 [2.04, 3.80]
Benditt 1999	23/184	6/69		1.45 [0.61, 3.46]
Channer 2004	3/61	0/38		5.24 [0.50, 55.02]
DIAMOND 2001	4/249	0/257		7.72 [1.08, 55.17]
PAFAC 2004	20/383	2/88		1.94 [0.65, 5.80]
SOPAT 2004	2/264	3/251		0.63 [0.11, 3.69]
Subtotal (95% CI)	**3665**	**3254**		**2.85 [2.20, 3.70]**
Total events: 201 (Antiarrhythmic), 54 (Control)				
Heterogeneity: Chi?? = 12.60, df = 6 (P = 0.05); I?? =52%				
Test for overall effect: Z = 7.94 (P < 0.00001)				
Test for subgroup differences: Chi?? = 7.17, df = 4 (P = 0.13), I?? =44%				

Analysis 3.9. Comparison 3 Pro-arrhythmia, Outcome 9 Sensitivity analysis: Studies > 200 patients.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 3 Pro-arrhythmia

Outcome: 9 Sensitivity analysis: Studies > 200 patients



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Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Heterogeneity: Chi?? = 12.02, df = 5 (P = 0.03); I?? =58%				
Test for overall effect: Z = 4.40 (P = 0.000011)				
5 All class III antiarrhythmics				
A-COMET-I 2006	19/227	1/219		6.32 [2.58, 15.48]
A-COMET-II 2006	27/223	1/224		7.25 [3.38, 15.58]
A-STAR 2006	5/216	0/215		7.49 [1.29, 43.61]
ASAP 2003	11/891	1/489		3.30 [1.01, 10.82]
ATHENA 2009	122/2301	42/2327		2.78 [2.04, 3.80]
Benditt 1999	23/184	6/69		1.45 [0.61, 3.46]
DIAMOND 2001	4/249	0/257		7.72 [1.08, 55.17]
EMERALD 2000	2/108	0/106		7.32 [0.45, 117.84]
EMERALD 2000	7/321	0/106		3.85 [0.69, 21.68]
EURIDIS ADONIS 2007	18/831	8/413		1.12 [0.49, 2.55]
PAFAC 2004	20/383	2/88		1.94 [0.65, 5.80]
SAFE-T 2005	15/528	2/132		1.69 [0.51, 5.64]
SAFIRE-D 2000	12/182	1/68		2.82 [0.80, 9.85]
SOPAT 2004	2/264	3/251		0.63 [0.11, 3.69]
SVA-4 2008	10/211	2/211		3.93 [1.25, 12.38]
Subtotal (95% CI)	**7119**	**5175**	◆	**2.85 [2.30, 3.55]**
Total events: 297 (Antiarrhythmic), 69 (Control)				
Heterogeneity: Chi?? = 23.12, df = 14 (P = 0.06); I?? =39%				
Test for overall effect: Z = 9.43 (P < 0.00001)				
Test for subgroup differences: Chi?? = 7.81, df = 4 (P = 0.10), I?? =49%				

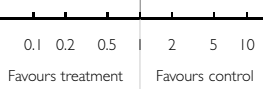
Analysis 4.1. Comparison 4 Atrial fibrillation recurrence, Outcome 1 Individual antiarrhythmics.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 4 Atrial fibrillation recurrence

Outcome: 1 Individual antiarrhythmics

Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia: Quinidine					
Byrne-Quinn 1970	24/32	40/42		0.4 %	0.18 [0.05, 0.69]
Hillestad 1971	14/26	16/22		0.5 %	0.45 [0.14, 1.45]
Lloyd 1984	16/28	17/25		0.6 %	0.64 [0.21, 1.91]
PAFAC 2004	244/377	73/88		2.7 %	0.43 [0.26, 0.71]
Sodermark 1975	58/110	54/75		1.9 %	0.45 [0.25, 0.82]
SOPAT 2004	375/518	204/251		5.5 %	0.62 [0.44, 0.88]
Steinbeck 1988	10/15	13/15		0.2 %	0.34 [0.06, 1.79]
Subtotal (95% CI)	**1106**	**518**		**11.7 %**	**0.51 [0.40, 0.65]**
Total events: 741 (Antiarrhythmic), 417 (Control)					
Heterogeneity: Chi?? = 4.54, df = 6 (P = 0.60); I?? =0.0%					
Test for overall effect: Z = 5.54 (P < 0.00001)					
2 Class Ia: Disopyramide					
Karlson 1998	24/46	32/46		1.0 %	0.49 [0.21, 1.12]
Lloyd 1984	16/29	17/25		0.6 %	0.59 [0.20, 1.75]
Subtotal (95% CI)	**75**	**71**		**1.5 %**	**0.52 [0.27, 1.01]**
Total events: 40 (Antiarrhythmic), 49 (Control)					
Heterogeneity: Chi?? = 0.08, df = 1 (P = 0.78); I?? =0.0%					
Test for overall effect: Z = 1.93 (P = 0.054)					
3 Class Ic: Flecainide					
Carunchio 1995	6/20	19/26		0.5 %	0.18 [0.06, 0.58]
Steinbeck 1988	6/15	13/15		0.3 %	0.14 [0.03, 0.62]
Van Gelder 1989	19/36	24/37		0.8 %	0.61 [0.24, 1.54]
Subtotal (95% CI)	**71**	**78**		**1.6 %**	**0.31 [0.16, 0.60]**
Total events: 31 (Antiarrhythmic), 56 (Control)					
Heterogeneity: Chi?? = 3.93, df = 2 (P = 0.14); I?? =49%					
Test for overall effect: Z = 3.50 (P = 0.00047)					
4 Class Ic: Propafenone					
Bellandi 2001	45/102	62/92		2.1 %	0.39 [0.22, 0.69]
Dogan 2004	27/58	35/52		1.2 %	0.43 [0.20, 0.92]



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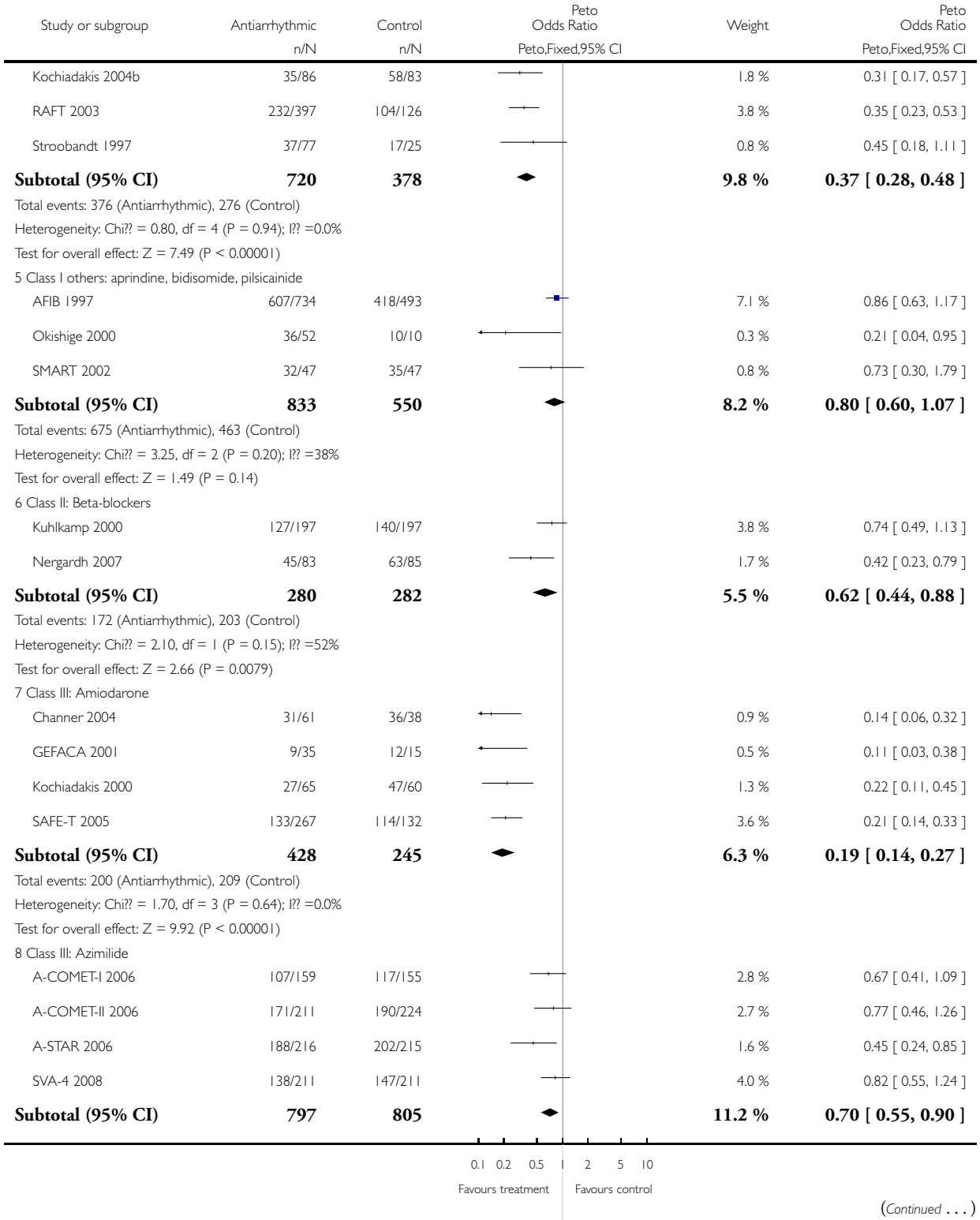

