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Amiodarone versus other pharmacological interventions for prevention of sudden cardiac death (Review)

Claro JC, Candia R, Rada G, Baraona F, Larrondo F, Letelier LM

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[Intervention Review]

Amiodarone versus other pharmacological interventions for prevention of sudden cardiac death

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ABSTRACT

Background

Sudden cardiac death (SCD) is one of the main causes of cardiac death. There are two main strategies to prevent it: managing cardiovascular risk factors and reducing the risk of ventricular arrhythmias. Implantable cardiac defibrillators (ICDs) constitute the standard therapy for both primary and secondary prevention; however, they are not widely available in settings with limited resources. The antiarrhythmic amiodarone has been proposed as an alternative to ICD.

Objectives

To evaluate the effectiveness of amiodarone for primary or secondary prevention in SCD compared with placebo or no intervention or any other antiarrhythmic drugs in participants at high risk (primary prevention) or who have recovered from a cardiac arrest or a syncope due to Ventricular Tachycardia/Ventricular Fibrillation, or VT/VF (secondary prevention).

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (OVID), EMBASE (OVID), CINAHL (EBSCO) and LILACS on 26 March 2015. We reviewed reference lists of included studies and selected reviews on the topic, contacted authors of included studies, screened relevant meetings and searched in registers for ongoing trials. We applied no language restrictions.

Selection criteria

Randomised and quasi-randomised trials assessing the efficacy of amiodarone versus placebo, no intervention, or other antiarrhythmics in adults. For primary prevention we considered participants at high risk for SCD. For secondary prevention we considered participants recovered from cardiac arrest or syncope due to ventricular arrhythmias.

Data collection and analysis

Two authors independently assessed the trials for inclusion and extracted relevant data. We contacted trial authors for missing data. We performed meta-analyses using a random-effects model. We calculated risk ratios (RR) for dichotomous outcomes with 95% confidence intervals (CIs). Three studies included more than one comparison.

Main results

We included 24 studies (9,997 participants). Eighteen studies evaluated amiodarone for primary prevention and six for secondary prevention. Only three studies used an ICD concomitantly with amiodarone for the comparison (all of them for secondary prevention).

For primary prevention, amiodarone compared to placebo or no intervention (17 studies, 8383 participants) reduced SCD (RR 0.76; 95% CI 0.66 to 0.88), cardiac mortality (RR 0.86; 95% CI 0.77 to 0.96) and all-cause mortality (RR 0.88; 95% CI 0.78 to 1.00). The quality of the evidence was low.

Compared to other antiarrhythmics (three studies, 540 participants), amiodarone reduced SCD (RR 0.44; 95% CI 0.19 to 1.00), cardiac mortality (RR 0.41; 95% CI 0.20 to 0.86) and all-cause mortality (RR 0.37; 95% CI 0.18 to 0.76). The quality of the evidence was moderate.

For secondary prevention, amiodarone compared to placebo or no intervention (two studies, 440 participants) appeared to increase the risk of SCD (RR 4.32; 95% CI 0.87 to 21.49) and all-cause mortality (RR 3.05; 1.33 to 7.01). However, the quality of the evidence was very low. Compared to other antiarrhythmics (four studies, 839 participants) amiodarone appeared to increase the risk of SCD (RR 1.40; 95% CI 0.56 to 3.52; very low quality of evidence), but there was no effect in all-cause mortality (RR 1.03; 95% CI 0.75 to 1.42; low quality evidence).

Amiodarone was associated with an increase in pulmonary and thyroid adverse events.

Authors' conclusions

There is low to moderate quality evidence that amiodarone reduces SCD, cardiac and all-cause mortality when compared to placebo or no intervention for primary prevention, and its effects are superior to other antiarrhythmics.

It is uncertain if amiodarone reduces or increases SCD and mortality for secondary prevention because the quality of the evidence was very low.

PLAIN LANGUAGE SUMMARY

Amiodarone for preventing sudden cardiac death

Background

Sudden cardiac death (SCD) is an important cause of death nowadays. People at high risk (mainly with any sort of heart disease) die unexpectedly from cardiac causes, primarily from arrhythmia (an irregular heartbeat). The treatment of choice is a device called an implantable cardiac defibrillator (ICD), but it is not widely available in low- or middle-income countries. Amiodarone, an antiarrhythmic medication, might reduce the occurrence of these events and could be an alternative when an ICD is not available.

Study characteristics

We searched scientific databases for clinical trials comparing the effects of amiodarone versus other antiarrhythmics or placebo on SCD, mortality and any side effects. We included adult participants at high risk or who had previously presented with sudden cardiac arrest, a serious heart malfunction that causes the arrhythmia. The evidence is current to March 2015.

Key results

We found 24 studies comprising 9,997 participants. In participants at high risk, the evidence showed that amiodarone may prevent SCD or mortality when compared to placebo, and it is probably better than other antiarrhythmics.

On the other hand, in participants who have already suffered a prior cardiac arrest, it is uncertain whether amiodarone increases or reduces the risk of a new episode of cardiac arrest or death.

Furthermore, amiodarone may lead to or worsen adverse effects in the thyroid or lungs, when compared with placebo or other antiarrhythmics.

Quality of the evidence

The overall quality of evidence of these studies was low.

Summary of findings for the main comparison. Amiodarone compared to placebo or no treatment for high risk of Sudden Cardiac Death (primary prevention)

Amiodarone versus placebo or no treatment for primary prevention

Patient or population: participants with high risk of sudden cardiac death (primary prevention)
Settings: any setting
Intervention: amiodarone
Comparison: placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo or no treatment	Amiodarone			
Sudden cardiac death	**Study population**		**RR 0.76** (0.66 to 0.88)	8383 (17 studies)	⊕⊕⊝⊝ **low**[a,b]
	91 per 1000	**70 per 1000** (61 to 81)			
	Moderate				
	114 per 1000	**87 per 1000** (76 to 101)			
All-cause mortality	**Study population**		**RR 0.88** (0.78 to 1.00)	8383 (17 studies)	⊕⊕⊝⊝ **low**[a,b]
	203 per 1000	**178 per 1000** (158 to 203)			
	Moderate				
	190 per 1000	**167 per 1000** (148 to 190)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR**: Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Randomisation and allocation concealment methods not clear or not adequate in 10/16 studies, including studies with more weight.
[b]Funnel plot compatible with publication bias. Given the nature of the intervention and the absence of other explanatory factors, publication bias is the most likely explanation.

Summary of findings 2. Amiodarone compared to beta blockers for high risk of sudden cardiac death (primary prevention)

Amiodarone versus beta blockers

Patient or population: beta blockers
Settings: any setting
Intervention: amiodarone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Amiodarone			
Sudden cardiac death	Study population		RR 0.37 (0.11 to 1.22)	342 (2 studies)	⊕⊕⊝⊝ low[a,b]
	56 per 1000	21 per 1000 (6 to 68)			
	Moderate				
	45 per 1000	17 per 1000 (5 to 55)			
All-cause mortality	Study population		RR 0.27 (0.1 to 0.75)	342 (2 studies)	⊕⊕⊝⊝ low[a,b]
	101 per 1000	27 per 1000 (10 to 75)			
	Moderate				
	76 per 1000	21 per 1000 (8 to 57)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR**: Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Both studies had serious limitations, including lack of blinding for participants and unclear generation of random sequence and allocation concealment.
[b]Wide confidence interval that does not exclude risk. However, point estimate shows a high magnitude effect.

Summary of findings 3. Amiodarone compared to other antiarrhythmics for high risk of sudden cardiac death (primary prevention)

Amiodarone versus other antiarrhythmics for high risk of sudden cardiac death (primary prevention)

Patient or population: participants with high risk of sudden cardiac death (primary prevention)
Settings: any setting
Intervention: amiodarone
Comparison: other antiarrhythmics

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Other antiarrhythmics	Amiodarone			
Sudden cardiac death	**Study population**		**RR 0.44** (0.19 to 1)	540 (3 studies)	⊕⊕⊕⊖ **moderate**[a,b]
	65 per 1000	**28 per 1000** (12 to 65)			
All-cause mortality	**Study population**		**RR 0.37** (0.18 to 0.76)	540 (3 studies)	⊕⊕⊕⊖ **moderate**[a]
	100 per 1000	**37 per 1000** (18 to 76)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR**: Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]All studies had serious limitations, including lack of blinding for participants and unclear allocation concealment.
[b]Even though the CI crosses the line of null effect, we did not decrease the quality of the evidence since the point estimate clearly shows benefit and is consistent with the direction of the other outcomes.

Summary of findings 4. Amiodarone compared to placebo or no treatment for high risk of sudden cardiac death (secondary prevention)

Amiodarone compared to placebo or no treatment for high risk of sudden cardiac death (secondary prevention)

Patient or population: participants with high risk of sudden cardiac death (secondary prevention)
Settings: any setting
Intervention: amiodarone
Comparison: placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo or no treatment	Amiodarone			
Sudden cardiac death	Study population		RR 4.32 (0.87 to 21.49)	440 (2 studies)	⊕⊝⊝⊝ very low[a,b]
	8 per 1000	35 per 1000 (7 to 174)			
All-cause mortality	Study population		RR 3.05 (1.33 to 7.01)	440 (2 studies)	⊕⊝⊝⊝ very low[a,b]
	32 per 1000	99 per 1000 (43 to 227)			
	Moderate				
	35 per 1000	107 per 1000 (47 to 245)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR**: Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Very serious imprecision: quality of the evidence was downgraded two levels because the CI was very wide and includes both important risks and benefits, and because there was a very low number of events.
[b]Publication bias suspected, given likelihood of publication bias in the studies of primary prevention for the same comparison, and the results showing possible harm.

Summary of findings 5. Amiodarone compared to other antiarrhythmics for high risk of sudden cardiac death (secondary prevention)

Amiodarone versus other antiarrhythmics for high risk of sudden cardiac death (secondary prevention)

Patient or population: participants with high risk of sudden cardiac death (secondary prevention)
Settings: any setting
Intervention: amiodarone
Comparison: other antiarrhythmics

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Other antiarrhythmics	Amiodarone			
Sudden cardiac death	Study population		RR 1.40 (0.56 to 3.52)	839 (4 studies)	⊕⊝⊝⊝ very low[a,b,c]
	99 per 1000	138 per 1000 (55 to 347)			
All-cause mortality	Study population		RR 1.03 (0.75 to 1.42)	898 (5 studies)	⊕⊕⊝⊝ low[a,b]
	193 per 1000	198 per 1000 (144 to 273)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]All studies had serious limitations, including 4/5 not blinded for participants.
[b]Wide confidence interval that does not rule out important benefit or risk.
[c]Downgraded due to inconsistency (I^2 = 72%).

Summary of findings 6. Amiodarone compared to beta blockers for high risk of sudden cardiac death (secondary prevention)

Amiodarone compared to beta blockers for high risk of sudden cardiac death (secondary prevention)

Patient or population: participants with high risk of sudden cardiac death (secondary prevention)
Settings: any setting
Intervention: amiodarone
Comparison: beta blockers

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Beta blockers	Amiodarone			
Sudden cardiac death	Study population		RR 0.84 (0.55 to 1.27)	189 (1 study)	⊕⊝⊝⊝ very low[a,b]
	351 per 1000	294 per 1000 (193 to 445)			
All-cause mortality	Study population		RR 0.96 (0.7 to 1.32)	189 (1 study)	⊕⊝⊝⊝ very low[a,b]
	454 per 1000	435 per 1000 (318 to 599)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR**: Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]The only study has serious limitations, including lack of blinding for participants.
[b]Only one study; quality of the evidence was downgraded two levels because confidence interval includes both important benefit and risk.

Summary of findings 7. Amiodarone compared to sotalol for high risk of sudden cardiac death (secondary prevention)

Amiodarone versus sotalol for high risk of sudden cardiac death (secondary prevention)

Patient or population: participants with high risk of sudden cardiac death (secondary prevention)
Settings: any setting
Intervention: amiodarone
Comparison: sotalol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Sotalol	Amiodarone			
Sudden cardiac death	Study population		RR 2.87 (0.32 to 25.55)	45 (1 study)	⊕⊝⊝⊝ very low[a,b]
	45 per 1000	130 per 1000 (15 to 1000)			
All-cause mortality	Study population		RR 1.08 (0.41 to 2.83)	104 (2 studies)	⊕⊝⊝⊝ very low[a,b]
	137 per 1000	148 per 1000 (56 to 388)			
	Moderate				
	132 per 1000	143 per 1000 (54 to 374)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR**: Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]The only study has serious limitations, including lack of blinding for participants.
[b]Only one study; quality of the evidence was downgraded two levels because confidence interval includes both important benefit and risk.

BACKGROUND

Description of the condition

From a clinical point of view, any unexpected death can be considered a 'sudden death', brought on by conditions as diverse as arrhythmias, aortic dissection, subarachnoid haemorrhage, acute myocardial infarction or massive pulmonary embolism. Traumatic death is usually excluded from this category. As there may be prognostic and therapeutic differences (i.e. subarachnoid haemorrhage or pulmonary embolism), researchers and clinicians recognise a distinct category known as 'sudden cardiac death' (SCD). A widely accepted definition is "natural death due to cardiac causes, heralded by abrupt loss of consciousness within an hour of the onset of acute symptoms; pre-existing heart disease may have been known to be present, but the time and mode of death are unexpected" (Myerburg 2004).

SCD is one of the leading causes of cardiac death. Incidence increases with age and is three to four times more frequent in men than women at all ages (Merghani 2013; MMWR 2002). Accurately estimating its real incidence is difficult, but according to data obtained from death certificates, SCD may cause 63.4% of total cardiac mortality in the United States (MMWR 2002). This data probably overestimates SCD prevalence, as it is based only on clinical presentation (MMWR 2002; Zheng 2001). Incidence rates, varying from 0.36 to 1.28/100,000 participants per year, have been reported by some emergency services, but these tend to underestimate the real incidence, as it only refers to participants who survive to the hospital (Sara 2014). Incidence increases from 1/100,000 for those aged < 35 years to 100/100,000 in individuals aged ≥ 35 years old (John 2012). A prospective observational study reported that 7% to 18% of overall mortality in the general population (of all ages) in the USA was due to SCD (Stecker 2014). Globally, estimated incidence of SCD would then be approximately 4 to 5 million cases every year. However, this number may be inaccurate, as, on the one hand, SCD incidence rates in low- and middle-income countries may not be equivalent to those in high-income countries (Vedanthan 2012), and on the other hand, incidence has declined over the past two decades, from 4.7 per 1000 person-years in 1990–2000 to 2.1 per 1000 person-years in 2001–2010 (Niemeijer 2015).

The main pre-existing heart disease leading to SCD in high-income countries is coronary heart disease (CHD); there is a general acceptance that SCD accounts for around 50% of all CHD-related death and that the proportion of all SCDs resulting from CHD is around 80% (Myerburg 2012). Other types of cardiopathy (e.g. hypertrophic cardiomyopathy, non-ischaemic cardiomyopathy, arrhythmogenic right ventricular dysplasia) can also lead to SCD, while there is no structural abnormality in only 5% of cases (Consensus 1997). The SCD event is most commonly caused by the sudden onset of monomorphic ventricular tachycardia (VT) that degenerates into ventricular fibrillation (VF), and less frequently by the abrupt onset of polymorphic VT/VF, bradyarrhythmias or heart blocks (Priori 2001; Zipes 2006). However, the proportion of participants with pulseless electrical activity or asystole has increased over the past two decades (Teodorescu 2010).

More recently, research has identified diabetes mellitus as an independent risk factor for SCD (Jouven 2005).

The downward trend in SCD incidence might be due to better diagnosis and treatment of heart disease and most importantly primary prevention of SCD and cardiovascular disease in general through improved management of behaviours and other risk factors (Niemeijer 2015).