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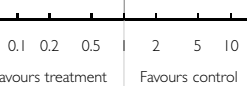
Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 604 (Antiarrhythmic), 656 (Control)					
Heterogeneity: Chi?? = 2.60, df = 3 (P = 0.46); I?? =0.0%					
Test for overall effect: Z = 2.81 (P = 0.0049)					
9 Class III: Dofetilide					
DIAMOND 2001	132/249	221/257		4.7 %	0.21 [0.14, 0.31]
EMERALD 2000	196/321	89/106		3.1 %	0.36 [0.22, 0.57]
SAFIRE-D 2000	120/182	53/68		1.8 %	0.57 [0.31, 1.04]
Subtotal (95% CI)	**752**	**431**		**9.6 %**	**0.30 [0.23, 0.39]**
Total events: 448 (Antiarrhythmic), 363 (Control)					
Heterogeneity: Chi?? = 8.31, df = 2 (P = 0.02); I?? =76%					
Test for overall effect: Z = 8.88 (P < 0.00001)					
10 Class III: Dronedarone					
DAFNE 2003	116/151	43/48		1.0 %	0.45 [0.20, 1.02]
EURIDIS ADONIS 2007	532/831	310/413		10.5 %	0.60 [0.47, 0.78]
Subtotal (95% CI)	**982**	**461**		**11.6 %**	**0.59 [0.46, 0.75]**
Total events: 648 (Antiarrhythmic), 353 (Control)					
Heterogeneity: Chi?? = 0.44, df = 1 (P = 0.51); I?? =0.0%					
Test for overall effect: Z = 4.31 (P = 0.000016)					
11 Class III: Sotalol					
A-COMET-II 2006	150/223	190/224		3.6 %	0.38 [0.25, 0.59]
Bellandi 2001	41/106	62/92		2.2 %	0.32 [0.18, 0.56]
Benditt 1999	138/184	53/69		1.6 %	0.91 [0.48, 1.72]
Carunchio 1995	8/20	19/26		0.5 %	0.26 [0.08, 0.85]
DAPHNE 2008	57/69	54/66		0.9 %	1.06 [0.44, 2.54]
EMERALD 2000	74/108	89/106		1.7 %	0.43 [0.23, 0.80]
Kochiadakis 2004b	43/85	58/83		1.8 %	0.45 [0.24, 0.83]
PAFAC 2004	255/383	73/88		2.6 %	0.46 [0.28, 0.76]
Plewan 2001	31/64	29/64		1.4 %	1.13 [0.57, 2.26]
SAFE-T 2005	183/261	114/132		2.8 %	0.42 [0.26, 0.68]
Singh 1991	19/24	10/10		0.2 %	0.20 [0.03, 1.55]
SOPAT 2004	198/264	204/251		3.9 %	0.69 [0.46, 1.05]
Subtotal (95% CI)	**1791**	**1211**		**23.0 %**	**0.51 [0.43, 0.60]**
Total events: 1197 (Antiarrhythmic), 955 (Control)					
Heterogeneity: Chi?? = 20.68, df = 11 (P = 0.04); I?? =47%					
Test for overall effect: Z = 7.74 (P < 0.00001)					
Total (95% CI)	**7835**	**5030**		**100.0 %**	**0.48 [0.45, 0.53]**



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Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 5132 (Antiarrhythmic), 4000 (Control)					
Heterogeneity: Chi?? = 123.59, df = 46 (P<0.00001); I?? =63%					
Test for overall effect: Z = 17.34 (P < 0.00001)					
Test for subgroup differences: Chi?? = 75.15, df = 10 (P = 0.00), I?? =87%					

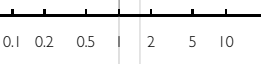
Analysis 4.2. Comparison 4 Atrial fibrillation recurrence, Outcome 2 Quinidine: old and recent studies.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 4 Atrial fibrillation recurrence

Outcome: 2 Quinidine: old and recent studies

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Older studies, higher dose					
Byrne-Quinn 1970	24/32	40/42		3.2 %	0.18 [0.05, 0.69]
Hillestad 1971	14/26	16/22		4.2 %	0.45 [0.14, 1.45]
Lloyd 1984	16/28	17/25		4.7 %	0.64 [0.21, 1.91]
Sodermark 1975	58/110	54/75		15.9 %	0.45 [0.25, 0.82]
Steinbeck 1988	10/15	13/15		2.1 %	0.34 [0.06, 1.79]
Subtotal (95% CI)	**211**	**179**		**30.1 %**	**0.42 [0.27, 0.65]**
Total events: 122 (Treatment), 140 (Control)					
Heterogeneity: Chi?? = 2.19, df = 4 (P = 0.70); I?? =0.0%					
Test for overall effect: Z = 3.88 (P = 0.00011)					
2 More recent studies, lower dose					
PAFAC 2004	244/377	73/88		23.1 %	0.43 [0.26, 0.71]
SOPAT 2004	375/518	204/251		46.8 %	0.62 [0.44, 0.88]
Subtotal (95% CI)	**895**	**339**		**69.9 %**	**0.55 [0.41, 0.73]**
Total events: 619 (Treatment), 277 (Control)					
Heterogeneity: Chi?? = 1.36, df = 1 (P = 0.24); I?? =26%					
Test for overall effect: Z = 4.09 (P = 0.000044)					



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Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Total (95% CI)	**1106**	**518**	◆	**100.0 %**	**0.51 [0.40, 0.65]**
Total events: 741 (Treatment), 417 (Control)					
Heterogeneity: Chi?? = 4.54, df = 6 (P = 0.60); I?? =0.0%					
Test for overall effect: Z = 5.54 (P < 0.00001)					
Test for subgroup differences: Chi?? = 1.00, df = 1 (P = 0.32), I?? =0.0%					

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

Analysis 4.3. Comparison 4 Atrial fibrillation recurrence, Outcome 3 Class I antiarrhythmics.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 4 Atrial fibrillation recurrence

Outcome: 3 Class I antiarrhythmics

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia					
Byrne-Quinn 1970	24/32	40/42		1.2 %	0.18 [0.05, 0.69]
Hillestad 1971	14/26	16/22		1.5 %	0.45 [0.14, 1.45]
Karlson 1998	24/46	32/46		3.0 %	0.49 [0.21, 1.12]
Lloyd 1984	32/57	17/25		2.3 %	0.61 [0.24, 1.59]
PAFAC 2004	244/377	73/88		8.3 %	0.43 [0.26, 0.71]
Sodermark 1975	58/110	54/75		5.8 %	0.45 [0.25, 0.82]
SOPAT 2004	375/518	204/251		16.9 %	0.62 [0.44, 0.88]
Steinbeck 1988	10/15	13/15		0.7 %	0.34 [0.06, 1.79]
Subtotal (95% CI)	**1181**	**564**	◆	**39.7 %**	**0.51 [0.40, 0.64]**
Total events: 781 (Treatment), 449 (Control)					
Heterogeneity: Chi?? = 4.55, df = 7 (P = 0.71); I?? =0.0%					
Test for overall effect: Z = 5.83 (P < 0.00001)					
2 Class Ib					
AFIB 1997	607/734	418/493		21.8 %	0.86 [0.63, 1.17]

0.1 0.2 0.5 1 2 5 10
Favours treatment Favours control

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Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
SMART 2002	32/47	35/47		2.6 %	0.73 [0.30, 1.79]
Subtotal (95% CI)	**781**	**540**		**24.4 %**	**0.84 [0.63, 1.13]**
Total events: 639 (Treatment), 453 (Control)					
Heterogeneity: Chi?? = 0.11, df = 1 (P = 0.74); I?? =0.0%					
Test for overall effect: Z = 1.14 (P = 0.26)					
3 Class Ic					
Bellandi 2001	45/102	62/92		6.5 %	0.39 [0.22, 0.69]
Carunchio 1995	6/20	19/26		1.5 %	0.18 [0.06, 0.58]
Dogan 2004	27/58	35/52		3.7 %	0.43 [0.20, 0.92]
Kochiadakis 2004b	35/86	58/83		5.6 %	0.31 [0.17, 0.57]
Okishige 2000	36/52	10/10		0.9 %	0.21 [0.04, 0.95]
RAFT 2003	232/397	104/126		11.8 %	0.35 [0.23, 0.53]
Steinbeck 1988	6/15	13/15		1.0 %	0.14 [0.03, 0.62]
Stroobandt 1997	37/77	17/25		2.5 %	0.45 [0.18, 1.11]
Van Gelder 1989	19/36	24/37		2.4 %	0.61 [0.24, 1.54]
Subtotal (95% CI)	**843**	**466**		**35.9 %**	**0.36 [0.28, 0.45]**
Total events: 443 (Treatment), 342 (Control)					
Heterogeneity: Chi?? = 5.42, df = 8 (P = 0.71); I?? =0.0%					
Test for overall effect: Z = 8.47 (P < 0.00001)					
Total (95% CI)	**2805**	**1570**		**100.0 %**	**0.51 [0.44, 0.58]**
Total events: 1863 (Treatment), 1244 (Control)					
Heterogeneity: Chi?? = 30.40, df = 18 (P = 0.03); I?? =41%					
Test for overall effect: Z = 9.31 (P < 0.00001)					
Test for subgroup differences: Chi?? = 20.33, df = 2 (P = 0.00), I?? =90%					

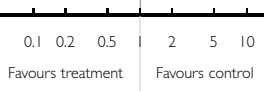
Analysis 4.4. Comparison 4 Atrial fibrillation recurrence, Outcome 4 Class III antiarrhythmics.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 4 Atrial fibrillation recurrence

Outcome: 4 Class III antiarrhythmics

Study or subgroup	Antiarrhythmic n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Amiodarone					
Channer 2004	31/61	36/38		1.5 %	0.14 [0.06, 0.32]
GEFACA 2001	9/35	12/15		0.7 %	0.11 [0.03, 0.38]
Kochiadakis 2000	27/65	47/60		2.1 %	0.22 [0.11, 0.45]
SAFE-T 2005	133/267	114/132		5.9 %	0.21 [0.14, 0.33]
Subtotal (95% CI)	**428**	**245**		**10.3 %**	**0.19 [0.14, 0.27]**
Total events: 200 (Antiarrhythmic), 209 (Placebo)					
Heterogeneity: Chi?? = 1.70, df = 3 (P = 0.64); I?? =0.0%					
Test for overall effect: Z = 9.92 (P < 0.00001)					
2 Azimilide					
A-COMET-I 2006	107/159	117/155		4.6 %	0.67 [0.41, 1.09]
A-COMET-II 2006	171/211	190/224		4.3 %	0.77 [0.46, 1.26]
A-STAR 2006	188/216	202/215		2.6 %	0.45 [0.24, 0.85]
SVA-4 2008	138/211	147/211		6.6 %	0.82 [0.55, 1.24]
Subtotal (95% CI)	**797**	**805**		**18.1 %**	**0.70 [0.55, 0.90]**
Total events: 604 (Antiarrhythmic), 656 (Placebo)					
Heterogeneity: Chi?? = 2.60, df = 3 (P = 0.46); I?? =0.0%					
Test for overall effect: Z = 2.81 (P = 0.0049)					
3 Dofetilide					
DIAMOND 2001	132/249	221/257		7.6 %	0.21 [0.14, 0.31]
EMERALD 2000	196/321	89/106		5.0 %	0.36 [0.22, 0.57]
SAFIRE-D 2000	120/182	53/68		3.0 %	0.57 [0.31, 1.04]
Subtotal (95% CI)	**752**	**431**		**15.6 %**	**0.30 [0.23, 0.39]**
Total events: 448 (Antiarrhythmic), 363 (Placebo)					
Heterogeneity: Chi?? = 8.31, df = 2 (P = 0.02); I?? =76%					
Test for overall effect: Z = 8.88 (P < 0.00001)					
4 Dronedarone					
DAFNE 2003	116/151	43/48		1.7 %	0.45 [0.20, 1.02]
EURIDIS ADONIS 2007	532/831	310/413		17.1 %	0.60 [0.47, 0.78]
Subtotal (95% CI)	**982**	**461**		**18.7 %**	**0.59 [0.46, 0.75]**



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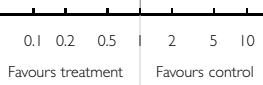
Study or subgroup	Antiarrhythmic n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 648 (Antiarrhythmic), 353 (Placebo)					
Heterogeneity: Chi?? = 0.44, df = 1 (P = 0.51); I?? =0.0%					
Test for overall effect: Z = 4.31 (P = 0.000016)					
5 Sotalol					
A-COMET-II 2006	150/223	190/224		5.8 %	0.38 [0.25, 0.59]
Bellandi 2001	41/106	62/92		3.5 %	0.32 [0.18, 0.56]
Benditt 1999	138/184	53/69		2.6 %	0.91 [0.48, 1.72]
Carunchio 1995	8/20	19/26		0.8 %	0.26 [0.08, 0.85]
DAPHNE 2008	57/69	54/66		1.4 %	1.06 [0.44, 2.54]
EMERALD 2000	74/108	89/106		2.8 %	0.43 [0.23, 0.80]
Kochiadakis 2004b	43/85	58/83		2.9 %	0.45 [0.24, 0.83]
PAFAC 2004	255/383	73/88		4.3 %	0.46 [0.28, 0.76]
Plewan 2001	31/64	29/64		2.3 %	1.13 [0.57, 2.26]
SAFE-T 2005	183/261	114/132		4.6 %	0.42 [0.26, 0.68]
Singh 1991	19/24	10/10		0.3 %	0.20 [0.03, 1.55]
SOPAT 2004	198/264	204/251		6.2 %	0.69 [0.46, 1.05]
Subtotal (95% CI)	**1791**	**1211**		**37.4 %**	**0.51 [0.43, 0.60]**
Total events: 1197 (Antiarrhythmic), 955 (Placebo)					
Heterogeneity: Chi?? = 20.68, df = 11 (P = 0.04); I?? =47%					
Test for overall effect: Z = 7.74 (P < 0.00001)					
Total (95% CI)	**4750**	**3153**		**100.0 %**	**0.46 [0.42, 0.51]**
Total events: 3097 (Antiarrhythmic), 2536 (Placebo)					
Heterogeneity: Chi?? = 87.96, df = 24 (P<0.00001); I?? =73%					
Test for overall effect: Z = 14.48 (P < 0.00001)					
Test for subgroup differences: Chi?? = 54.22, df = 4 (P = 0.00), I?? =93%					