In this context, clinicians use electrophysiological (EP) testing with intracardiac recording and electrical stimulation at baseline, followed by administration of antiarrhythmic drugs for arrhythmia assessment and risk stratification. EP testing has been used to document the inducibility of VT, evaluate drug effects, assess the risks of recurrent VT or SCD, and assess the indications for implantable cardiac defibrillator (ICD) therapy. For example, in participants with CHD, asymptomatic non-sustained VT and a left ventricular ejection fraction (LVEF) less than 40%, the inducibility of sustained VT ranges from 20% to 40% and confers worse prognosis, with an increased risk of SCD or death from other causes (Buxton 2000). However, in participants with CHD and a lower LVEF (less than 30%), non-inducibility doesn't necessarily portend a good prognosis (Buxton 2002), and persistent inducibility while receiving antiarrhythmic drugs confers an even worse prognosis (Wilber 1990).

Description of the intervention

Amiodarone, one of the main class III antiarrhythmics, is a benzofuran derivative approved by the US Food and Drug Administration (FDA) for the treatment of patients with life-threatening ventricular tachyarrhythmias when other drugs are ineffective or not tolerated (FDA 2013). Researchers have proposed the drug as an alternative to ICD, categorising it as having a 2a level of evidence (weight of evidence is in favour of usefulness/efficacy) for prophylaxis of SCD in participants with CHD and left ventricular (LV) dysfunction (Zipes 2006).

The onset of action after intravenous administration is generally within one to two hours, but after oral administration, the onset of action may require anywhere from two to three days and often from one to three weeks. On occasion, it may take even longer, to the point that achieving a steady state without a loading dose takes about 265 days (Braunwald 2001).

However, research has also associated the use of amiodarone with toxicity involving the lungs, thyroid gland, liver, eyes, skin and nerves (Connolly 1997). Pulmonary toxicity is the drug's most serious potential adverse effect, and some series have described its frequency as high as 17%, although the incidence when compared with placebo is less than 1% (Pollak 1999). Thyroid toxicity is the most common complication requiring intervention, occurring in up to 10% of participants receiving long-term amiodarone therapy. Minor adverse effects are nausea, anorexia, photosensitivity, and a blue discolouration of the skin (Siddoway 2003).

The frequency of most adverse effects is related to total amiodarone exposure (Siddoway 2003), but amiodarone is slowly, variably and incompletely absorbed, which makes adverse events unpredictable. Extensive hepatic metabolism occurs with desethylamiodarone as a major metabolite, both extensively accumulating in the liver, lung, fat, 'blue' skin, and other tissues.

How the intervention might work

Generally speaking, class III antiarrhythmic drugs act by prolonging the action potential´s duration of the myocardial

cell by lengthening the repolarisation phase and thus the effective refractory period. This prolongation is believed to facilitate termination and prevention of both ventricular re-entry arrhythmias by producing block within re-entry circuits, and thus providing both an elevation of the ventricular fibrillation threshold and a reduction of the ventricular defibrillation threshold (Brendorp 2002).

As a class III antiarrhythmic drug, amiodarone prolongs the QT interval, slows the heart rate and atrioventricular nodal conduction (via calcium channel and beta-receptor blockade), prolongs refractoriness (via potassium and sodium channel blockade), and slows intracardiac conduction (via sodium channel blockade) (Siddoway 2003). By blocking the potassium repolarisation currents, it can inhibit or terminate ventricular arrhythmias by increasing the wavelength for reentry (Zipes 2006).

Why it is important to do this review

According to current evidence, ICD therapy, when compared with antiarrhythmic drugs, reduces mortality in high risk participants with reduced LVEF in both CHD and non-ischaemic cardiopathy, for both primary and secondary prevention (AVID 1997; Connolly 2000; Desai 2004; Kuck 2000).

While ICD therapy may improve survival in selected patient populations, it may diminish patients' quality of life (Gehi 2006). In a study comparing ICD versus no ICD in participants who underwent coronary artery bypass graft surgery, the use of ICD was associated with lower levels of psychological well-being and reduced physical and emotional role functioning (Namerow 1999). On the other hand, a recent analysis by Marks et al. from the Sudden Cardiac Death - Heart Failure Trial (SCD-HeFT) showed that subjective measures of physical function did not differ significantly between the ICD and placebo groups at any time point, but there was a short-term increase in psychological well-being among participants with ICD therapy throughout the first year after implantation, a benefit that did not persist at 30 months (Bardy 2005–SCD-HeFT). The occurrence of ICD shocks reduced the quality of life, but only if quality of life was measured within one to two months after the shock (Bardy 2005–SCD-HeFT).

However, the elevated up-front costs of ICD therapy (between EUR 11,000 and 19,000) impede its ready availability in the health systems of low- and middle-income countries, even though costs tend to diminish along patients' longevity (Biffi 2011).

Regarding amiodarone, evidence from trials has been inconsistent, with some studies showing a moderate effect and others no effect at all (Bardy 2005–SCD-HeFT; Heidenreich 2002; Strickberger 2003). Indirect evidence of effect comes from a recent systematic review concluding that ICD discharges were reduced in participants with ICD plus amiodarone compared to participants with ICD alone. Assuming ICD discharges follow ventricular arrhythmias, one could infer that amiodarone reduces the number of arrhythmic episodes (Ferreira 2007), provided the ICDs were programmed with similar arrhythmia detection times, as different detection times could mean different thresholds for considering any disturbance to be an arrhythmic episode (Scott 2014).

On the other hand, data collected since the 1980s has convincingly proven that beta-blocking treatment is associated with an improved clinical outcome in several patient groups. The efficacy of this treatment in people with post-myocardial infarction (MI) relates to a drug-associated reduction in all-cause mortality and is not necessarily related to the time after the acute event, when therapy starts (Yusuf 1985). People with a history of congestive heart failure (CHF) or depressed left ventricular function tend to experience the greatest benefits in mortality reduction.

Data suggests that in participants post-MI, potasium channel blockers such as dofetilide or d-sotalol have neutral or even harmful effects regarding all-cause mortality (Køber 2000; Torp-Pedersen 1999; Waldo 1996), and, for example, both of these drugs result in a higher rate of Torsade de Pointes than amiodarone (Brendorp 2002). However, calcium-channel blockers such as verapamil have shown favourable effects, if only in people without heart failure (DAVIT II 1990).

It is also important to note that chronic treatment with antiarrhythmic drugs is associated with severe adverse effects, including the potential induction of life-threatening arrhythmias (e.g. increased mortality is associated with the long-term use of quinidine; Coplen 1990).

A previous systematic review of randomised controlled trials, which evaluated amiodarone versus other antiarrhythmics or placebo for the prevention of SCD in participants with or without ICD, concluded that it significantly reduced SCD and cardiac mortality, but not all-cause mortality. However, the authors did not carry out a separate analysis for participants with or without ICD, and the review only evaluated amiodarone for primary prevention (Piccini 2009).

If amiodarone proves to be beneficial in SCD prevention, it would constitute a valid alternative in situations where economic constraints limit the widespread use of ICD.

OBJECTIVES

To evaluate the effectiveness of amiodarone for primary or secondary prevention in SCD compared with placebo or no intervention or any other antiarrhythmic drugs in participants with high risk (primary prevention), or who have recovered from a cardiac arrest or a syncope due to Ventricular Tachycardia/ Ventricular Fibrillation, or VT/VF (secondary prevention).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials. We considered a trial as quasi-randomised when the authors used methods such as alternation or case record number.

Types of participants

Primary prevention

Adults (16 years or older) with:

1. reduced LVEF (< 40%), independent of the aetiology (ischaemic or non-ischaemic); or
2. high risk for SCD, e.g. participants without structural heart disease but with a high risk cardiac condition, such as refractory

sustained or non sustained VT, or non-suppressible malignant arrhythmias induced by EP study.

Secondary prevention

Adults (16 years or older) who have recovered from cardiac arrest or syncope due to VT/VF of non-ischaemic aetiology, or of ischaemic aetiology after 48 hours from the ischaemic event.

We also included studies involving participants with an ICD plus amiodarone versus ICD plus placebo or another antiarrhythmic drug.

Exclusion criteria

People with genetic arrhythmia syndromes with specific treatments, such as:

- Brugada syndrome;
- long QT syndrome;
- arrhythmogenic right ventricular dysplasia.

Types of interventions

Amiodarone at ≥ 200 mg/d, by any route of administration, for at least six months, compared to other antiarrhythmics, placebo or no intervention.We excluded studies of amiodarone combined with other antiarrhythmic drugs in a sequential manner (i.e. based on EP studies).

Types of outcome measures

Primary outcomes

- Sudden cardiac death (as defined in the studies)
- All-cause mortality
- Cardiac mortality (as defined in the studies)

Secondary outcomes

- Quality of life
- Adverse effects

Search methods for identification of studies

Electronic searches

We conducted sensitive electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 2 of 12, 2015), MEDLINE (OVID, 1946 to March week 4 2015), EMBASE (OVID, 1980 to 2015 week 12), CINAHL (EBSCO, 1937 to 26 March 2015), LILACS (1982 to 26 March 2015), Database of Abstracts of Reviews of Effects (DARE) (Issue 3, 2014) and the NHS Economic Evaluation Database (NEED) (*The Cochrane Library,* Issue 3, 2014) on 26 March 2015. We based our search strategies on a combination of controlled vocabulary and the randomised clinical trials phases of the highly sensitive search strategy for MEDLINE (Lefebvre 2008), the EMBASE strategy for EMBASE or an adaptation of these for the other databases. The detailed strategies for the different databases are in Appendix 1.

We applied no language restrictions.

Searching other resources

We handsearched reference lists of included trials and relevant review articles. We looked for ongoing trials from the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/) and ClinicalTrials.gov (http://www.clinicaltrials.gov/). We also handsearched for relevant abstracts from the following conferences: World Congress of Cardiology, European Society of Cardiology (ESC) Congress, American College of Cardiology (ACC) Annual Scientific Sessions, the Heart Rhythm Society's Annual Scientific Sessions, and the European Heart Rhythm Association (EUROPACE) Congress for the last eight years (2005-2013).

We also contacted experts in the field, pharmaceutical companies and authors of identified trials in order to identify studies missed by our search strategy.

Data collection and analysis

Selection of studies

Two authors (JC, RC) independently scanned all the titles and abstracts, selecting potentially eligible studies to be evaluated in full text. JC and RC independently assessed the full text of all potentially eligible studies. A third author (LML) resolved discrepancies.

Data extraction and management

Two authors (JC, RC) independently extracted data from included studies using forms designed by the review authors. We resolved discrepancies by discussion and when we could not reach a consensus, we consulted a third author (LML). We contacted authors by email to provide missing data.

Assessment of risk of bias in included studies

Two authors (JC, RC) independently assessed the risk of bias of each included study using the Cochrane 'Risk of bias' assessment tool for seven domains (Higgins 2011a). We resolved discrepancies by discussion and when we could not reach a consensus, we consulted a third author (LML). The seven domains assessed were: sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias.

Following the definitions presented in the *Cochrane Handbook for Systematic Reviews of Interventions*, we decided whether the risk of bias was high, low, or unclear for each domain. We contacted authors whenever there were missing or unclear descriptions.

Measures of treatment effect

We reported pooled outcomes as risk ratios (RRs) with 95% confidence intervals (CI) for dichotomous outcomes. We reported mean difference (MD) with 95% CI for continuous outcomes, or standardised mean differences (SMD) when studies reported outcomes using different scales.

Unit of analysis issues

We analysed data using participants as the unit of analysis. If there were more than two active treatment arms, we pooled the participants included in each arm into a single group (e.g. 'other antiarrhythmics'). We took appropriate action to avoid double-counting participants between study arms.

Dealing with missing data

We attempted to contact the main author of trials with missing data in order to verify key study characteristics and obtain missing numerical outcome data.

Assessment of heterogeneity

We assessed heterogeneity quantitatively with a formal statistical test (Q statistic) and the I^2 statistic. We defined statistically significant heterogeneity as at least one positive test (establishing a cut-off value of P = 0.10 for the Mantel-Haenszel Chi^2 test, or values over 50% using the I^2 statistic) (Higgins 2011b).

Data synthesis

We performed statistical analysis in accordance with the guidelines for statistical analysis developed by Cochrane (Higgins 2011b). Whenever possible, we carried out meta-analyses using the random-effects model.

One author (RC) entered data into Review Manager (RevMan 2014) and a second author (JC) checked them (RevMan 2014).

We conducted all our analyses separately for primary and secondary prevention. We conducted separate analyses for participants with and without an ICD, given the much lower baseline risk of the former.

For participants in all of these groups, we evaluated the following comparisons.

1. Amiodarone versus placebo or no intervention.
2. Amiodarone versus other antiarrhythmics (including beta-blockers).
3. Amiodarone versus beta-blockers alone.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses for participants with and without ICD, LVEF above and below 35% and ischaemic and non-ischaemic aetiology, both for primary and secondary prevention, but we were only partly able to do so.

Sensitivity analysis

We intended to perform a sensitivity analysis including and excluding quasi-randomised trials, but since we did not find any quasi-randomised trials, we did not perform the analysis.

Summary of findings table and GRADE assessment

We have created summary of findings table for the outcomes sudden cardiac death and all-cause mortality. We rated the quality of the evidence according to GRADE.

RESULTS

Description of studies

Results of the search

The search yielded 6778 original records. After assessing titles and abstracts, we retrieved 75 full text articles and reviewed them for inclusion. Finally, we included 24 eligible studies comprising 9,997 participants in the review (Figure 1). The trials were reported in 40 records, as some studies presented the information in separate articles (Bardy 2005–SCD-HeFT; Burkart 1990–BASIS; Ceremuzynski 1992; Elizari 2000–GEMICA; Greene 1993–CASCADE; Hockings 1987; Julian 1997–EMIAT; Kovoor 1999; Kowey 2011–ALPHEE; Navarro-López 1993–SSSD; Singh 1995–STAT-CHF; Zehender 1992).

Figure 1. Study flow diagram.