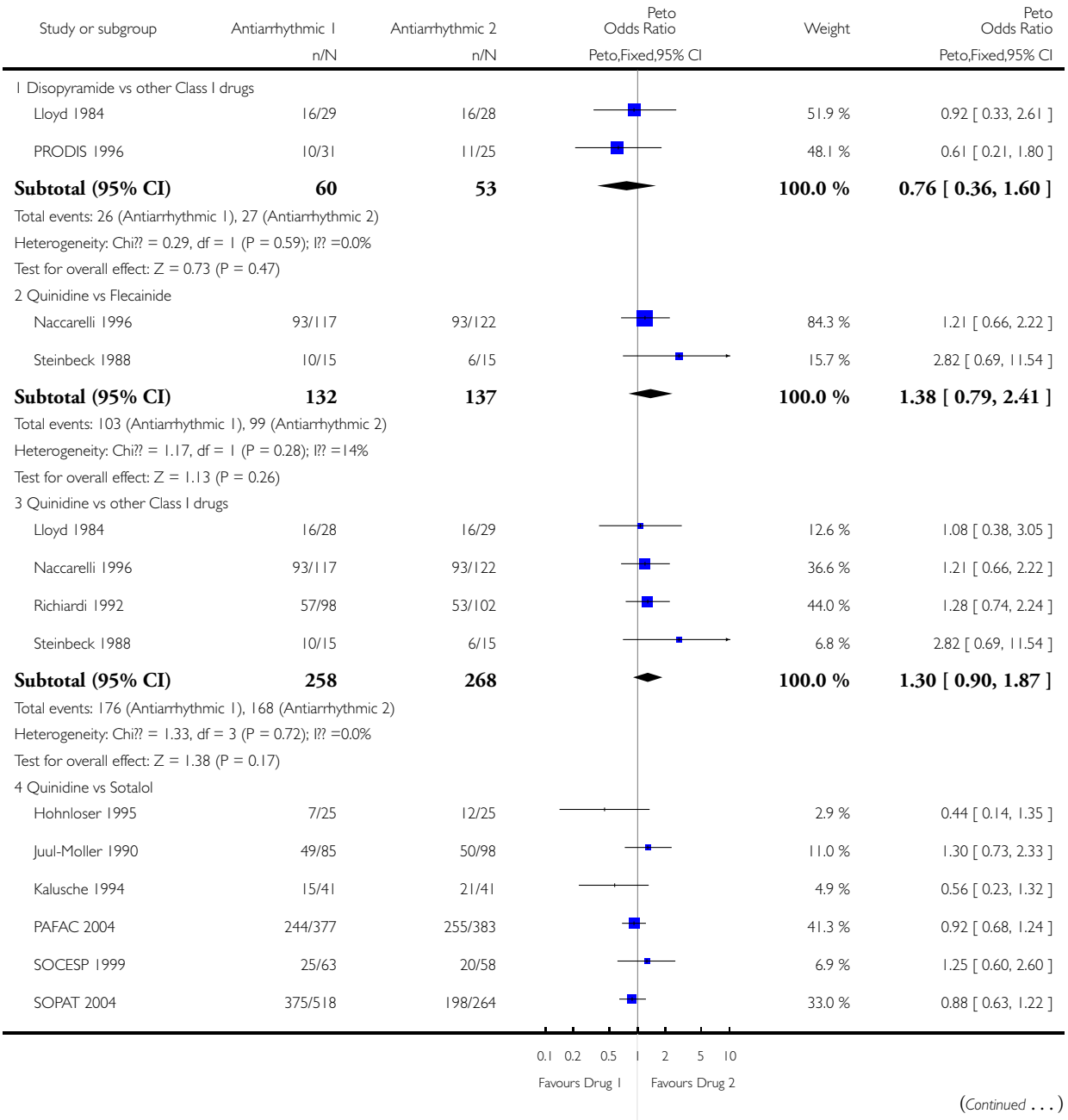


Analysis 4.5. Comparison 4 Atrial fibrillation recurrence, Outcome 5 Comparing antiarrhythmic drugs.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 4 Atrial fibrillation recurrence

Outcome: 5 Comparing antiarrhythmic drugs



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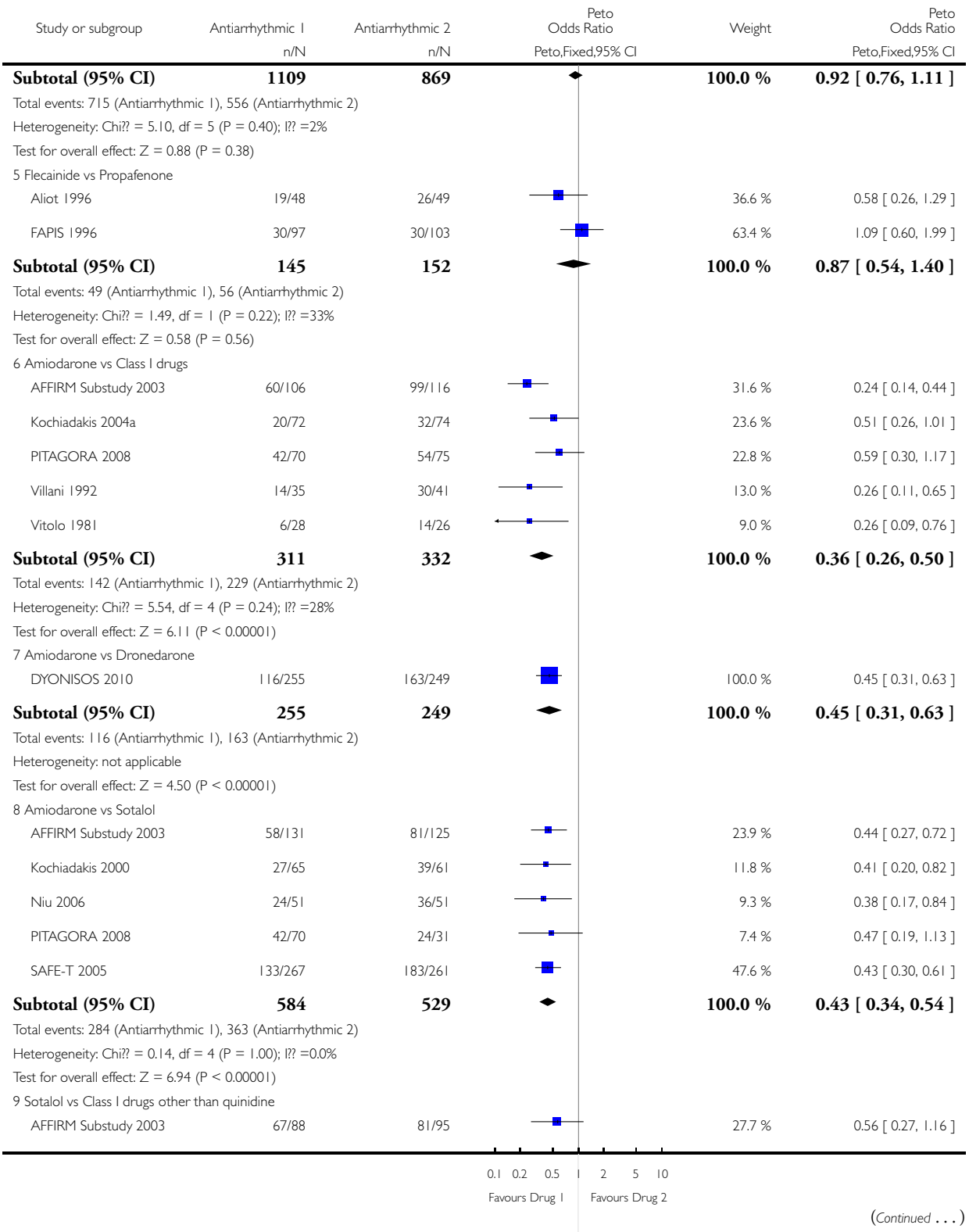