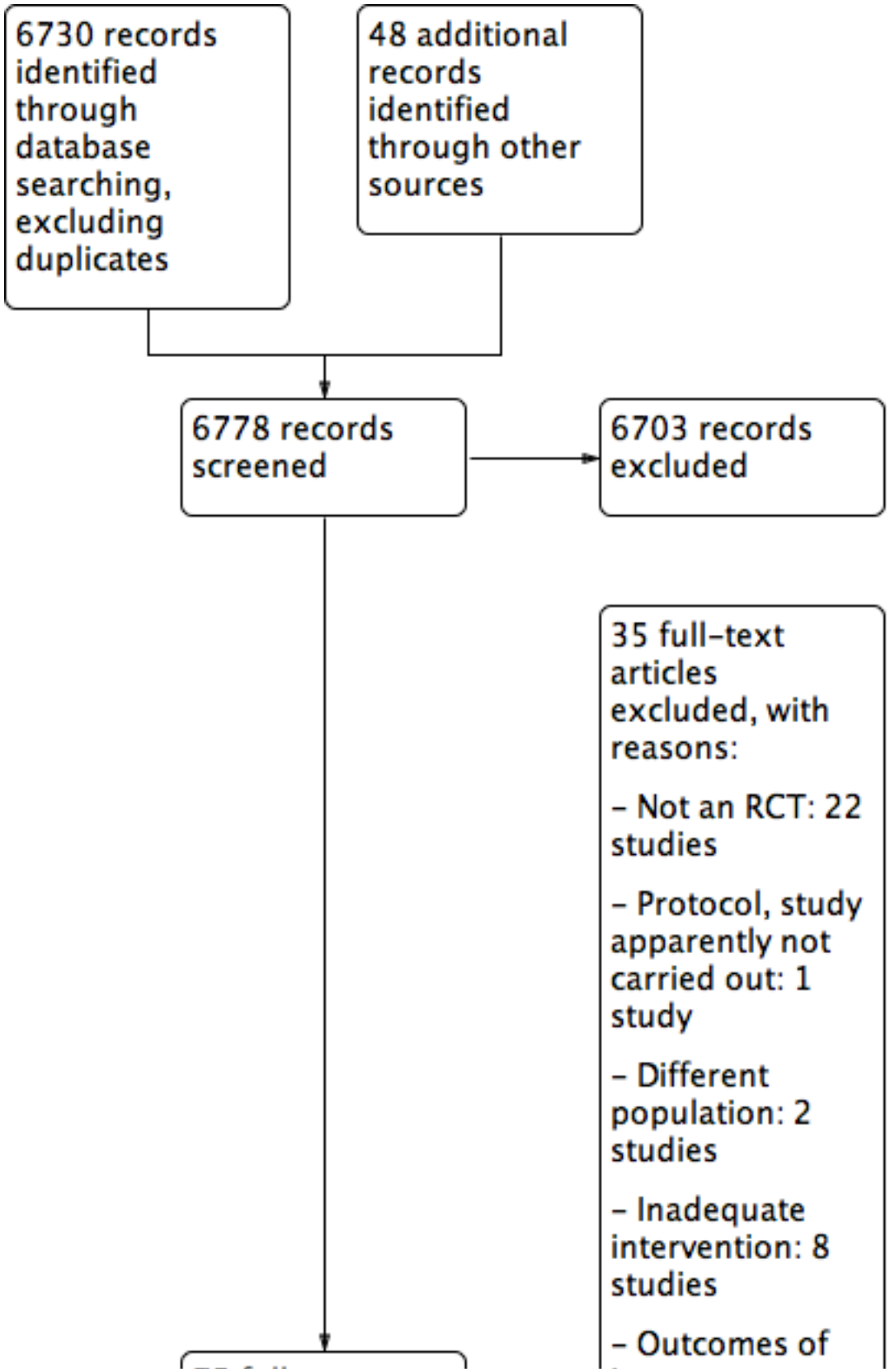
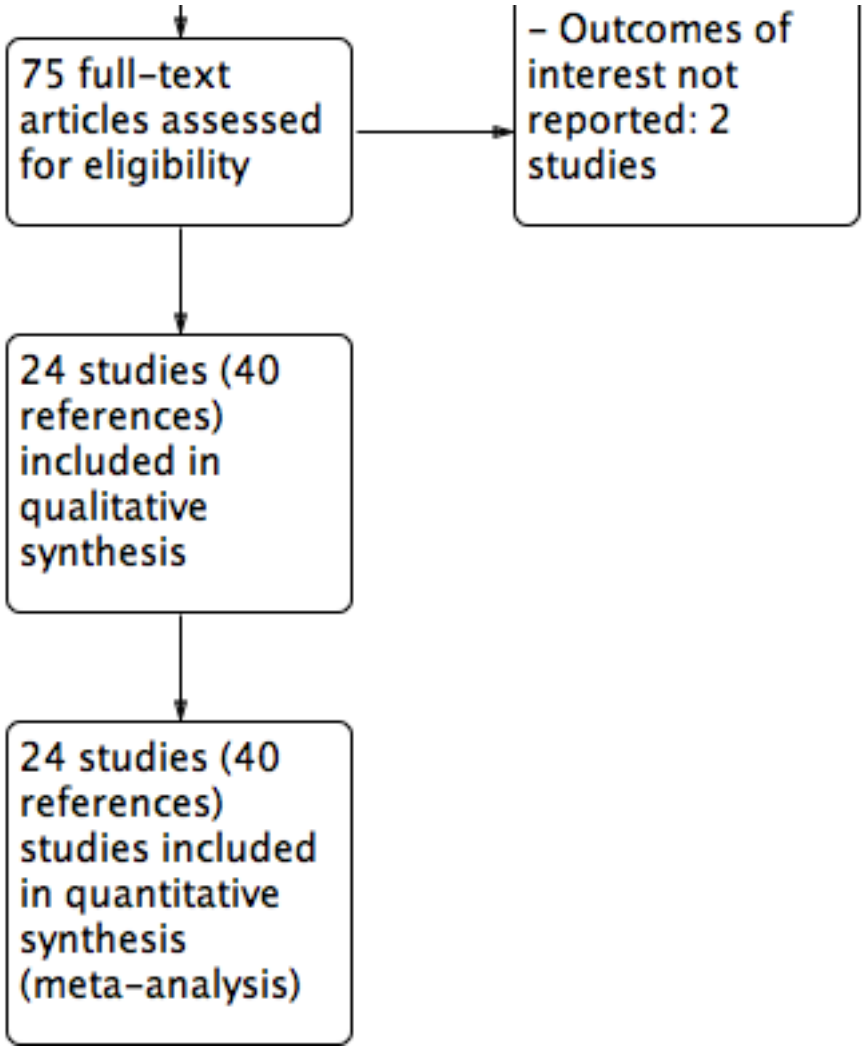


Figure 1. (Continued)



Included studies

Eighteen studies assessed the role of amiodarone for primary prevention (Bardy 2005–SCD-HeFT; Biswas 1996; Burkart 1990–BASIS; Cairns 1991–CAMIATpilot; Cairns 1997–CAMIAT; Ceremuzynski 1992; Doval 1994–GESICA; Elizari 2000–GEMICA; Fournier 1989; Garguichevich 1995–EPAMSA; Hamer 1989; Hockings 1987; Julian 1997–EMIAT; Navarro-López 1993–SSSD; Nicklas 1991; Singh 1995–STAT-CHF; Sousonis 2014; Zehender 1992). Of these, all but Fournier 1989 compared amiodarone with placebo or no intervention. Two compared amiodarone with beta-blockers (Fournier 1989; Navarro-López 1993–SSSD), and one compared amiodarone with other antiarrhythmics (Burkart 1990–BASIS). We did not identify any study of amiodarone plus ICD versus ICD alone for primary prevention.

Six studies evaluated amiodarone for secondary prevention (Connolly 2006–OPTIC; Greene 1993–CASCADE; Harper 1989; Kovoor 1999; Kowey 2011–ALPHEE; Kuck 2000–CASH). Three of them evaluated amiodarone plus ICD (Connolly 2006–OPTIC; Greene 1993–CASCADE; Kowey 2011–ALPHEE).

Three studies included more than one comparison (Burkart 1990–BASIS; Kowey 2011–ALPHEE; Navarro-López 1993–SSSD).

Excluded studies

We excluded 35 studies after reviewing the full text reports, mainly because they were not randomised or were narrative reviews. We considered one study (originally presented as an abstract) to be eligible, but in the end we excluded it because it did not provide enough information, and there was no response from the author (Warner-Stevenson 1996). One study was published in the form of a protocol, and investigators have not published its results yet (NIPPON 2006). We have attempted to contact the author twice, with no success. For further information see Characteristics of excluded studies and Characteristics of ongoing studies.

Risk of bias in included studies

We present details of our 'Risk of bias' judgments in Characteristics of included studies, and in the summary graphs in Figure 2 and Figure 3.

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

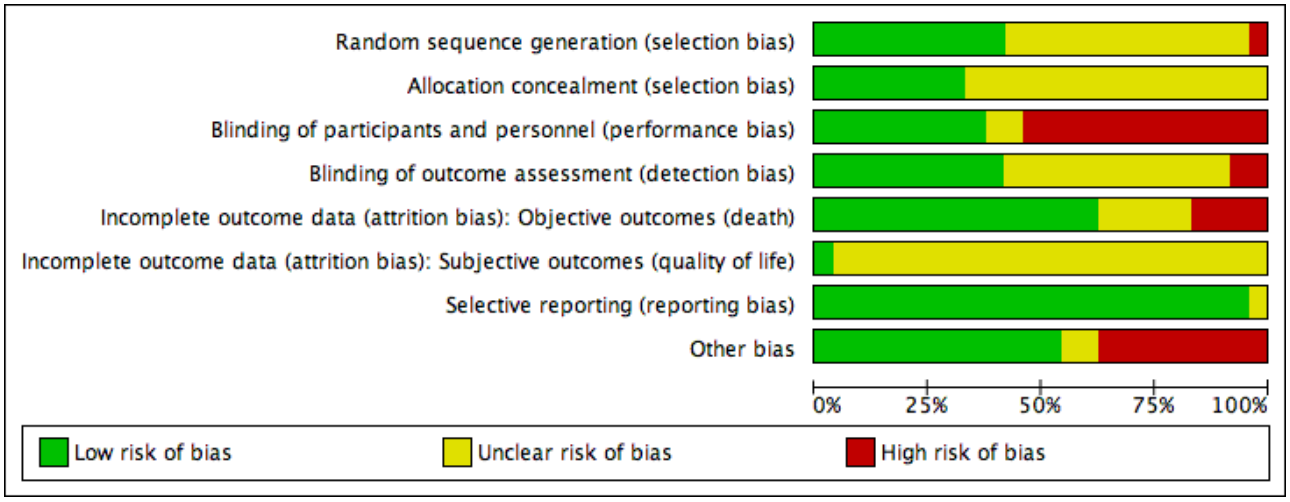


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

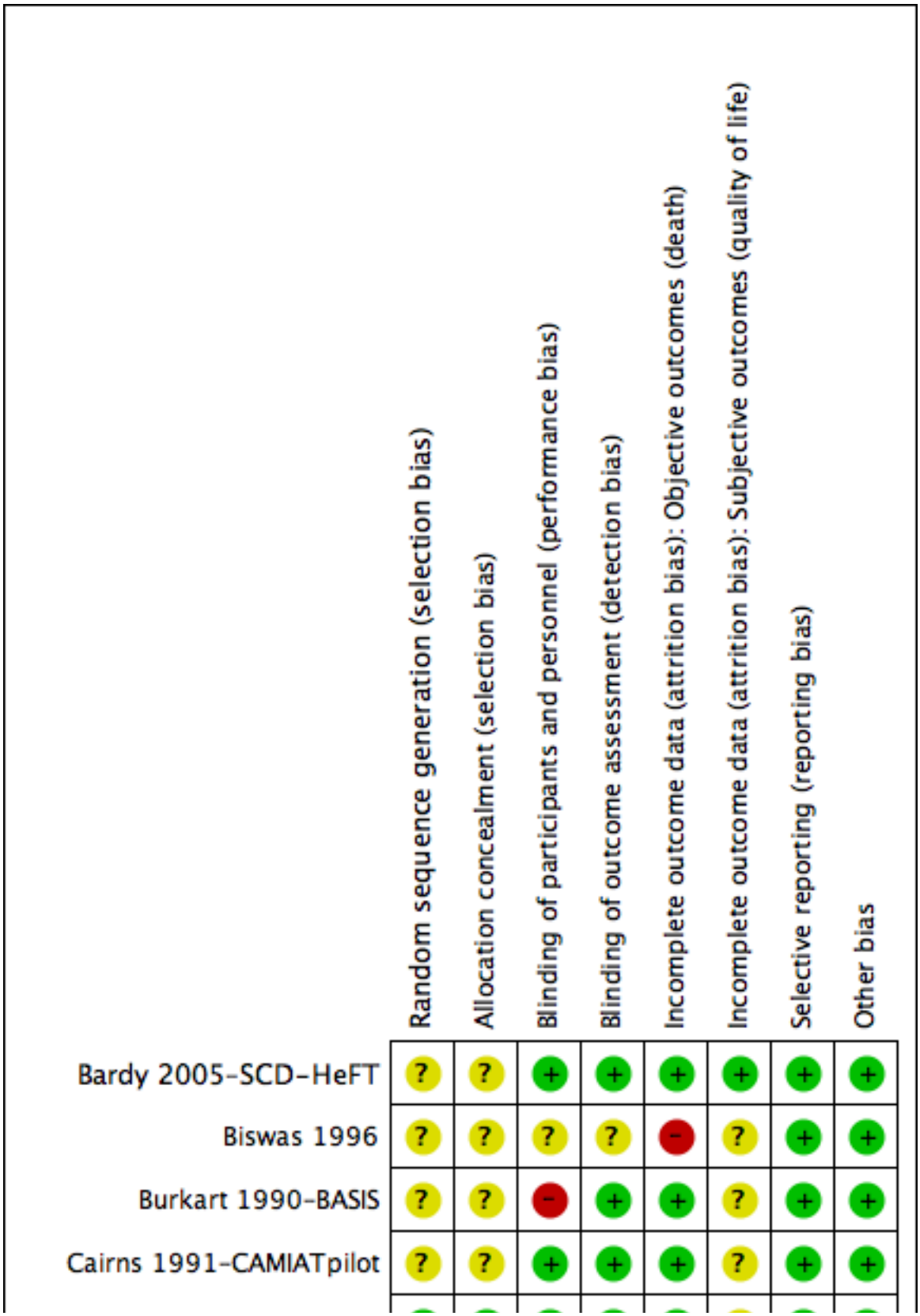
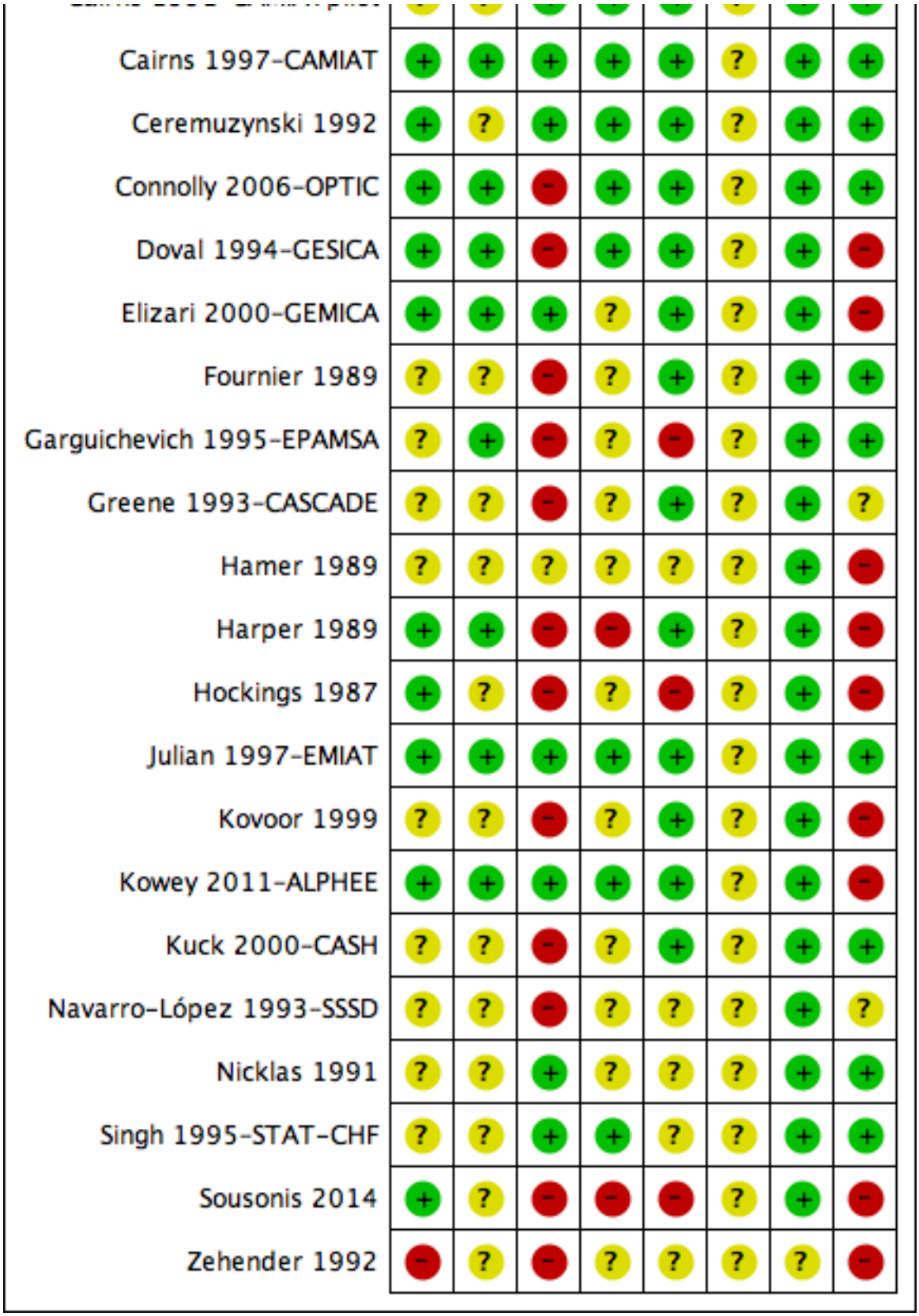


Figure 3. (Continued)



Allocation

Only one study had high risk of bias for allocation because some participants were included without proper randomisation (Zehender 1992).

Sixteen studies had an unclear risk of bias, since they stated that randomisation took place but did not provide details on the process of random sequence generation or allocation concealment (Bardy 2005–SCD-HeFT; Biswas 1996; Burkart 1990–BASIS; Cairns 1991–CAMIATpilot; Ceremuzynski 1992; Fournier 1989; Garguichevich 1995–EPAMSA; Greene 1993–CASCADE; Hamer 1989; Hockings 1987; Kovoor 1999; Kuck 2000–CASH; Navarro-López 1993–SSSD; Nicklas 1991; Singh 1995–STAT-CHF; Sousonis 2014).

Blinding

More than half of the studies lacked an appropriate method for patient and personnel blinding (Biswas 1996; Burkart 1990–BASIS; Connolly 2006–OPTIC; Doval 1994–GESICA; Fournier 1989; Garguichevich 1995–EPAMSA; Greene 1993–CASCADE; Hamer 1989; Harper 1989; Hockings 1987; Kovoor 1999; Kuck 2000–CASH; Navarro-López 1993–SSSD; Sousonis 2014; Zehender 1992). Fourteen studies had an unclear risk of bias in blinding of outcome assessment (Biswas 1996; Elizari 2000–GEMICA; Fournier 1989; Garguichevich 1995–EPAMSA; Greene 1993–CASCADE; Hamer 1989; Harper 1989; Hockings 1987; Kovoor 1999; Kuck 2000–CASH; Navarro-López 1993–SSSD; Nicklas 1991; Sousonis 2014; Zehender 1992), mainly because of poor reporting.

Incomplete outcome data

We judged four studies to be at high risk of bias due to incomplete outcome data (Biswas 1996; Garguichevich 1995–EPAMSA; Hockings 1987; Sousonis 2014), mainly because of an important loss of participants to follow-up (up to 21%).

Selective reporting

We judged all of the studies to be at low risk of bias for selective reporting, except Zehender 1992, which we deemed at unclear risk, as it provided little information.

Other potential sources of bias

One study provided different numbers of participants in two reports of the same study (Elizari 2000–GEMICA). Kowey 2011–ALPHEE presented some inconsistencies in the reporting of mortality rates. We deemed four studies as being at high risk of bias because of their small size, which could unbalance some confounding factors (Hamer 1989; Kovoor 1999; Sousonis 2014; Zehender 1992). Two studies stopped early for benefit (Doval 1994–GESICA; Elizari 2000–GEMICA), and another two had a high risk of performance bias due to participants receiving co-interventions (Harper 1989; Hockings 1987).

Effects of interventions

See: **Summary of findings for the main comparison** Amiodarone compared to placebo or no treatment for high risk of Sudden Cardiac Death (primary prevention); **Summary of findings 2** Amiodarone compared to beta blockers for high risk of sudden cardiac death (primary prevention); **Summary of findings 3** Amiodarone compared to other antiarrhythmics for high risk of sudden cardiac death (primary prevention); **Summary of findings 4** Amiodarone compared to placebo or no treatment for high risk of sudden cardiac death (secondary prevention); **Summary of findings 5** Amiodarone compared to other antiarrhythmics for high risk of sudden cardiac death (secondary prevention); **Summary of findings 6** Amiodarone compared to beta blockers for high risk of sudden cardiac death (secondary prevention); **Summary of findings 7** Amiodarone compared to sotalol for high risk of sudden cardiac death (secondary prevention)

Primary Prevention

Sudden Cardiac Death

Seventeen studies comprising 8383 participants reported sudden cardiac death when comparing amiodarone versus placebo or no treatment. Amiodarone decreased the risk of SCD (RR 0.76; 95% CI 0.66 to 0.88; I^2= 0%; Analysis 1.1).

In absolute terms, using the average SCD in the control group of the studies as baseline risk, the number of SCD may decrease from 91 per 1000 people to 70 per 1000 (95% CI 61 to 81), but the quality of the evidence is low for this outcome (Summary of findings for the main comparison).

In two studies (342 participants) that compared amiodarone with beta-blockers, amiodarone decreased the risk for SCD (RR 0.37; 95% CI 0.11 to 1.22, I^2= 0%, Chi^2 P = 0.95, Analysis 3.1).

In absolute terms, based on the baseline risk of these two studies, the risk of SCD may decrease or increase (risk without amiodarone 56 per 1000 participants, with amiodarone to 21 per 1000, 95% CI 6 to 68). The quality of the evidence is low for this outcome (Summary of findings 2).

In three studies (540 participants) comparing amiodarone to other antiarrhythmics (including beta-blockers), amiodarone decreased the risk of SCD (RR 0.44; 95% CI 0.19 to 1.00, I^2= 0%; Analysis 2.1).

In absolute terms, based on the baseline risk of these three studies, the number of SCD may decrease from 65 per 1000 people to 28 per 1000 (95% CI 12 to 65). The quality of the evidence is moderate for this outcome (Summary of findings 3).

Cardiac mortality

Seventeen studies (comprising 8383 participants) reported cardiac mortality, comparing to placebo or no treatment. There was a slight but significant decrease in cardiac mortality among the amiodarone group (RR 0.86; 95% CI 0.77 to 0.96, Analysis 1.2). Compared to any other antiarrhythmics (3 studies, 540 participants), amiodarone reduced the risk of cardiac mortality (RR 0.41; 95% CI 0.20 to 0.86, Analysis 2.2), a reduction that persisted when compared solely to beta-blockers (2 studies, 342 participants), (RR 0.31, 95% CI 0.11 to 0.84, Analysis 3.2).

I^2 was < 10% for all the comparisons.

All-cause mortality

In 17 studies (8383 participants) that compared amiodarone versus placebo or no treatment, amiodarone reduced all-cause mortality (RR 0.88; 95% CI 0.78 to 1.00, I^2 = 28%) (Analysis 1.3).

In absolute terms, and compared to the baseline risk of these studies, the number of deaths may decrease from 203 per 1000 people to 178 per 1000 (95% CI 158 to 203); however, the quality of

the evidence is low for this outcome (Summary of findings for the main comparison).

Compared to beta-blockers, amiodarone significantly decreased the risk of mortality from any cause (RR 0.27; 95% CI 0.10 to 0.75, I^2= 0%; Analysis 3.3).

In absolute terms, based on the baseline risk of these studies, the number of deaths may decrease from 101 per 1000 people to 27 per 1000 (95% CI 10 to 75); however, the quality of the evidence is low for this outcome (Summary of findings 2).

Amiodarone also reduced all-cause mortality when compared with other antiarrhythmics (RR 0.37; 95% CI 0.18 to 0.76, I^2= 0%) (Analysis 2.3).

In absolute terms, compared to the baseline risk of these studies, the number of deaths may decrease from 100 per 1000 people to 37 per 1000 (95% CI 18 to 76), a finding supported by evidence of moderate quality (Summary of findings 3).

Subgroup analyses

When separately analysing the people at risk due to CHF versus those post-MI, amiodarone compared with placebo or no treatment reduced the risk of SCD in both subgroups (for post-MI participants: RR 0.65, 95% CI 0.46 to 0.91, Analysis 1.4; and for CHF participants: RR 0.79, 95% CI 0.67 to 0.93, Analysis 1.5; I^2 = 0% for both comparisons).

Regarding all-cause mortality, there was a small and non-significant difference favouring amiodarone over the control both in the post-MI (RR 0.84, 95% CI 0.61 to 1.16, Analysis 1.6) and in the CHF subgroups (RR 0.90, 95% CI 0.80 to 1.01 Analysis 1.7).

We were not able to carry out any other pre-planned subgroup analyses, as we did not obtain the information regarding different LVEF, and there was no concomitant ICD therapy in primary prevention.

Secondary Prevention

Sudden Cardiac Death

Regarding the role of amiodarone for secondary prevention of SCD when compared with placebo or no intervention, we found two studies comprising 440 participants. Amiodarone appeared to non-significantly increase the risk for SCD, as the RR is higher than 1 (RR 4.32, 95% CI 0.87 to 21.49, I^2= 0%; Analysis 4.1). However, it is not possible to conclude whether amiodarone increases or decreases the risk of SCD compared to placebo or no intervention because the quality of the evidence is very low for this outcome (Summary of findings 4).

Four studies with 839 participants compared amiodarone with other antiarrhythmics (RR f1.40, 95% CI 0.56 to 3.52, I^2 = 72%; Analysis 5.1. Again, it was not possible to determine whether amiodarone increases or decreases the risk of SCD (although it would seem it increases the risk) compared to other antiarrhythmics because the quality of the evidence is very low for this outcome (Summary of findings 5).

Only one study with 189 participants compared amiodarone with beta-blockers for secondary prevention of SCD (Kuck 2000–CASH). It would seem that amiodarone has a small, non-significant effect decreasing the risk of SCD (RR RR 0.84, 95% CI 0.55 to 1.27). However, we must be cautious, because the quality of the evidence, for this single study, is very low for this outcome (Summary of findings 6). It is not possible to determine whether amiodarone increases or decreases the risk of SCD compared to beta-blockers .

Likewise, only one study with 45 participants compared amiodarone with sotalol, another class III antiarrhythmic (Kovoor 1999) (RR 2.87, 95% CI 0.32 to 25.55). As stated above, it is not possible to determine whether amiodarone increases or decreases the risk of SCD (although the RR is higher than 1, thus increasing the risk) compared to sotalol because the quality of the evidence, for this single study, is very low for this outcome (Summary of findings 7).

Cardiac mortality

We found very little information about the effect of amiodarone on reducing the risk of cardiac mortality. Of the six studies evaluating amiodarone for secondary prevention, only two studies (243 participants) considered this outcome, comparing amiodarone with other antiarrhythmics (Greene 1993–CASCADE; Kovoor 1999) (RR of 0.77 with a 95% CI of 0.49 to 1.21, I^2=0%; Analysis 5.2) thus showing a small, non-significant decrease in risk.

All-cause mortality

The same two studies that evaluated the role of amiodarone in reducing the risk of SCD for secondary prevention when compared with placebo or no intervention evaluated its effect on reducing all-cause mortality (Connolly 2006–OPTIC; Kowey 2011–ALPHEE). Amiodarone increased the risk for all-cause mortality in this population (RR 3.05; 95% CI 1.33 to 7.01, I^2 = 0%, Chi^2 P = 0.96; Analysis 4.2).

In absolute terms, compared with the baseline risk of these studies, amiodarone may increase the risk of SCD from 32 per 1000 people to 99 per 1000 (95% CI 43 to 227), but the quality of the evidence is very low for this outcome (Summary of findings 4).

Five studies with 898 participants compared the effect of amiodarone versus other antiarrhythmics on all-cause mortality (RR 1.03, 95% CI 0.75 to 1.42, I^2 = 27%; (Analysis 5.3). In absolute terms, compared with the baseline risk of these studies, the risk of all-cause mortality may decrease or increase (risk without amiodarone 193 per 1000 people, with amiodarone 198 per 1000, 95% CI 144 to 273). The quality of the evidence is low for this outcome (Summary of findings 5).

Regarding all-cause mortality, the same study that compared amiodarone and beta-blockers for SCD prevention also compared them for all-cause mortality prevention (Kuck 2000–CASH) (RR 0.96, 95% CI 0.70 to 1.32). It was not possible to determine whether amiodarone increases or decreases the risk of SCD compared to beta-blockers because the quality of the evidence, for this single study, is very low for this outcome (Summary of findings 6).

However, there were two studies with 104 participants comparing the effect of amiodarone with sotalol on all-cause mortality (Harper 1989, Kovoor 1999) (RR 1.08, 95% CI 0.41 to 2.83). It was not possible to determine whether amiodarone increases or decreases the risk of SCD compared to sotalol because the quality of the evidence is very low for this outcome (Summary of findings 7).

Subgroup analyses

For secondary prevention, all of the studies comparing amiodarone with placebo or no intervention enrolled participants with ICD, so we were not able to carry out a subgroup analysis comparing participants with or without ICD. The only subgroup analysis we were able to perform was for amiodarone versus other antiarrhythmics for participants with or without ICD.

There were five studies with 898 participants included in that comparison (Greene 1993–CASCADE; Harper 1989; Kovoor 1999; Kowey 2011–ALPHEE; Kuck 2000–CASH). Of these, Harper 1989; Kovoor 1999 and Kuck 2000–CASH compared amiodarone with other antiarrhythmics in participants without an ICD, whereas Greene 1993–CASCADE and Kowey 2011–ALPHEE compared amiodarone with other antiarrhythmics but in participants with an ICD. However, while in Kowey 2011–ALPHEE all the participants enrolled had an ICD implanted before entering the study, this was true for only about half of the participants in Greene 1993–CASCADE, and we were not able to get the information on which participants in each arm had an ICD implanted before or during the study. Thus, we considered that only Kowey 2011–ALPHEE was fit for this analysis.

Regarding SCD in participants with ICD, amiodarone seemed to increase its risk (RR 24.45, 95% CI 2.79 to 214.59; Analysis 5.4), based solely on Kowey 2011–ALPHEE. However, when analysing the participants without ICD (two studies: Kovoor 1999; Kuck 2000–CASH) (RR 0.96, 95% CI 0.45 to 2.05, I^2= 16%; Analysis 5.5).

Furthermore, for all-cause mortality, amiodarone showed a similar effect; for participants with ICD (RR 1.96, 95% CI 0.98 to 3.93 (Analysis 5.6)), but for participants without ICD (RR is 0.97, 95% CI 0.72 to 1.31, I^2 = 0%; (Analysis 5.7).

It is important to acknowledge the fact that the use of amiodarone and sotalol as adjunctive therapy for suppression of supraventricular and ventricular arrhythmias is an important part of management of ICD patients, but one of the studies that evaluated the effect of amiodarone and sotalol on defibrillator thresholds (DFT), the OPTIC trial (Hohnloser 2006), found that although amiodarone increased DFT, the effect size was very small.

Quality of Life

There was only one study that analysed quality of life, in which Marks et al. reported the results in a separate paper from the primary study record (Bardy 2005–SCD-HeFT). Therefore, we were not able to perform a meta-analysis. However, it is worth mentioning the authors focused on two pre-specified primary outcomes, cardiac-specific physical functioning (laid down in the Duke Activity Status Index (DASI), which ranges from 0 to 58, with higher scores indicating better function), and psychological well-being (as measured by the Medical Outcomes Study 36-Item Short-Form (SF-36) Mental Health Inventory (MHI-5), which range from 0 to 100, with higher scores indicating better function).