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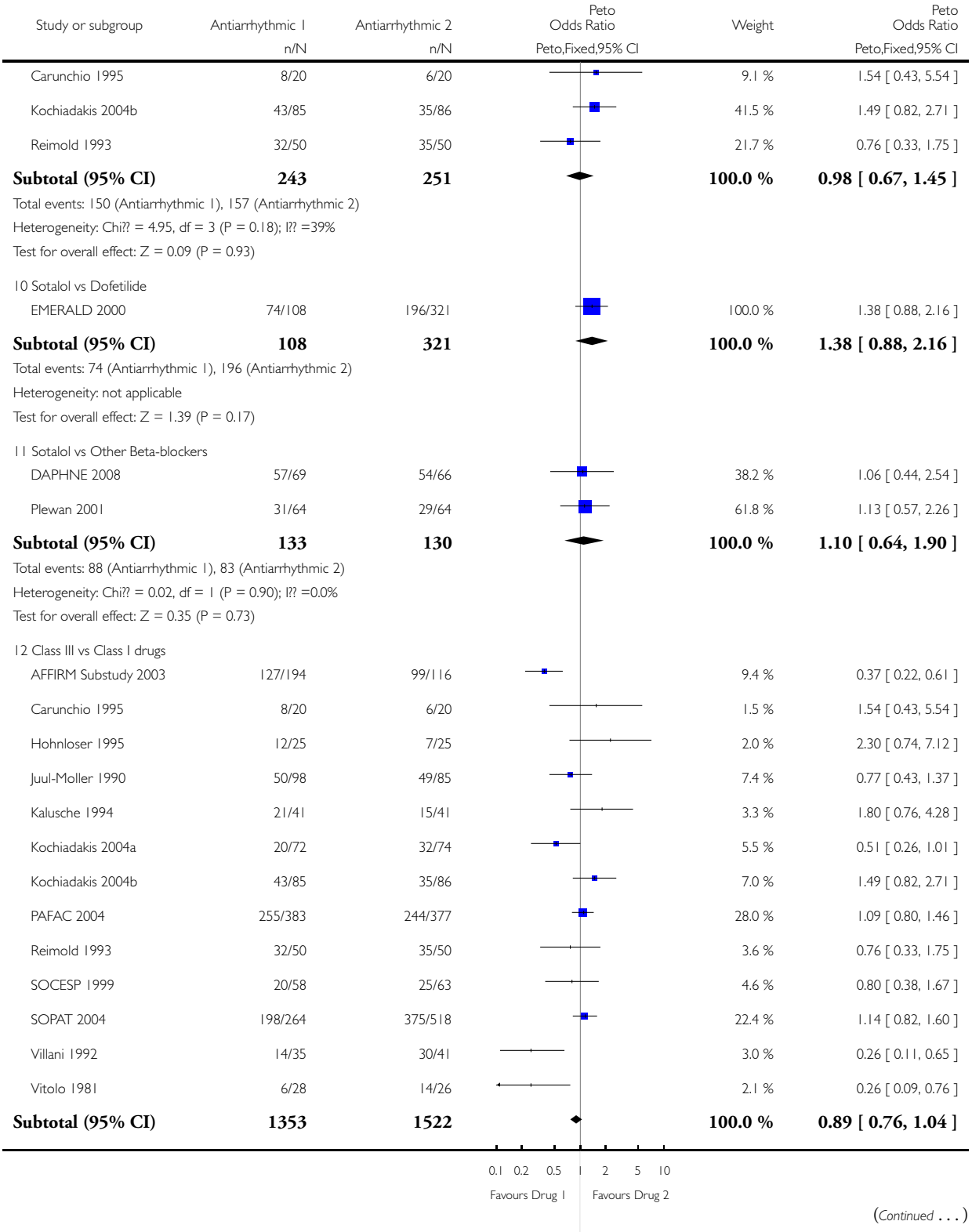

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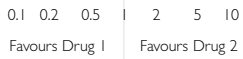
Study or subgroup	Antiarrhythmic 1 n/N	Antiarrhythmic 2 n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Total events: 806 (Antiarrhythmic 1), 966 (Antiarrhythmic 2)					
Heterogeneity: Chi?? = 38.91, df = 12 (P = 0.00011); I?? =69%					
Test for overall effect: Z = 1.45 (P = 0.15)					
Test for subgroup differences: Chi?? = 81.00, df = 11 (P = 0.00), I?? =86%					



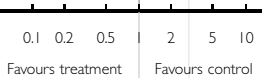
Analysis 4.6. Comparison 4 Atrial fibrillation recurrence, Outcome 6 Subgroup analysis: Persistent atrial fibrillation.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 4 Atrial fibrillation recurrence

Outcome: 6 Subgroup analysis: Persistent atrial fibrillation

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia: Quinidine					
Byrne-Quinn 1970	24/32	40/42		6.3 %	0.18 [0.05, 0.69]
Hillestad 1971	14/26	16/22		8.3 %	0.45 [0.14, 1.45]
Lloyd 1984	16/28	17/25		9.2 %	0.64 [0.21, 1.91]
PAFAC 2004	244/377	73/88		45.1 %	0.43 [0.26, 0.71]
Sodermark 1975	58/110	54/75		31.1 %	0.45 [0.25, 0.82]
Subtotal (95% CI)	**573**	**252**		**100.0 %**	**0.43 [0.31, 0.60]**
Total events: 356 (Treatment), 200 (Control)					
Heterogeneity: Chi?? = 2.12, df = 4 (P = 0.71); I?? =0.0%					
Test for overall effect: Z = 4.94 (P < 0.00001)					
2 All class I antiarrhythmics					
Byrne-Quinn 1970	24/32	40/42		4.6 %	0.18 [0.05, 0.69]
Hillestad 1971	14/26	16/22		6.1 %	0.45 [0.14, 1.45]
Karlson 1998	24/46	32/46		11.8 %	0.49 [0.21, 1.12]
Lloyd 1984	32/57	17/25		9.0 %	0.61 [0.24, 1.59]