In both outcomes, the difference in quality of life between amiodarone and placebo was not significant at any point throughout the study; we only displayed the differences at 30 months (Analysis 8.1; Analysis 8.2).

Adverse Effects

Most included studies considered adverse effects in one way or another. Adverse effects were significantly more frequent in the amiodarone arm.

Across all the studies, the incidence of thyroid-related adverse effects, whether they meant hypo- or hyperthyroidism, was higher with amiodarone, regardless of what it was compared to: placebo, no intervention, or other antiarrhythmics. However, it is important to remark that for most of the studies, the alterations in thyroid function were not clinical, but laboratory-related, both for hypo- and hyperthyroidism, which is an important fact to take into consideration when applying these findings to the clinical setting. The RR for the comparison with placebo is 4.14, 95% CI 1.54 to 11.17, I^2 = 63% for hyperthyroidism (Analysis 9.1) and a RR of 6.13, 95% CI 2.46 to 15.28, I^2 = 14% for hypothyroidism (Analysis 9.2). When comparing with other antiarrhythmics, the RR is 7.43, 95% CI 1.33 to 41.57, I^2 = 0% for hyperthyroidism (Analysis 10.1), a RR of 7.77, 95% CI 1.85 to 32.68, I^2 = 26% for hypothyroidism (Analysis 10.2) and when comparing with no treatment, the RR is 4.97, 95% CI 0.60 to 41.16, I^2 = 0% for hyperthyroidism (Analysis 11.1) and a RR of 12.82 with a 95% CI 0.73 to 225.33, based on events occurring on only one study, for hypothyroidism (Analysis 11.2).

Likewise, regarding the pulmonary effects, when comparing amiodarone with placebo, the RR is 1.66 (95% CI 1.15 to 2.40, I^2 = 0%, Analysis 9.3). When comparing it with other antiarrhythmics, the RR is 2.30, 95% CI 0.36 to 14.67, I^2 = 51% (Analysis 10.4). The comparison with no treatment has an RR of 14.79, 95% CI 0.85 to 256.43, based on solely one study (Analysis 11.3).

Finally, when we compared the rates of discontinuation as an adverse effect, amiodarone had a higher rate of discontinuation when compared with placebo (RR 1.45, 95% CI 1.26 to 1.67, I^2 = 51%, Chi^2 P = 0.02, Analysis 9.4). When comparing with other antiarrhythmics, the RR is 1.06, 95% 0.84 to 1.33, I^2 = 0%, Analysis 10.4).

Sensitivity analysis

We were unable to do perform a sensitivity analysis including and excluding quasi-randomised trials because we did not identify any trials using this design.

DISCUSSION

Summary of main results

Amiodarone vs placebo or no treatment

For primary prevention, the meta-analysis of 17 trials with 8383 participants did show beneficial effects of amiodarone compared with placebo or no treatment relative to SCD, cardiac mortality and all-cause mortality. However, amiodarone was associated with increased adverse effects, both thyroid and pulmonary (based on 12 studies), and increased risk of discontinuation (based on 13 studies) when compared with placebo.

Only one study reported on quality of life, with no conclusive effects of amiodarone over placebo.

The overall quality of evidence was low.

Regarding secondary prevention, this review could not conclusively rule out either beneficial or harmful effects of amiodarone compared with placebo or no treatment (two studies, 440 participants) relative to SCD, cardiac mortality or all-cause mortality.

The overall quality of evidence was low or very low.

We were not able to demonstrate a subgroup effect in post-MI population.

Amiodarone vs alternatives

For primary prevention, when compared to other antiarrhythmics, amiodarone also had a beneficial effect on SCD, cardiac mortality and all-cause mortality. Moreover, it did not conclusively increase the risk of pulmonary adverse effects (six studies) or discontinuation (eight studies); however, it did increase the risk of thyroid effects (seven studies).

Regarding secondary prevention, this review did not conclusively rule out either beneficial or harmful effects of amiodarone compared with other antiarrhythmics (five studies, 898 participants), relative to SCD or all-cause mortality because the quality of the evidence was very low.

Very little evidence supports more specific comparisons in this group, like amiodarone versus beta-blockers or sotalol, and what evidence exists does not change the overall effect of no benefit of amiodarone for any of the mentioned outcomes.

Overall completeness and applicability of evidence

SCD incidence rates may differ significantly between high-, and low- and-middle income countries, as well as between different geographical regions (Vedanthan 2012), although data regarding SCD in Latin America seems to be similar to high-income countries in terms of incidence and epidemiological profile, differing only in a higher prevalence of Chagas disease as the cause of SCD (Braggion-Santos 2015). However, and despite the methodological flaws that studies in low- and middle-income countries may have, CHD remains the most prevalent cause of SCD.

The included trials in our review recruited participants with different baseline risks (primary and secondary prevention) and risk factors for SCD; for example, 12% to 30% of participants across the studies had diabetes, and 11% to 100% had CHD. Trials used different definitions for CHF, and the use of beta-blockers in study participants varied from 3% in Singh 1995–STAT-CHF to 90% in Kowey 2011–ALPHEE. Despite this variability, most analyses did not reveal heterogeneity, which should increase the applicability of the results. Differences in clinical practice in some of the earlier trials may explain the variability in the use of beta-blockers, as their use was not yet widespread in the 1990s despite the evidence supporting the treatment for CHD or CHF (AHA Heart Failure 1995). In fact, analysing trials by descending order of publication date, we observe an increasing use of beta-blockers, particularly after the year 2000.

Likewise, we found pronounced differences in the definition of heart failure used as inclusion criteria for the primary studies, ranging from LVEF of 30% to 45%. One study did not even quantify LVEF, only stating that all participants had "severe congestive HF" (Hamer 1989).

Similarly, we found great variability regarding the time window after MI when participants were considered eligible for the primary studies, ranging from 24 hours to 28 days.

We had initially intended to carry out a separate analysis for participants with and without ICD. There were only three studies that included participants with ICD (Connolly 2006–OPTIC; Greene 1993–CASCADE; Kowey 2011–ALPHEE), and Greene 1993–CASCADE included participants with an ICD installed during the study, without being planned previously. Furthermore, it didn't state in any of its reports how many participants in each arm finally had an ICD implanted. We were unable to get that information from the authors.

We did not find any main study on primary prevention that enrolled participants with ICD and met our inclusion criteria, or on secondary prevention that compared amiodarone with placebo or no intervention that enrolled participants without ICD. Thus, we were not able to perform the majority of planned analyses.

As the data from Greene 1993–CASCADE did not allow us to clearly identify participants with or without an ICD, we were not able to include this study in any of our subgroup analyses on the effect of amiodarone in participants with or without ICD.

As far as we know, this is the first systematic review to take into account the outcome 'quality of life'. However, only Bardy 2005–SCD-HeFT included this outcome.

Quality of the evidence

Unfortunately, even though the clinical question we address has been the subject of research for over two decades, the quality of the evidence is very low for many relevant comparisons, and low or moderate for the rest.

For primary prevention in high risk participants, our results show that amiodarone may lead to lower SCD and all-cause mortality compared with placebo or no treatment, and it may also lead to lower mortality compared with beta blockers. The quality of this evidence is low (Summary of findings for the main comparison; Summary of findings 2).

Compared to other antiarrhythmics, amiodarone probably decreases the risk of both SCD and all-cause mortality in high risk participants. The quality of this evidence is moderate (Summary of findings 3).

The existing evidence of amiodarone for secondary prevention of SCD is of very low quality, so it is uncertain whether it has any impact on mortality (Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7).

We want to underline that when comparing amiodarone with placebo or no intervention in this setting, amiodarone seems to have a deleterious effect both on SCD and all-cause mortality, but evidence is based on only two studies (440 participants). When evaluating in detail both protocols, we can see that in Connolly 2006–OPTIC, the primary outcome was the number of appropriate shocks delivered by the ICD, while investigators considered death—whether due to arrhythmia or any other cause—to be an adverse effect. Thus, the study was not intended nor had the power to detect differences in mortality between the two groups of participants. Likewise, in Kowey 2011–ALPHEE, the main

comparison was celivarone versus placebo, with the inclusion of amiodarone as a positive control arm. For this reason, there was no sample size calculation for amiodarone in this study. Since neither study was designed to evaluate this outcome, we have to interpret their results with certain caution.

It is also important to underline that there is an important underreporting of clinical or methodological data in the primary studies, especially among earlier publications. This fact undoubtedly had an influence in our 'Risk of bias' assessment for the primary studies, which had high degrees of uncertainty for certain domains.

There may also be some publication bias (Figure 4, Figure 5; Figure 6).

Figure 4. Funnel plot of comparison: 1 Amiodarone versus placebo or no treatment for primary prevention, outcome: 1.1 Sudden cardiac death.

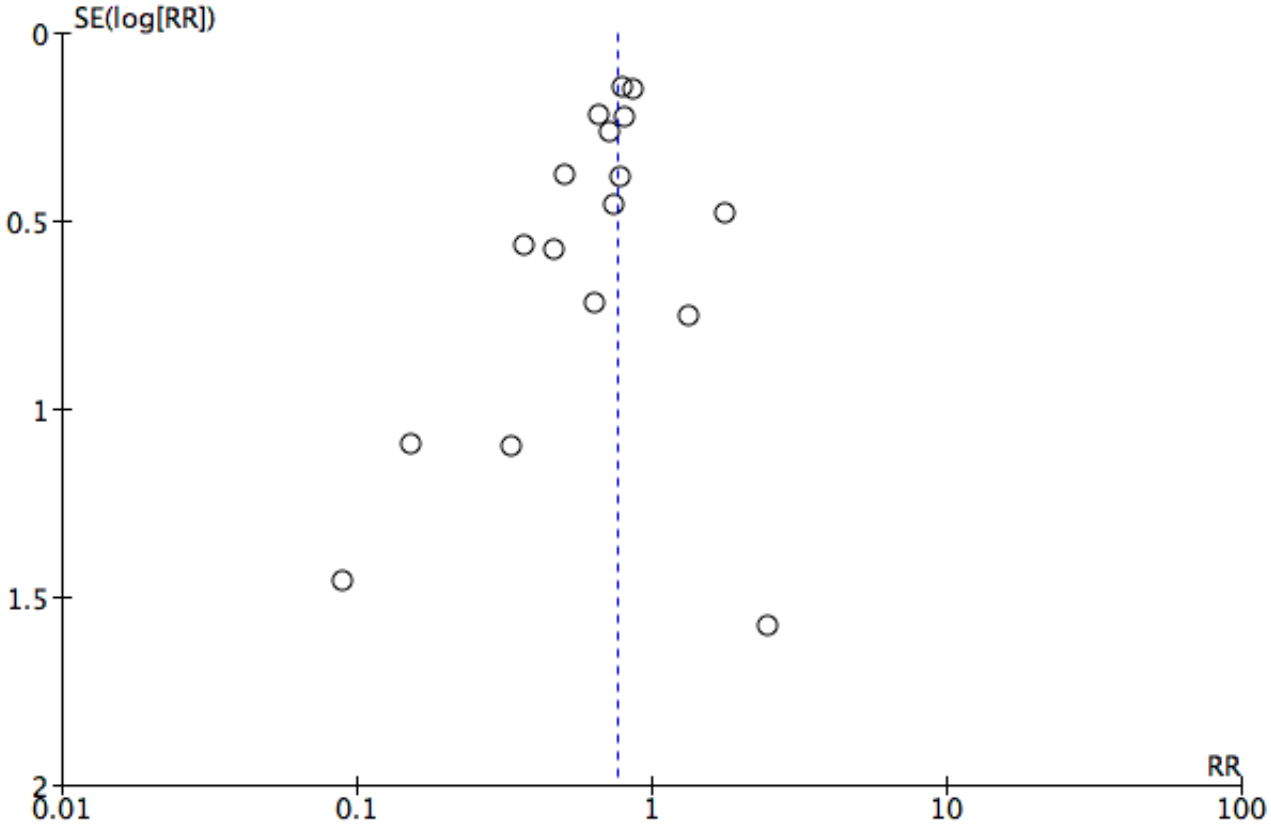


Figure 5. Funnel plot of comparison: 1 Amiodarone versus placebo or no treatment for primary prevention, outcome: 1.2 Cardiac mortality.

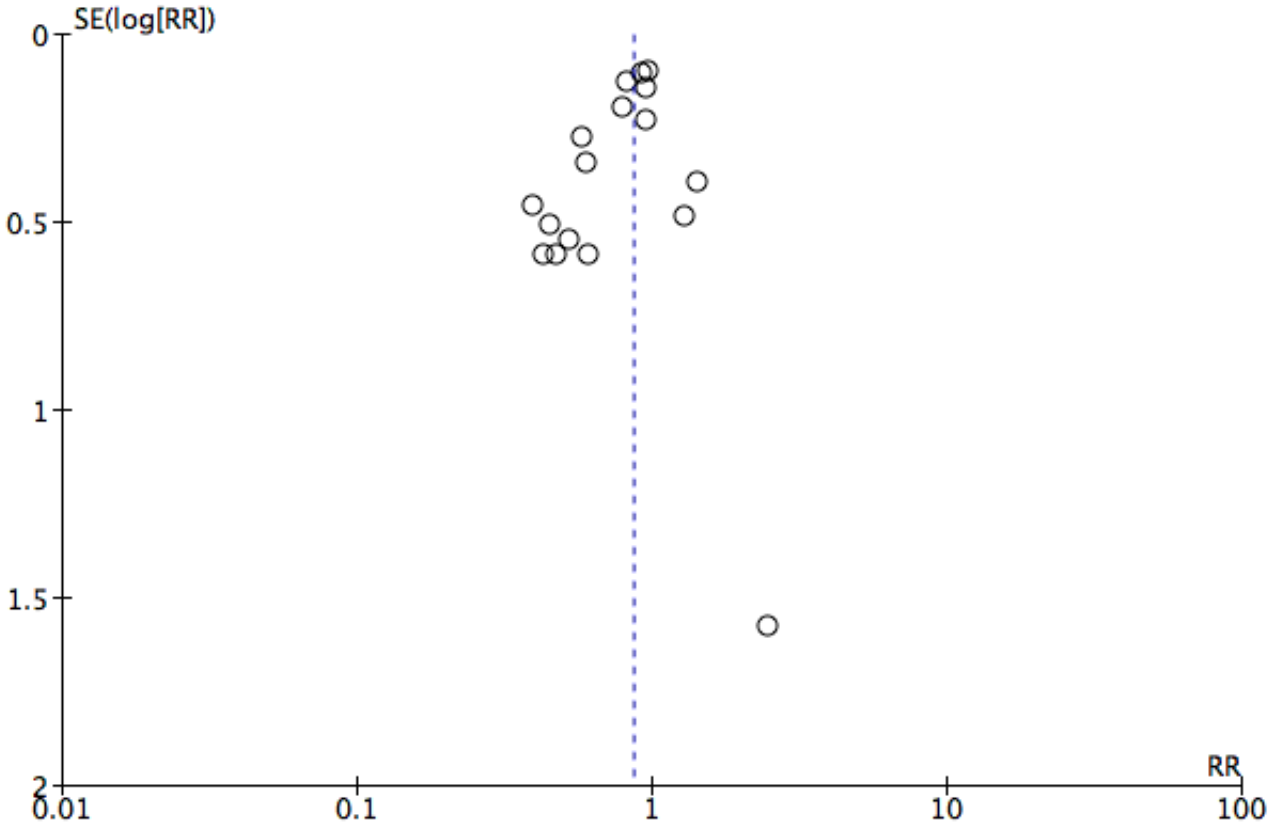
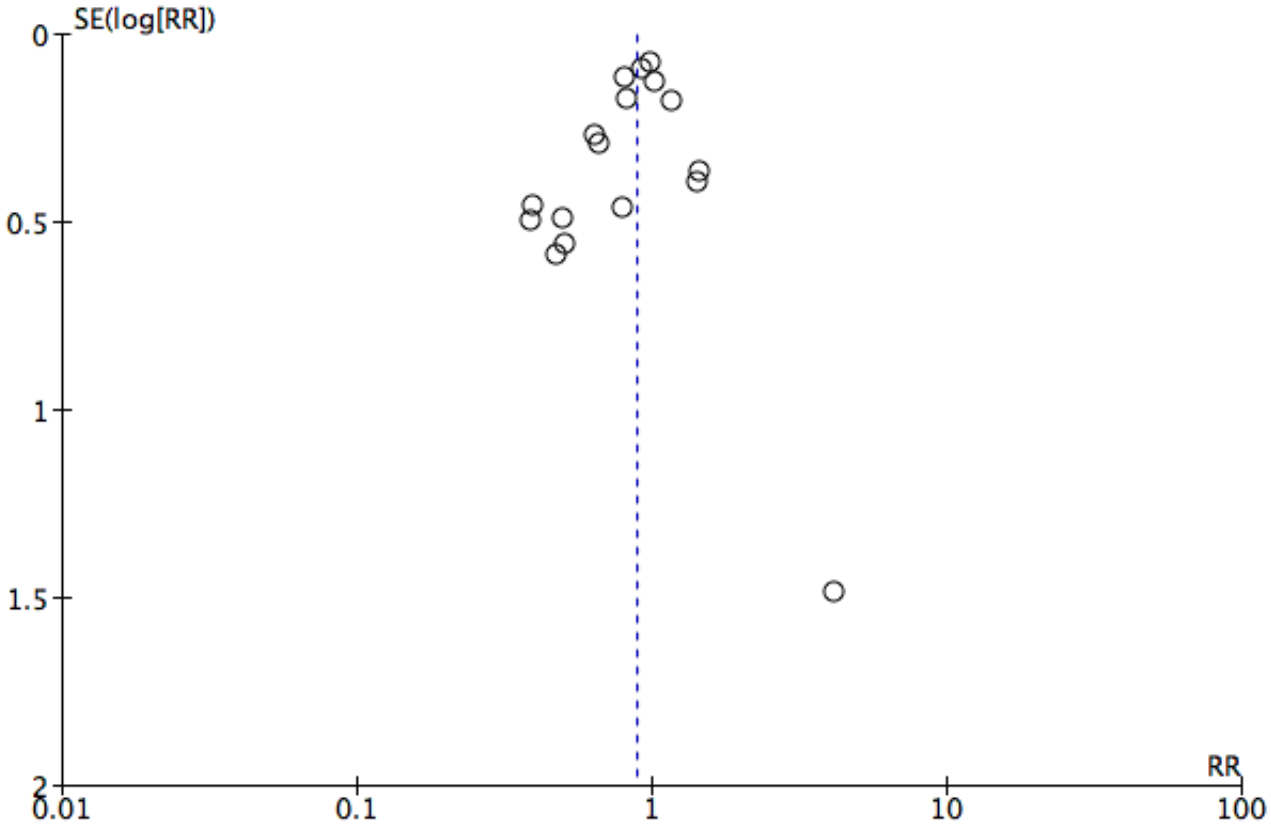


Figure 6. Funnel plot of comparison: 1 Amiodarone versus placebo or no treatment for primary prevention, outcome: 1.3 All-cause mortality.



Potential biases in the review process

Our systematic approach to searching, selecting studies, and extracting data should have minimised the likelihood of missing relevant trials. We excluded one trial that included participants with severe CHF but did not report either the rates of SCD or all-cause mortality (Warner-Stevenson 1996).

We were not able to obtain key information from several studies despite repeated attempts to contact the main author. This may have introduced bias.

We carried out a subgroup analysis comparing participants with CHF or MI as the main risk factor for presenting SCD. There were no major differences between them, but it is important to note that most of the studies included one or the other population, so the differences were analysed inter-study, not intra-study, with all the limitations this can entail (differences can be explained by population characteristics' differences, different co-interventions, different risks of bias, etc).

Agreements and disagreements with other studies or reviews

There are six previously published systematic reviews analysing the role of amiodarone for prevention of sudden death (Connolly 1997; Heidenreich 2002; Piccini 2009; Piepoli 1998; Sim 1997; Teo 1993). All of them show some benefit from amiodarone over placebo or no intervention, with reduction in death rates varying from 20% to 30%, mainly due to reductions in SCD and cardiac mortality, but with conflicting results regarding all-cause mortality.

Thus, Connolly 1997 classifies the studies included according to the main risk factor for SCD—CHF or post-MI—but does not carry out a separate analysis for each subgroup, only analysing the pool of studies as a whole.

However, these systematic reviews have two main differences from our review. First of all, the search strategy is not as comprehensive as the one we used. Secondly, previous meta-analyses combine studies which bear important differences between them, such as combining primary or secondary prevention, or including participants with and without ICD. These differences, if not taken into account, may distort or change the conclusions.

Thus, for this systematic review, we catalogued and analysed each study according to the baseline characteristics of the participants, whether the study was intended for primary or secondary prevention, whether it compared amiodarone with placebo or other antiarrhythmics, or whether the participants had an ICD implanted or not.

Our review included all of the studies considered in the previous reviews except Mahmarian 1994, which evaluated participants taking placebo or amiodarone in very low doses (two groups, each one taking 50 or 100 mg) and for only three months.

To sum up, we can conclude that our results are quite consistent with the findings of previous reviews, but with a more robust methodology, especially regarding the searching and assessment processes.

AUTHORS' CONCLUSIONS

Implications for practice

There is low quality evidence that amiodarone reduces the risk of SCD by 12% to 34% and may reduce the risk of all-cause mortality by up to 22% when compared with placebo or no intervention in a primary prevention setting. The evidence regarding the comparison with other antiarrhythmics is of moderate quality and goes in the same direction. This is very important for people in low-income countries, where an ICD may not be available, and for people awaiting an ICD in more resourceful health systems.

Regarding secondary prevention, however, the evidence is inconsistent. It would appear that, with very low quality evidence, amiodarone leads to a statistically non-significant increase in the risk of SCD and all-cause mortality (by 33% to 600%) when compared to placebo or no intervention. There are some methodological issues that warrant certain caution when interpreting these results.

Although amiodarone increases the risk for thyroid or pulmonary adverse events, the clinical benefits (reduction in SCD or all-cause mortality) for primary prevention seem to outweigh them, and amiodarone seems preferable to other antiarrhythmics and the usual (non-ICD) treatment in people at risk of SCD.

For secondary prevention, however, amiodarone does not appear to offer any benefit (and it may even be harmful) compared to other antiarrhythmics and usual treatment. ICD implantation is preferable in this group. Furthermore, given the results of our analyses, people using an ICD should use other antiarrhythmics as adjunctive therapy instead of amiodarone.

Overall, it would seem that in a limited-resource setting, the efforts to implement ICDs should focus on secondary prevention, because amiodarone seems to be a real alternative to placebo or other antiarrhythmics in terms of primary prevention.

The results of this review were limited mainly by variable methodological quality and risk of bias throughout the studies. There may also be some publication bias.

Although the evidence in which we support our findings was generated in high-income countries, we feel that those findings are applicable to a context of low- and middle-income countries, based on similar aetiology of SCD across the board.

Implications for research

An adequately powered, well-designed trial, with participants that are on optimal pharmacological treatment, could be performed in settings where an ICD is not available, like in low-income countries, in order to settle the question of the real benefit of amiodarone for secondary prevention of SCD.

We also feel that there is a need for more research on Chagas disease as a cause of SCD and the effectiveness of amiodarone in that setting.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bardy 2005–SCD-HeFT

Methods	Multicentre randomised controlled trial Setting: Patients with stable heart failure due to ischemic or nonischemic causes and a left ventricular ejection fraction of no more than 35 percent Country: United States & Canada
Participants	N = 1692 (845 amiodarone, 847 placebo) Sex: 76-77% male Age: median 60 years

Bardy 2005–SCD-HeFT *(Continued)*

	Inclusion: heart failure with LVEF < 35% (primary prevention)
Interventions	Group 1: ICD (not analysed) Group 2: amiodarone (up to 800 mg/day initially, 300 mg/d on average at the end of the study) Group 3: placebo Duration: 2 to 5 years
Outcomes	All-cause mortality, cardiac mortality, SCD, quality of life
Notes	The outcome 'quality of life was published in a separate report by Marks et al.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Allocation concealment (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Placebo and amiodarone were administered in a double-blind fashion with the use of identical appearing 200-mg tablets . . ."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Placebo and amiodarone were administered in a double-blind fashion with the use of identical appearing 200-mg tablets . . ."
Incomplete outcome data (attrition bias) Objective outcomes (death)	Low risk	Quote: "Pairwise comparisons of amiodarone with placebo and ICD with placebo were performed according to the intention-to-treat principle."
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Low risk	Quote: "Of 2521 patients who underwent randomisation, 2479 (98%) completed quality-of-life questionnaires at baseline . . . Overall, from a total of 9171 expected contacts with patients, 8747 quality-of-life questionnaires (95%) were collected. Only 1.2% of patients declined to complete the questionnaires, and only 1.4% of forms were judged to be incomplete."
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

Biswas 1996

Methods	Single centre randomised controlled trial Setting: Patients with heart failure with low ejection fraction and ventricular ectopies Country: India

Biswas 1996 *(Continued)*

Participants	N = 90 (46 amiodarone, 44 placebo) Sex: 67-69% male Age: male 56-58 years Inclusion: CHF with LVEF < 35% (primary prevention)
Interventions	Group 1: amiodarone (200 mg/day final dose) Group 2: placebo Duration: 1 year
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Allocation concealment (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The medication was given in a single-blind fashion." We are certain that the patients received placebo, but we don't know whether the physicians were blind.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of the methods used to assess the outcomes.
Incomplete outcome data (attrition bias) Objective outcomes (death)	High risk	Quote: "Forty-six participants were randomly selected to receive low-dose amiodarone and 44 patients received placebo . . ." In all the tables and figures, the numbers are 36 for amiodarone and 40 for placebo, with no explanation for the discrepancy. Furthermore, 5 participants from the amiodarone arm were excluded for showing "proarrhythmia on second Holter monitoring".
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome was made
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

Burkart 1990–BASIS

Methods	Multicentre randomised controlled trial

Burkart 1990–BASIS *(Continued)*

	Setting: Patients at after myocardial infarction who persisted with complex ventricular ectopic activity up to hospital discharge were entered into the study Country: Switzerland
Participants	N = 312 (98 amiodarone, 100 individualised antiarrhythmic drug, 114 no treatment) Sex: 86% male Age: mean 61 years Inclusion: 7 to 28 days post-AMI (primary prevention)
Interventions	Group 1: amiodarone 1000 mg/d first week, then 200 mg/d (final dose) Group 2: individualized antiarrhythmic drug Group 3: no antiarrhythmic therapy Duration: 1 year In the 'individualised antiarrhythmic drug' arm the participants used as first line quinidine or mexiletine. If the first drug did not achieve this goal, the second drug was tested. In case of failure of both drugs, clinicians tried other antiarrhythmic drugs (ajmaline, disopyramide, flecainide, propafenone or sotalol). If none of these drug regimens was effective, amiodarone was given.
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	Other measured outcomes were effectiveness of the different regimens in suppressing ventricular ectopic activity.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "They were then randomised to one of the three treatment groups on the basis of their hospital entry number and the randomisation list."
Allocation concealment (selection bias)	Unclear risk	The trial was performed at three hospitals, but there is no mention of the allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants included in the 'no therapy' arm didn't use placebo. The participants included in the individualised antiarrhythmic drug therapy used different schemes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Deaths were assessed without knowledge of the treatment group assignment; evaluation was based on death certificates, physician and hospital records, autopsy records and information obtained from relatives and witnesses."
Incomplete outcome data (attrition bias) Objective outcomes (death)	Low risk	Quote: "Each death was assigned to the treatment group according to the intention to treat principle." Quote: "Patients no longer willing to adhere to the treatment regimen or to show up for follow-up evaluation were contacted by telephone at the end of the year to obtain information about survival."
Incomplete outcome data (attrition bias)	Unclear risk	No description regarding any aspect of any subjective outcome was made.

Burkart 1990–BASIS *(Continued)*

Subjective outcomes (quality of life)		
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

Cairns 1991–CAMIATpilot

Methods	Multicentre randomised controlled trial Setting: Patients with recent AMI (on their 7th day at least) and a mean of at least 10 Ventricular Premature Depolarizations/hr or at least one run of VT in a 24hr electrocardiographic monitoring Country: Canada
Participants	N = 77 (48 amiodarone, 29 placebo) Sex: 73-79% male Age: mean 64-66 years Inclusion: ≥ 7 days postacute myocardial infarction (primary prevention)
Interventions	Group 1: amiodarone 10 mg/kg/d the first 2 weeks then 300-400 mg/d (final dose) Group 2: placebo Duration: 2 years
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	Quote: "The principal outcomes were the composite of arrhythmic death or resuscitated VF, arrhythmic death, other cardiac death, noncardiac vascular death, and nonvascular death."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Allocation concealment (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Eligible patients who gave informed consent were randomly allocated in a double-blind fashion in a 2:1 ratio to amiodarone or an identical-appearing placebo in 200-mg tablets."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "When a patient died or experienced cardiac arrest, details of the event were gathered from the hospital, ambulance, or emergency department records and from interviews with family, treating physicians, and nurses. The narrative summary was then reviewed independently and without knowledge of treatment allocation by two of the principal investigators (J.A.C. and S.J.C.)."

Cairns 1991–CAMIATpilot *(Continued)*

Incomplete outcome data (attrition bias) Objective outcomes (death)	Low risk	No missing data
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias.

Cairns 1997–CAMIAT

Methods	Multicentre randomised controlled trial Setting: Survivors of myocardial infarction with frequent or repetitive Ventricular Premature Depolarizations Country: Canada
Participants	N = 1202 (606 amiodarone, 596 placebo) Sex: 82% male Age: mean 64 years Inclusion: ≥ 7 days post acute MI (primary prevention)
Interventions	Group 1: amiodarone 10 mg/kg/d the first 2 weeks then 200-400 mg/d (final dose) Group 2: placebo Duration: 2 years
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: ". . . according to the computer generated randomisation code (stratified by centre in blocks of four) prepared by the External Safety and Efficacy Monitoring Committee . . ."
Allocation concealment (selection bias)	Low risk	Quote: "The complete randomisation code was available only to the chair of the External Safety and Efficacy Monitoring Committee. Thus, standard masked conditions were extended to include the Steering Committee, the External Safety and Efficacy Monitoring Committee, the Coordinating and Methods Centre, and Sanofi Winthrop, all of whom were unaware of treatment allocation."