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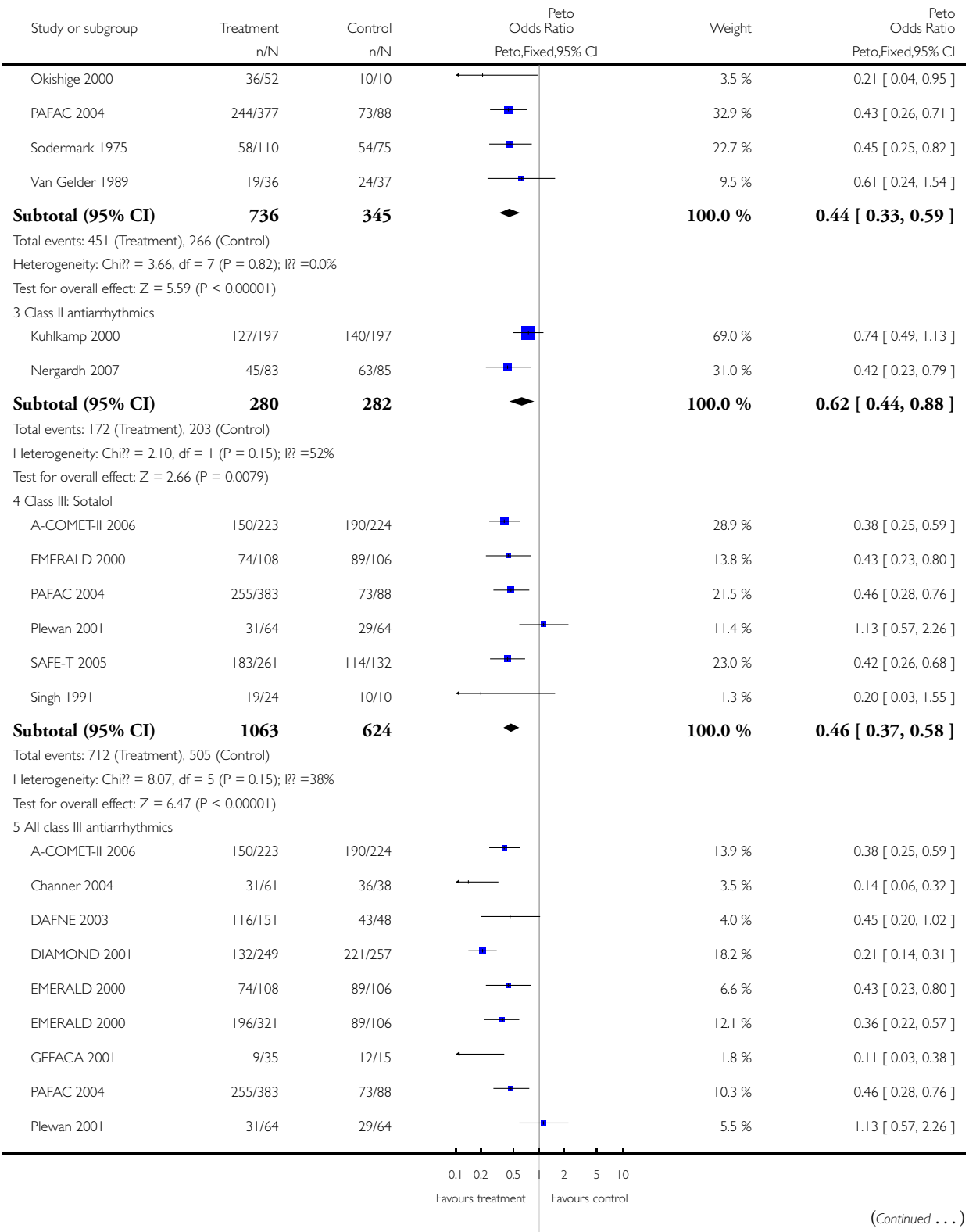

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Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
SAFE-T 2005	316/528	114/132		16.3 %	0.31 [0.21, 0.46]
SAFIRE-D 2000	120/182	53/68		7.2 %	0.57 [0.31, 1.04]
Singh 1991	19/24	10/10		0.6 %	0.20 [0.03, 1.55]
Subtotal (95% CI)	**2329**	**1156**		**100.0 %**	**0.35 [0.30, 0.41]**
Total events: 1449 (Treatment), 959 (Control)					
Heterogeneity: Chi?? = 31.22, df = 11 (P = 0.001); I?? =65%					
Test for overall effect: Z = 12.75 (P < 0.00001)					
Test for subgroup differences: Chi?? = 10.56, df = 4 (P = 0.03), I?? =62%					

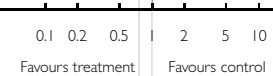
Analysis 4.7. Comparison 4 Atrial fibrillation recurrence, Outcome 7 Sensitivity analysis: Best quality studies.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 4 Atrial fibrillation recurrence

Outcome: 7 Sensitivity analysis: Best quality studies

Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia: Quinidine					
PAFAC 2004	244/377	73/88		33.0 %	0.43 [0.26, 0.71]
SOPAT 2004	375/518	204/251		67.0 %	0.62 [0.44, 0.88]
Subtotal (95% CI)	**895**	**339**		**100.0 %**	**0.55 [0.41, 0.73]**
Total events: 619 (Antiarrhythmic), 277 (Control)					
Heterogeneity: Chi?? = 1.36, df = 1 (P = 0.24); I?? =26%					
Test for overall effect: Z = 4.09 (P = 0.000044)					
2 All class I antiarrhythmics					
PAFAC 2004	244/377	73/88		25.4 %	0.43 [0.26, 0.71]
SMART 2002	32/47	35/47		8.0 %	0.73 [0.30, 1.79]
SOPAT 2004	375/518	204/251		51.5 %	0.62 [0.44, 0.88]



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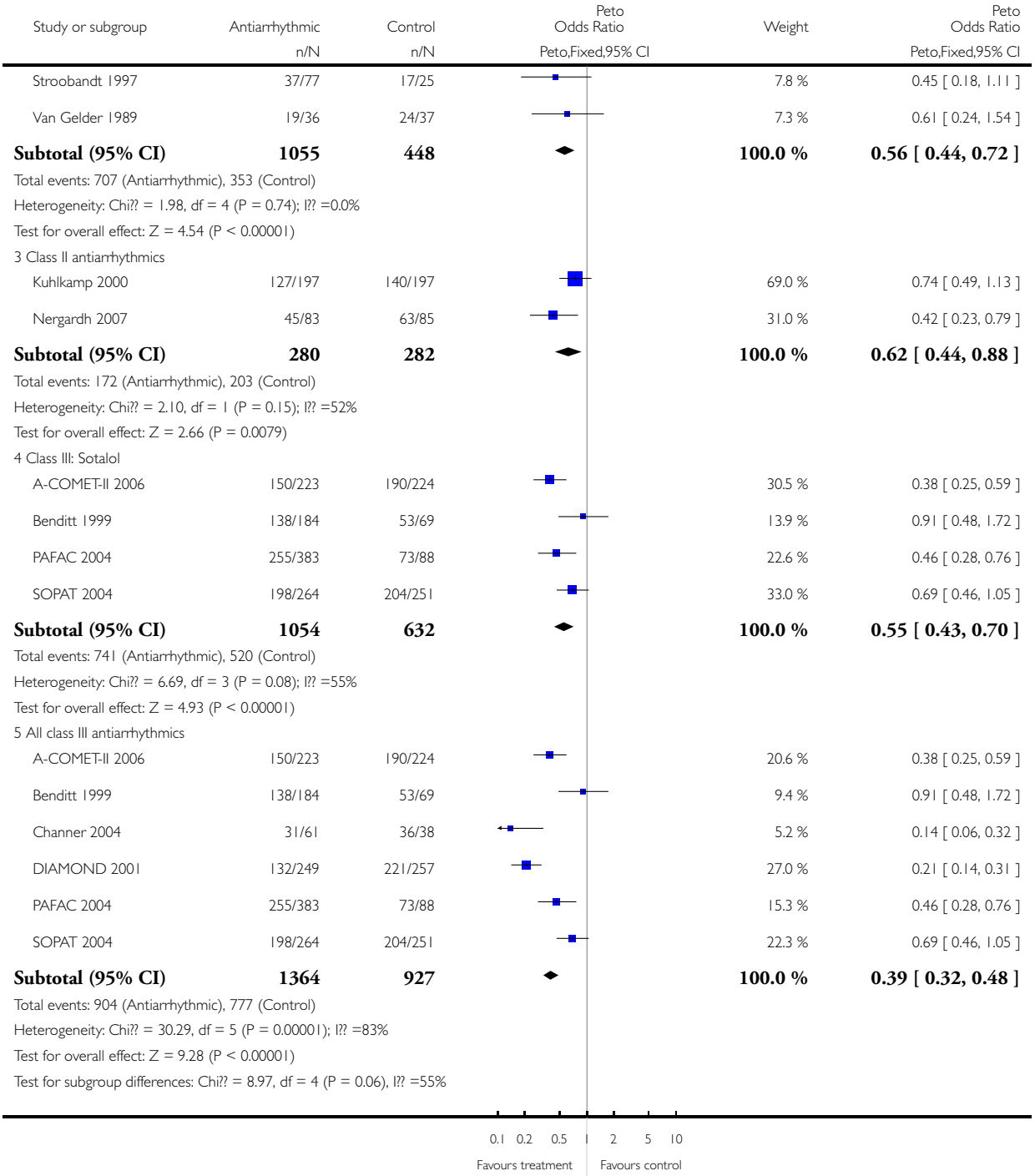


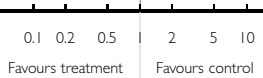
Analysis 4.8. Comparison 4 Atrial fibrillation recurrence, Outcome 8 Sensitivity analysis: Studies > 200 patients.