Cairns 1997–CAMIAT *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "An independent company was contracted to pack the active drug (amiodarone 200 mg tablets) and matching placebo tablets."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The outcome events reported by the clinical investigators were all reviewed by the External Validation Committee under masked conditions. This committee had final responsibility for the verification of resuscitated ventricular fibrillation and the classification of deaths."
Incomplete outcome data (attrition bias) Objective outcomes (death)	Low risk	Quote: "[A]ll outcomes were also analysed by the intention-to-treat principle, in which all patients were judged to be at risk from the time of enrollment until the predefined completion of follow-up, irrespective of whether the study drug was discontinued." Quote: ". . . intention-to-treat analyses included all randomised patients . . ."
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome was made
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Ceremuzynski 1992

Methods	Multicentre randomised controlled trial Setting: Patients who survived the early phase of myocardial infarction and who were considered unsuitable to receive beta-blockers because of contraindications. Country: Poland
Participants	N = 613 (305 amiodarone, 308 to placebo) Sex: 68-71% male Age: mean 58-59 years Inclusion: 5-7 days post acute MI (primary prevention)
Interventions	Group 1: amiodarone (400 mg/d final dose) Group 2: placebo Duration: 1 year
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement

Ceremuzynski 1992 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "[P]atients were randomised between the 5th and 7th days after admission, separately in each centre according to random numbers in sealed envelopes prepared by the independent statistical unit."
Allocation concealment (selection bias)	Unclear risk	The authors used sealed envelopes for patient allocation, but it is not stated whether these envelopes were opaque.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ". . . allocated to treatment in double-blind fashion . . ."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Independent consultants who were unaware of treatment allocation verified classification of each event."
Incomplete outcome data (attrition bias) Objective outcomes (death)	Low risk	Quote: "All patients who were randomised were included in the analysis whether or not the allocated regimen had been discontinued. Follow-up for clinical events was 100% complete."
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome was made
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias

Connolly 2006–OPTIC

Methods	Multicentre randomised controlled trial Setting: Patients with spontaneous or inducible VT or VF, receiving a dual chamber ICD Countries: Canada, Germany, United States, England, Sweden, and Austria
Participants	N = 278 (140 amiodarone + beta blocker (BB), 138 to BB alone) Sex: 78-83% male Age: mean 63-65 years Inclusion: participants with ICD (secondary prevention)
Interventions	Group 1: amiodarone 800 mg/d for 6 weeks then 200 mg/d (final dose) + BB Group 2: beta-blocker alone Group 3: sotalol alone (not analyzed) Duration: 1 year
Outcomes	All-cause mortality, SCD and ICD shocks

Connolly 2006–OPTIC *(Continued)*

Notes	Primary outcome was the delivery of ICD shocks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: ". . . predetermined random sequence incorporating random block sizes of 3 and 6, with stratification for center and the rate of the slowest documented VT (150/min)".
Allocation concealment (selection bias)	Low risk	Quote: "Eligible consenting patients were registered and allocated to open-study treatment via a call to an automatic computer-based system at the study's Coordinating and Methods Center . . ."
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no matching placebo in the BB alone arm.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: ". . . adjudicated by a committee blinded to treatment allocation to determine the underlying heart rhythm before the event and the appropriateness of the delivered therapy". There is no mention to the assessment of the clinical outcomes, but it should not be different from what is stated above.
Incomplete outcome data (attrition bias) Objective outcomes (death)	Low risk	Quote: ". . . with the analysis based on intention to treat (patients were included in the analysis even if they never took or stopped the assigned therapy)". Loss to follow-up was less than 5%.
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

Doval 1994–GESICA

Methods	Multicentre randomised controlled trial Setting: Patients with severe Heart failure adequately treated Country: Argentina
Participants	N = 516 (260 amiodarone, 256 standard treatment) Sex: 79-82% male Age: mean 58-60 years Inclusion: CHF with LVEF < 35% (primary prevention)

Doval 1994–GESICA *(Continued)*

Interventions	Group 1: amiodarone (600 mg/day for 2 weeks, then 300 mg/day) Group 2: standard treatment Duration: 2 years
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was carried out with a computer allocation schedule in 10-patient blocks, stratified . . ."
Allocation concealment (selection bias)	Low risk	Quote: " [H]istory . . . of eligible patients w[as] submitted to and analysed by the coordinating centre"
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants included in the control arm didn't use matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The information was reclassified at the coordinating centre, blinded to the assigned group.
Incomplete outcome data (attrition bias) Objective outcomes (death)	Low risk	Quote: "These patients remained in the assigned group according to the intention to treat."
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes
Other bias	High risk	The trial was stopped early for benefit.

Elizari 2000–GEMICA

Methods	Multicentre randomised controlled trial Setting: patients admitted within 24 h of the onset of symptoms of an acute myocardial infarction and heart failure Country: Argentina
Participants	N= 1073 (542 amiodarone, 531 to placebo) Sex: 75-80% male

Elizari 2000–GEMICA *(Continued)*

	Age: mean 60 years Inclusion: ≥ 24 h postacute MI (primary prevention)
Interventions	Group 1: amiodarone Group 2: placebo Original protocol: "The overall dose of intravenous amiodarone or placebo was 2700 mg in the first 48 hours. Meanwhile, oral amiodarone/placebo was started at the same time as the intravenous infusion, at a dose of 600 mg every 12 h during the first 4 days. From day 5 to day 90 the oral dose consisted of a single daily dose of 400 mg of amiodarone/placebo. Afterwards and until completion of the study (180 days) the patients received 200 mg/day orally." Amended protocol: ". . . first and second day: 600 mg intravenous/day plus oral amiodarone/placebo 800 mg/ day in one intake; from day 3 to day 90, 400 mg/day and from day 91 to day 180, 200 mg/day. This amendment of the protocol meant a 52% reduction in the amiodarone loading dose in the initial 96 h of treatment for those persons assigned to the amiodarone group." Duration: 6 months
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	Quote: "the second interim analysis [516 participants] showed higher mortality among patients receiving amiodarone. This difference in mortality was suspected to be related to arterial hypotension with or without myocardial ischaemia during intravenous and/or oral administration of the drug. Consequently, the Safety and Monitoring Board suggested to the Steering Committee the need to change the amiodarone/placebo doses . . ." Quote: "This amendment of the protocol meant a 52% reduction in the amiodarone loading dose in the initial 96 h of treatment for those persons assigned to the amiodarone group."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned to receive either amiodarone or placebo in a double-blind manner. The complete randomisation list was made before the beginning of the study . . . Randomisation was carried out in balanced blocks of four patients (two for each treatment) in such a way that each centre incorporated an equal number of patients for each treatment. The actual treatment composition was not identifiable unless the corresponding codes were opened."
Allocation concealment (selection bias)	Low risk	Quote: "Patients were . . . centrally assigned to treatment in a random fashion."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients were randomly assigned . . . in a double-blind manner."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "On discharge, case report forms . . . were submitted by the researcher to the coordinating centre." We think that because it is not explicitly stated, and there's no mention about the analysis of the causes of death, the risk of bias is unclear.
Incomplete outcome data (attrition bias)	Low risk	Quote: "All the randomised patients were included in the analysis of results, whether having completed the protocol or not."

Elizari 2000–GEMICA *(Continued)*

Objective outcomes (death)		
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	High risk	There are small and unexplained differences between the sample size reported in the English and Spanish (Carbajales 1997) published data. This trial was stopped early for lack of benefit for the primary outcome.

Fournier 1989

Methods	Single centre randomised controlled trial Setting: Efficacy in the treatment of ventricular arrhythmias during the post-AMI period Country: France
Participants	N = 97 (48 amiodarone, 49 propanolol) Sex: 83-85% male Age: mean 53.9-56.4 years Inclusion: ≥ 9 days postacute MI (primary prevention)
Interventions	Group 1: amiodarone 600 mg/d for 8 days then 400 mg/d for 5 days a week (final dose) Group 2: propanolol 60 mg/d initially which then was increased to 160 mg/d over a few days Duration: 6 months
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	Electrocardiographic alterations were the main outcome for the study authors.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Allocation concealment (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants included in propanolol arm used a different scheme than participants included in the amiodarone arm.

Fournier 1989 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated for the outcome of death. For the electrocardiographical outcomes, there is a quote: "The investigators who read the LEM, although this remark can apply to them, did not know for certain which drug the patients were receiving."
Incomplete outcome data (attrition bias) Objective outcomes (death)	Low risk	Quote: "[T]he analysis should also take into account patients who stopped treatment because of side effects and patients lost to follow-up who could have stopped treatment and follow-up for the same reason. All these patients were regarded as failures. This approach, thus, took account of all patients in the study."
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

Garguichevich 1995–EPAMSA

Methods	Multicentre randomised controlled trial Setting: Patients with heart failure and asymptomatic complex ventricular arrhythmias Country: Argentina
Participants	N = 127 (66 amiodarone, 61 no treatment) Sex: 73-82% male Age: mean 60-62 years Inclusion: CHF with LVEF < 35% (primary prevention)
Interventions	Group 1: amiodarone (800 mg/day for 2 weeks, and 400 mg/d as the final dose) Group 2: no treatment Duration: 1 year
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Allocation concealment (selection bias)	Low risk	Quote: "[T]he researchers telephoned the corresponding provincial coordinator for treatment assignment. Only the provincial coordinator and the directors of the study knew about the randomisation procedures."

Garguichevich 1995–EPAMSA *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	In this trial the participants included in the control arm didn't use placebo.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is no mention in the report regarding the outcome assessment.
Incomplete outcome data (attrition bias) Objective outcomes (death)	High risk	21 participants were lost of follow-up (9 in amiodarone arm, 12 in non-treatment arm).
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Greene 1993–CASCADE

Methods	Single centre randomised controlled trial Setting: PAtients who had been resuscitated from an episode of out-of-hospital VF without a privary reversible cause and in whom a myocardial infarction did not occur at the time of the episode of VF. Country: United States
Participants	N = 228 (113 amiodarone, 115 conventional therapy) Sex: 89% male Age: mean 62 years Inclusion: resuscitated SCD (secondary prevention)
Interventions	Group 1: amiodarone 1200 mg/d for 10 days, then 200-800 mg/d for up to 2 months and finally 100-400 mg/d Group 2: other antiarrhythmic drugs (conventional therapy) guided by EP testing Duration: 2 years The participants included in the 'conventional therapy' arm used procainamide, quinidine, disopyramide, tocainide, mexiletine, encainide, flecainide, propafenone, or combination therapy
Outcomes	All-cause mortality (primary outcome), cardiac death, SCD and ICD shocks
Notes	50% of participants had an ICD installed during the trial. The implantation rate increased from 11% in 1984 to 73% in 1990. We were not able to obtain the individual data for the participants with or without ICD. Many data were retrieved from the protocol.

Greene 1993–CASCADE *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Allocation concealment (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "[T]he study is not blinded with respect to the drug assignment."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There's no mention to the outcome assessment except for the cardiac mortality, which is stated to be "an end point difficult to misclassify and includes sudden arrhythmic cardiac deaths, documented resuscitated out-of-hospital VF, and nonarrhythmic cardiac death".
Incomplete outcome data (attrition bias) Objective outcomes (death)	Low risk	Quote: "Patients are analysed by intention to treat, remaining in their randomisation group even if they discontinue the drug or cross over to the alternate therapy." Quote: "No patients were lost to follow-up, and only 8 patients in each group crossed over to the alternative therapy."
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome was made
Selective reporting (reporting bias)	Low risk	According to the protocol, the published report includes all expected outcomes
Other bias	Unclear risk	We don't have the data regarding the outcomes divided by ICD status and pharmacological arm. The ICD status should be similar for both arms, but we don't know for sure.

Hamer 1989

Methods	Single centre randomised controlled trial Setting: Patients with a history of severe heart failure stabilized on optimal medical therapy Country: Australia
Participants	N = 34 (19 amiodarone, 15 placebo) Sex: data not available Age: mean 66-70 years Inclusion: CHF with LVEF (threshold not stated in the report, only that they had to have a history of severe CHF; primary prevention)
Interventions	Group 1: amiodarone 200 mg tid for 2 weeks and then 200 mg qd (final dose)

Hamer 1989 *(Continued)*

	Group 2: placebo Duration: 6 months
Outcomes	All-cause mortality, cardiac death, SCD
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Allocation concealment (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "[T]he double blind nature of the trial was maintained as far as possible." However, in 7 participants the 'blind' was lost.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There's no mention in the report regarding the outcome assessment
Incomplete outcome data (attrition bias) Objective outcomes (death)	Unclear risk	The authors have data for all of the participants at 6 months except for 3 of them (10%)
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	High risk	Due to the small number of participants, it is difficult to adequately consider other confounding factors

Harper 1989

Methods	Multicentre randomised controlled trial Setting: Patients with at least one documented episode of VF or VT which had been associated with a ventricular rate in excess of 130 beats per minute for at least 30 seconds with resultant syncope or the need for cardioversion Country: Australia and New Zealand
Participants	N = 59 (30 amiodarone, 29 sotalol) Sex: 81% male Age: mean 59.8-60.8 years

Harper 1989 *(Continued)*

	Inclusion: resuscitated SCD (secondary prevention)
Interventions	Group 1: amiodarone 1200 mg qd for 3 weeks, then 400 mg qd (final dose) Group 2: sotalol 160-320 mg/d (640 mg/d final dose) Duration: 1 year
Outcomes	Suppression of sustained ventricular tachycardia and prevention of SCD, clinically significant adverse events
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participants were randomised using ". . . the next in a series of cards . . . to designate therapy with amiodarone or sotalol"
Allocation concealment (selection bias)	Low risk	Quote: "Patients were stratified before entry. . .. This information was telephoned to the central registry."
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants included in the sotalol arm used a different scheme than participants included in amiodarone arm.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "The open design of this study was dictated by the properties of amiodarone. . . . its long half-life made blind evaluation or a cross-over design impractical."
Incomplete outcome data (attrition bias) Objective outcomes (death)	Low risk	Quote: "All deaths and withdrawals were regarded as treatment failures and notified to the central registry." Quote: "When our results are considered by intention to treat there is no evidence that amiodarone is more effective."
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	High risk	There were co-interventions that could easily affect the study, as neither participants nor physicians were blinded.

Hockings 1987

Methods	Single centre randomised controlled trial Setting: Patients with a recent AMI (24 hours from onset of pain) Country: Australia

Hockings 1987 *(Continued)*

Participants	N = 200 (100 amiodarone, 100 placebo) Sex: 97% male Age: less than 70 years old (a exclusion criteria as being 70 years old or older) Inclusion: postacute MI (48 h after onset of chest pain; primary prevention)
Interventions	Group 1: amiodarone 600 mg/d for 1 month, then 200 mg/d (final dose) Group 2: placebo Duration: 6-42 months in the participants analysed for mortality
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	Mortality data only available for 172 participants; there is no data about the final number of participants analysed in each group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Shuffled envelopes
Allocation concealment (selection bias)	Unclear risk	It is not stated anywhere in the published report whether the envelopes were opaque or not.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Although the physicians concerned with routine care were aware of the nature of treatment, neither the subjects nor the investigators knew whether treatment was with active drug or placebo."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated anywhere in the published report whether outcome assessors were blinded or not to the nature of the treatment
Incomplete outcome data (attrition bias) Objective outcomes (death)	High risk	28 participants were not considered when calculating mortality rates in the report, with no explanation for it.
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	High risk	There were co-interventions that could easily affect the study, as physicians were not blinded.