Review: Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation

Comparison: 4 Atrial fibrillation recurrence

Outcome: 8 Sensitivity analysis: Studies > 200 patients

Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Class Ia: Quinidine					
PAFAC 2004	244/377	73/88		33.0 %	0.43 [0.26, 0.71]
SOPAT 2004	375/518	204/251		67.0 %	0.62 [0.44, 0.88]
Subtotal (95% CI)	**895**	**339**		**100.0 %**	**0.55 [0.41, 0.73]**
Total events: 619 (Antiarrhythmic), 277 (Control)					
Heterogeneity: Chi?? = 1.36, df = 1 (P = 0.24); I?? =26%					
Test for overall effect: Z = 4.09 (P = 0.000044)					
2 All class I antiarrhythmics					
AFIB 1997	607/734	418/493		37.0 %	0.86 [0.63, 1.17]
PAFAC 2004	244/377	73/88		14.2 %	0.43 [0.26, 0.71]
RAFT 2003	232/397	104/126		20.1 %	0.35 [0.23, 0.53]
SOPAT 2004	375/518	204/251		28.7 %	0.62 [0.44, 0.88]
Subtotal (95% CI)	**2026**	**958**		**100.0 %**	**0.59 [0.49, 0.72]**
Total events: 1458 (Antiarrhythmic), 799 (Control)					
Heterogeneity: Chi?? = 13.25, df = 3 (P = 0.004); I?? =77%					
Test for overall effect: Z = 5.47 (P < 0.00001)					
3 Class II antiarrhythmics					
Kuhlkamp 2000	127/197	140/197		100.0 %	0.74 [0.49, 1.13]
Subtotal (95% CI)	**197**	**197**		**100.0 %**	**0.74 [0.49, 1.13]**
Total events: 127 (Antiarrhythmic), 140 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.40 (P = 0.16)					
4 Class III: Sotalol					
A-COMET-II 2006	150/223	190/224		21.9 %	0.38 [0.25, 0.59]
Benditt 1999	138/184	53/69		10.0 %	0.91 [0.48, 1.72]
EMERALD 2000	74/108	89/106		10.5 %	0.43 [0.23, 0.80]
PAFAC 2004	255/383	73/88		16.3 %	0.46 [0.28, 0.76]
SAFE-T 2005	183/261	114/132		17.5 %	0.42 [0.26, 0.68]
SOPAT 2004	198/264	204/251		23.8 %	0.69 [0.46, 1.05]



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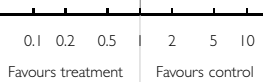
Study or subgroup	Antiarrhythmic n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Subtotal (95% CI)	**1423**	**870**	◆	**100.0 %**	**0.51 [0.42, 0.62]**
Total events: 998 (Antiarrhythmic), 723 (Control)					
Heterogeneity: Chi?? = 8.00, df = 5 (P = 0.16); I?? =38%					
Test for overall effect: Z = 6.52 (P < 0.00001)					
5 All class III antiarrhythmics					
A-COMET-I 2006	107/159	117/155		6.1 %	0.67 [0.41, 1.09]
A-COMET-II 2006	150/223	190/224		7.7 %	0.38 [0.25, 0.59]
A-STAR 2006	188/216	202/215		3.5 %	0.45 [0.24, 0.85]
Benditt 1999	138/184	53/69		3.5 %	0.91 [0.48, 1.72]
DIAMOND 2001	132/249	221/257		10.1 %	0.21 [0.14, 0.31]
EMERALD 2000	196/321	89/106		6.7 %	0.36 [0.22, 0.57]
EMERALD 2000	74/108	89/106		3.7 %	0.43 [0.23, 0.80]
EURIDIS ADONIS 2007	532/831	310/413		22.8 %	0.60 [0.47, 0.78]
PAFAC 2004	255/383	73/88		5.7 %	0.46 [0.28, 0.76]
SAFE-T 2005	316/528	114/132		9.1 %	0.31 [0.21, 0.46]
SAFIRE-D 2000	120/182	53/68		4.0 %	0.57 [0.31, 1.04]
SOPAT 2004	198/264	204/251		8.3 %	0.69 [0.46, 1.05]
SVA-4 2008	138/211	147/211		8.8 %	0.82 [0.55, 1.24]
Subtotal (95% CI)	**3859**	**2295**	◆	**100.0 %**	**0.49 [0.43, 0.55]**
Total events: 2544 (Antiarrhythmic), 1862 (Control)					
Heterogeneity: Chi?? = 44.34, df = 12 (P = 0.00001); I?? =73%					
Test for overall effect: Z = 11.76 (P < 0.00001)					
Test for subgroup differences: Chi?? = 6.00, df = 4 (P = 0.20), I?? =33%					



APPENDICES

Appendix 1. Search strategies 2005

CENTRAL

1 ATRIAL FIBRILLATION
2 (atrial near fibrillat*)
3 (auricular* near fibrillat*)
4 (atrium near fibrillat*)
5 (atrial next arrhythmi*)
6 (#1 or #2 or #3 or #4 or #5)
7 ANTI-ARRHYTHMIA AGENTS
8 antiarrhythmi*
9 anti-arrhythmi*
10 (anti next arrhythmi*)
11 procainamide
12 disopyramide
13 quinidine
14 mexiletine
15 flecainide
16 propafenone
17 bisoprolol
18 esmolol
19 amiodarone
20 dofetilide
21 sotalol
22 azimilide
23 ibutilide
24 cibenzoline
25 moricizine
26 (#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17)
27 (#18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26)
28 (#26 or #27)
29 (#6 and #28)

Search strategy for MEDLINE on PubMed

("Atrial Fibrillation" [mh] OR ((atrial OR atrium OR auricular) AND fibrillat*))
AND
("Anti-Arrhythmia Agents" [mh] OR antiarrhythmi* [tw] OR anti-arrhythmi* [tw] OR procainamide [tw] OR disopyramide [tw] OR quinidine [tw] OR mexiletine [tw] OR flecainide [tw] propafenone [tw] OR bisoprolol [tw] OR esmolol [tw] OR amiodarone [tw] OR dofetilide [tw] OR sotalol [tw] OR ibutilide [tw] OR azimilide [tw] OR moricizine [tw] OR cibenzoline [tw])
AND
("randomized controlled trial" [pt] OR "controlled clinical trial" [pt] OR "randomized controlled trials" [mh] OR "random allocation" [mh] OR "double-blind method" [mh] OR "single-blind method" [mh] OR "clinical trial" [pt] OR "clinical trials" [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR "research design" [mh:noexp] OR "comparative study" [mh] OR "evaluation studies" [mh] OR "follow-up studies" [mh] OR "prospective studies" [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh]))

Notes: The strategy to locate randomized controlled trials is the Cochrane highly sensitive search strategy (all phases), as contained in the Cochrane Reviewer's Handbook (ref: CR Handbook 2003).

The “related articles” feature of PubMed MEDLINE was also used.

Search strategy for EMBASE.com

1 (atrial OR ’atrium’/exp OR auricular) AND fibrillat*

2 ’anti-arrhythmic’ OR antiarrhythmi* OR ’procainamide’/exp OR ’disopyramide’/exp OR ’quinidine’/exp OR ’mexiletine’/exp OR ’flecainide’/exp OR ’propafenone’/exp OR ’bisoprolol’/exp OR ’esmolol’/exp OR ’amiodarone’/exp OR ’dofetilide’/exp OR ’sotalol’/exp OR ’ibutilide’/exp OR ’azimilide’/exp OR ’dronedarone’/exp OR ’moricizine’/exp OR ’cibenzoline’/exp

3 ’randomized controlled trial’/exp OR ’controlled clinical trial’/exp OR ’randomized controlled trials’/exp OR ’random allocation’/exp OR ’double-blind method’/exp OR ’single-blind method’/exp OR ’clinical trial’/exp OR ’clinical trials’/exp OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR (’placebos’/exp OR placebo* OR random* OR ’comparative study’/exp OR ’evaluation studies’/exp OR ’follow-up studies’/exp OR ’prospective studies’/exp OR control* OR prospectiv* OR volunteer*)

4 #1 AND #2 AND #3

Note: The “related articles” feature was also used.

Appendix 2. Search strategies 2010

CENTRAL on The Cochrane Library

#1 MeSH descriptor Atrial Fibrillation this term only
#2 (atrial in All Text near/3 fibrillat* in All Text)
#3 (auricular* in All Text near/3 fibrillat* in All Text)
#4 (atrium in All Text near/3 fibrillat* in All Text)
#5 atrial next arrhythmi* in All Text
#6 (#1 or #2 or #3 or #4 or #5)
#7 MeSH descriptor Anti-Arrhythmia Agents explode all trees
#8 antiarrhythmi* in All Text
#9 anti-arrhythmi* in All Text
#10 dronedarone in All Text
#11 amiodarone in All Text
#12 bisoprolol in All Text
#13 disopyramide in All Text
#14 dofetilide in All Text
#15 azimilide in All Text
#16 ibutilide in All Text
#17 flecainide in All Text
#18 propafenone in All Text
#19 quinidine in All Text
#20 cibenzoline in All Text
#21 moricizine in All Text
#22 mexiletine in All Text
#23 procainamide in All Text
#24 sotalol in All Text
#25 esmolol in All Text
#26 (#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16)
#27 (#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25)
#28 (#26 or #27)

#29 (#6 and #28)

MEDLINE on Ovid

1 Atrial Fibrillation/
2 atrial fibrillation.tw.
3 atrium fibrillation.tw.
4 auricular fibrillation.tw.
5 or/1-4
6 exp Anti-Arrhythmia Agents/
7 antiarrhythmi$.tw.
8 anti-arrhythmi$.tw.
9 dronedarone.tw.
10 amiodarone.tw.
11 bisoprolol.tw.
12 disopyramide.tw.
13 dofetilide.tw.
14 azimilide.tw.
15 ibutilide.tw.
16 flecainide.tw.
17 propafenone.tw.
18 quinidine.tw.
19 cibenzoline.tw.
20 moricizine.tw.
21 mexiletine.tw.
22 procainamide.tw.
23 sotalol.tw.
24 esmolol.tw.
25 or/6-24
26 5 and 25
27 randomized controlled trial.pt.
28 controlled clinical trial.pt.
29 Randomized controlled trials/
30 random allocation/
31 double blind method/
32 single-blind method/
33 or/27-32
34 exp animal/ not humans/
35 33 not 34
36 clinical trial.pt.
37 exp Clinical Trials as Topic/
38 (clin$ adj25 trial$).ti,ab.
39 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
40 placebos/
41 placebo$.ti,ab.
42 random$.ti,ab.
43 research design/
44 or/36-43
45 44 not 34
46 35 or 45
47 26 and 46
48 limit 47 to yr="2005 - 2010"

EMBASE on Ovid to 2010 Week 06

1 heart atrium fibrillation/
2 atrial fibrillation.tw.
3 atrium fibrillation.tw.
4 auricular fibrillation.tw.
5 or/1-4
6 exp antiarrhythmic agent/
7 antiarrhythmi$.tw.
8 anti-arrhythmi$.tw.
9 dronedarone.tw.
10 amiodarone.tw.
11 bisoprolol.tw.
12 disopyramide.tw.
13 dofetilide.tw.
14 azimilide.tw.
15 ibutilide.tw.
16 flecainide.tw.
17 propafenone.tw.
18 quinidine.tw.
19 cibenzoline.tw.
20 moricizine.tw.
21 mexiletine.tw.
22 procainamide.tw.
23 sotalol.tw.
24 esmolol.tw.
25 or/6-24
26 5 and 25
27 random$.tw.
28 factorial$.tw.
29 (crossover$ or cross-over$).tw.
30 placebo$.tw.
31 (doubl$ adj blind$).tw.
32 (singl$ adj blind$).tw.
33 assign$.tw.
34 allocat$.tw.
35 volunteer$.tw.
36 Crossover Procedure/
37 Double-blind Procedure/
38 Randomized Controlled Trial/
39 Single-blind Procedure/
40 or/27-39
41 (animal/ or nonhuman/) not human/
42 40 not 41
43 26 and 42
44 limit 43 to yr="2005 - 2010"

WHAT'S NEW

Last assessed as up-to-date: 17 February 2010.

Date	Event	Description
15 March 2011	New citation required and conclusions have changed	Searches were re-run for this update to February 2010. Eleven new publications were included. This new trials studied several drugs (amiodarone, azimilide, dofetilide, dronedarone, metoprolol and sotalol) and added 8 212 more patients. Some of the conclusions have changed in light of this new evidence: a) Beta-blockers (metoprolol) showed a significant effect in preventing AF recurrence; b) In addition to Class IA drugs, sotalol was also associated with increased all-cause mortality
25 February 2011	New search has been performed	Eleven new studies added and results changed

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 4, 2007

Date	Event	Description
8 September 2008	Amended	Converted to new review format.
23 June 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Carmelo Lafuente-Lafuente: prepared and designed the protocol, searched for primary studies, assessed papers for inclusion and quality, extracted data, performed analysis and interpreted data, contacted authors of primary studies when needed and wrote the review.

Miguel Angel Longás-Tejero: screened search results, retrieved papers, assessed papers for inclusion and quality, extracted data from papers and wrote the review.

Joël Belmin: assessed papers for inclusion and quality, extracted data from papers, interpreted data and reviewed the manuscript.

Jean François Bergmann: designed the review, assessed papers for inclusion and quality, interpreted data and reviewed the manuscript.

DECLARATIONS OF INTEREST

Carmelo Lafuente-Lafuente has received consultant fees (less than 5 000 EURO total) from Sanofi-Aventis, in 2009 and 2010, for helping to conduct a study (a mixed treatment comparison meta-analysis) on several antiarrhythmic drugs for the management of atrial fibrillation. Sanofi-Aventis is the manufacturer of amiodarone and dronedarone, two of the antiarrhythmics studied in this review.

SOURCES OF SUPPORT

Internal sources

- Unité de Recherches Thérapeutiques, Hôpital Lariboisière, Paris, France.
- Assistance Publique - Hôpitaux de Paris, France.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None of the methods or the outcomes stated in the original protocol were modified. Some of the outcomes and planned subgroup analysis could not be performed because the data needed were not recorded or not reported in the original studies.

INDEX TERMS

Medical Subject Headings (MeSH)

*Electric Countershock; Anti-Arrhythmia Agents [*therapeutic use]; Atrial Fibrillation [mortality; prevention & control; *therapy]; Randomized Controlled Trials as Topic; Recurrence [prevention & control]

MeSH check words

Humans