Julian 1997–EMIAT

Methods	Multicentre randomised controlled trial

Julian 1997–EMIAT *(Continued)*

	Setting: Patients with documented myocardial infarction surviving 5 days and with EF less than 40% Country: 15 European countries
Participants	N = 1486 (743 amiodarone, 743 placebo) Sex: 84-85% male Age: mean 60 years Inclusion: LV dysfunction (LVEF < 40%) postacute MI (≥ 5 days) (primary prevention)
Interventions	Group 1: amiodarone (800 mg for 14 days, 400 mg for 14 weeks, and then 200 mg until the end of the study follow-up) Group 2: placebo Duration: 6 to 24 months (median follow-up 21 months)
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	Grant from Sanofi Recherche

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Computer-generated randomisation was done in balanced blocks of four patients . . ."
Allocation concealment (selection bias)	Low risk	Quote: "Treatment allocation was assigned under masked conditions by the EMIAT Coordinating Centre, and sent by fax to the investigators. The Coordinating Centre had no access to the treatment code."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: ". . . this randomised double-blind placebo controlled trial . . ."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The Validation Committee reviewed deaths under masked conditions"
Incomplete outcome data (attrition bias) Objective outcomes (death)	Low risk	Quote: "[A]ll patients were followed up and included in the intention-to-treat analysis" Quote: "Data on mortality was sought for all patients at the end of the planned follow-up"
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

Kovoor 1999

Methods	Single centre randomised controlled trial Setting: Patients with documented spontaneous sustained ventricular tachyarrhythmia occurring late after myocardial infarction Country: Australia
Participants	N = 45 (23 amiodarone, 22 sotalol) Sex: 83-86% male Age:mean 58-64 years Inclusion: Sustained Ventricular Tachyarrhythmia in participants with CHD
Interventions	Group 1: amiodarone, loading dose of 800 mg orally per day for 1 week followed by a maintenance dose of 400 mg per day orally Group 2: sotalol at a dose of 160 mg bid orally Duration: 3 years follow-up
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	The primary outcome variable was the time to first episode of spontaneous sustained ventricular tachyarrhythmia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Allocation concealment (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants included in the sotalol arm used a different scheme than participants included in the amiodarone arm.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is nothing stated in the published report about the outcome assessment.
Incomplete outcome data (attrition bias) Objective outcomes (death)	Low risk	Quote: "The results were analysed using an intention-to-treat analysis." There were no loss to follow-up during the study
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome was made

Kovoor 1999 *(Continued)*

Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes
Other bias	High risk	Due to the small number of participants, it is difficult to adequately consider other confounding factors

Kowey 2011–ALPHEE

Methods	Multicentre randomised controlled trial Setting: Patients at high risk for a severe ventricular arrhythmia Country: 26 countries
Participants	N = 486 (53 amiodarone, 324 celivarone (50 mg/d: 109 participants, 100 mg/d: 102 participants; 300 mg/d: 113 participants), 109 to placebo) Sex: 88,7% male Age: mean 64,4 years Inclusion: resuscitated SCD with ICD, or patients that had suffered VT or VF the previous month requiring ICD intervention (secondary prevention)
Interventions	Group 1: amiodarone 600 mg/d for 1 week then 200 mg/d (final dose) Group 2: celivarone 50-300 mg/d Group 3: placebo Duration: 9 months (median follow-up)
Outcomes	All-cause mortality, SCD, and ICD shocks
Notes	Quote: "The primary objective was to assess the efficacy of celivarone . . . versus placebo, with the use of amiodarone . . . as a calibrator, for the prevention of ICD interventions or sudden death."

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A centralized randomisation list . . . was generated."
Allocation concealment (selection bias)	Low risk	Quote: "A centralized randomisation list was generated with an interactive voice response system or interactive Web response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients were randomised to receive double-blind, once-daily oral therapy for at least 6 months with celivarone . . . amiodarone . . . or placebo."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An independent steering committee of academic physicians and 1 industry representative was responsible for the design and conduct of the study, data analysis, central blinded adjudication of deaths, and reporting of the study."

Kowey 2011–ALPHEE *(Continued)*

Incomplete outcome data (attrition bias) Objective outcomes (death)	Low risk	Quote: "The main efficacy population included all randomised patients (intention-to-treat population)."
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	High risk	Mortality reporting was inconsistent

Kuck 2000–CASH

Methods	Multicentre randomised controlled trial Setting: Survivors of cardiac arrest secondary to documented ventricular arrhythmias Country: Germany
Participants	N = 189 (92 amiodarone, 97 metoprolol) Sex: 79-82% male Age: male 56-59 years Inclusion: resuscitated from cardiac arrest secondary to documented sustained ventricular arrhythmias (secondary prevention)
Interventions	Group 1: implantable cardioverter-defibrillator (not included in analyses) Group 2: amiodarone, loading dose of 1000 mg/d for 7 days, followed by a maintenance dose of 200 to 600 mg/d) Group 3: metoprolol (initiated at a dose of 12.5 to 25.0 mg/d and increased within 7 to 14 days to a maximum of 200 mg/d, if tolerated) Duration: 24 months
Outcomes	All-cause mortality, SCD
Notes	Only the comparison amiodarone vs metoprolol is included in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Allocation concealment (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.

Kuck 2000–CASH *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants included in the metoprolol arm used a different scheme than participants included in the amiodarone arm.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is no mention in the report about how the authors handled outcome assessment.
Incomplete outcome data (attrition bias) Objective outcomes (death)	Low risk	Quote: "[Intention-to-treat analysis] was used with the patients grouped as randomised."
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

Navarro-López 1993–SSSD

Methods	Multicentre randomised controlled trial Setting: Patients with a previous (10 to 60 days) AMI, left ventricular disfunction and frequent Ventricular premature depolarizations Country: Spain
Participants	N = 368 (115 amiodarone, 130 metoprolol, 123 no treatment) Sex: 87-95% male Age: mean 57-59 years Inclusion: LV dysfunction (LVEF < 45%) postacute MI (primary prevention)
Interventions	Group 1: amiodarone (200 mg/d final dose) Group 2: metoprolol (50 to 100 mg bid final dose) Group 3: no treatment Duration: 3 years
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement

Navarro-López 1993–SSSD *(Continued)*

Random sequence generation (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Allocation concealment (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants included in the metoprolol arm used a different scheme than participants included in the amiodarone arm. Furthermore, in the control arm the participants didn't use placebo.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is no mention in the report to the way the authors handled outcome assessment.
Incomplete outcome data (attrition bias) Objective outcomes (death)	Unclear risk	Quote: "[A]ll data were analysed according to the intention-to-treat approach." However, the distribution per group of lost participants (7) is unclear.
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	Unclear risk	The study terminated its recruitment earlier than was stated in the protocol, but continued its follow-up for a longer period.

Nicklas 1991

Methods	Multicentre randomised controlled trial Setting: Patients with congestive heart failure and frequent asymptomatic ventricular ectopy Country: UK and United States
Participants	N = 101 (49 amiodarone, 52 placebo) Sex: 83-86% male Age: mean 56-59 years Inclusion: CHF with LVEF ≤ 30% (primary prevention)
Interventions	Group 1: amiodarone 400 mg/d for 4 weeks, then 200 mg/d (final dose) Group 2: placebo Duration: 1 year
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	—

Nicklas 1991 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Allocation concealment (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study medication was administered in a double-blind fashion"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There is nothing stated in the report regarding the outcome assessment
Incomplete outcome data (attrition bias) Objective outcomes (death)	Unclear risk	Quote: "All data were analysed according to the intention-to-treat principle" 2 participants were lost (5% of sample size)
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes.
Other bias	Low risk	The study appears to be free of other sources of bias.

Singh 1995–STAT-CHF

Methods	Multicentre randomised controlled trial Setting: Patients with heart failure and asymptomatic ventricular premature beats Country: United States
Participants	N = 674 (336 participants were randomised to amiodarone, 338 to placebo) Sex: 99% male Age: mean 65-66 years Inclusion: CHF with LVEF < 40% (primary prevention)
Interventions	Group 1: amiodarone (800 mg/d for 2 weeks, 400 mg/d for 50 weeks, then 300 mg/d, final dose) Group 2: placebo Duration: 24 to 45 months
Outcomes	All-cause mortality, cardiac mortality, SCD

Singh 1995–STAT-CHF *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was randomised, but the mechanism wasn't described in detail.
Allocation concealment (selection bias)	Unclear risk	The trial was randomised, but the allocation concealment mechanism wasn't described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Each patient was randomly assigned to receive amiodarone . . . or placebo throughout the trial."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Death and aborted cardiac arrests were reviewed in a blinded manner by a committee and classified as sudden or nonsudden deaths from cardiac causes or death from other causes."
Incomplete outcome data (attrition bias) Objective outcomes (death)	Unclear risk	Quote: "All patients were followed until the completion of the study and were included in the statistical analysis according to the intention-to-treat principle." However, there were 78 participants lost to follow-up, and it is not stated anywhere in the report how the authors addressed the issue
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes
Other bias	Low risk	The study appears to be free of other sources of bias

Sousonis 2014

Methods	Single centre randomised controlled trial Setting: Patients with heart failure and with more than 7000 PVCs/24 h Country: Greece
Participants	N = 20 (10 amiodarone + standard medical therapy, 10 standard medical therapy) Sex: 80-100% male Age: mean 59-62 years Inclusion: consecutive HF patients (LVEF ≤ 40%, mean LVEF: 31 ± 7%) with more than 7000 PVCs/24 h (primary prevention)
Interventions	Group 1: amiodarone (200 mg/d) + standard medical therapy Group 2: standard medical therapy alone

Sousonis 2014 *(Continued)*

	Duration: 6 months
Outcomes	All-cause mortality, cardiac mortality, SCD
Notes	Presented as a poster in the 2014 Heart Failure Congress, we have unpublished data given to us by the author. At 6 months follow-up, only 8 patients´s status was known in the control group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from the author: "a total of 20 consecutive patients were randomised in a 1:1 treatment allocation"
Allocation concealment (selection bias)	Unclear risk	The trial was randomised, but allocation concealment wasn't described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote from the author: "Only the 24 h Holter overreading physician was blinded during the study."
Blinding of outcome assessment (detection bias) All outcomes	High risk	From the author: The outcome assessor was not blind to the group which the patients were assigned to.
Incomplete outcome data (attrition bias) Objective outcomes (death)	High risk	There were 2 patients lost in the control group at the 6-month follow-up
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Low risk	The study protocol was not available, but it is clear that the published report includes all expected outcomes
Other bias	High risk	Due to the small number of participants, it is difficult to adequately consider other confounding factors

Zehender 1992

Methods	Randomised controlled trial Setting: Patients with idiopathic dilated cardiomyopathy and heart failure Country: Germany
Participants	N = 30 (15 amiodarone, 15 conventional antiarrhythmic or no therapy) Sex: 83% male Age: 52 years mean Inclusion: CHF with LVEF < 45% (idiopathic dilated cardiomyopathy; primary prevention)

Zehender 1992 *(Continued)*

Interventions	Group 1: amiodarone 800 mg/d for 10 days then 200 mg/d (final dose) Group 2: conventional antiarrhythmic or no therapy Duration: 2 years
Outcomes	Electrocardiographic alterations, all-cause mortality, cardiac mortality, SCD
Notes	Only published data, original paper in German

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The randomisation was incomplete: 4 participants were documented to have spontaneous continuous ventricular tachycardia or ventricular fibrillation and were therefore excluded from the randomisation. They started with amiodarone immediately.
Allocation concealment (selection bias)	Unclear risk	The allocation concealment mechanism wasn't described in detail.
Blinding of participants and personnel (performance bias) All outcomes	High risk	In the control arm the participants used conventional therapy or no therapy.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated anywhere in the published report whether the outcome assessment was blinded or not.
Incomplete outcome data (attrition bias) Objective outcomes (death)	Unclear risk	Reporting of these data is confusing. Furthermore, 2 participants withdrew from the study. It is not stated whether the authors included them in the analysis (apparently they did)
Incomplete outcome data (attrition bias) Subjective outcomes (quality of life)	Unclear risk	No description regarding any aspect of any subjective outcome
Selective reporting (reporting bias)	Unclear risk	There is not much clarity about this item with the information we possess
Other bias	High risk	Due to the small number of participants, it is difficult to adequately consider other confounding factors

AMI: acute myocardial infarction; **BB**: beta blockers; **bid**: bis in die, or twice a day **CHD**: coronary heart disease; **CHF**: coronary heart failure; **EP**: electrophysiological; **HF**: heart failure; **ICD**: implantable cardiac defibrillators; **LEM**: Long-term electrocardiographs monitoring ; **LVEF**: left ventricular ejection fraction; **MI**: myocardial infarction; **PVC**: premature ventricular contraction; **qd**: quaque die, or once a day; **SCD**: sudden cardiac death; **tid**: ter in die, or three times a day; **VF**: ventricular fibrillation; **VT**: ventricular tachycardia.

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

Study	Reason for exclusion
ALIVE 2001	Study designed not for secondary prevention of SCD, but for the acute management of refractory ventricular arrhythmia
Anderson 1994	Amiodarone was not randomised
Ballas 1991	Not an RCT
Banasiak 1988	Not an RCT
Bates 1993	Not a clinical study
Bodem 1997	Not a clinical study
Brakhmann 1992	Not a RCT
Cleland 1986	Treatment for less than 6 months
Dluzniewski 1987	Treatment for less than 6 months
Dolack 1994	Not a clinical study
Formulary 1997	Not a clinical study
Gao 2014	Lower dose of amiodarone (100 mg/day)
Giani 1992	Amiodarone used in combination with other antiarrhythmic drugs in a sequential manner
Good God 2005	Not an RCT
Iavelov 2006	Not a clinical study
Jung 1992	It didn't evaluate relevant outcomes
Kanorskii 2005	Main intervention was perindopril, only sometimes combined with amiodarone
Kasanuki 1994	Not an RCT
Kerin 1991	Not an RCT
Koch-Weser 1978	Not an RCT
Lau 2004	Amiodarone used in combination with other antiarrhythmic drugs in a sequential manner
Lu 2009	Not an RCT
Luderitz 1983	Not an RCT
Modica 1975	Treatment for less than 6 months
Mostow 1985	Not a clinical study
Oleinikov 1985	Study carried out on dogs
Poplawska 1987	Not an RCT

Study	Reason for exclusion
Santini 2011	Not an RCT
Satomi 2006	Not a RCT
Shaughnessy 1998	Not a clinical study
Teo 1990	Not a RCT
Torp-Pedersen 2007	Comparison was between Carvedilol and Metoprolol (COMET study), this was a post hoc analysis of the use of amiodarone in the study.
Toyama 2008	Lower dose of amiodarone (100 mg/day)
Warner-Stevenson 1996	Relevant outcomes were not described, we were not able to contact the author

RCT: randomised controlled trial.

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

NIPPON 2006

Trial name or title	Nippon ICD Plus Pharmacologic Option Necessity (NIPPON Study)
Methods	Multicentre, randomised controlled trial
Participants	440 patients, all with spontaneous episodes of sustained VT or VF; all patients will have organic heart disease as documented either by electrocardiography, echocardiography, cardiac catheterisation, nuclear scintigraphy, computed tomography or magnetic resonance imaging;
Interventions	Patients will be randomly assigned to one of 2 groups; amiodarone group and non-amiodarone group. An ICD (basically, dual chamber types) will be implanted in every patient as soon as possible after randomisation. Amiodarone loading dose of 400 mg/day, and two weeks after the loading dose period, amiodarone will be reduced to a maintenance dose of 200 mg/day
Outcomes	Listed as secondary end points: total death; arrhythmic death; cardiac death; impairment of patient's quality of life; occurrence of side-effects from amiodarone
Starting date	Paper published in March 2006
Contact information	Takashi Kurita, MD, Department of Cardiovascular Medicine, National Cardiovascular Center, 5-7-1 Fujishirodai, Suita 565-8565, Japan. E-mail: kuritat@med.kindai.ac.jp
Notes	There have been no published results from this study, although the design was published in 2006.

ICD: implantable cardiac defibrillators.

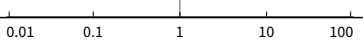
DATA AND ANALYSES

Comparison 1. Amiodarone versus placebo or no treatment for primary prevention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sudden cardiac death	17	8383	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.66, 0.88]
2 Cardiac mortality	17	8383	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.77, 0.96]
3 All-cause mortality	17	8383	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.78, 1.00]
4 Sudden cardiac death subgroup post- AMI patients	6	3377	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.46, 0.91]
5 Sudden cardiac death subgroup heart failure	11	5006	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.67, 0.93]
6 All-cause mortality subgroup post-AMI	6	3377	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.61, 1.16]
7 All-cause mortality subgroup heart failure	11	5006	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]

Analysis 1.1. Comparison 1 Amiodarone versus placebo or no treatment for primary prevention, Outcome 1 Sudden cardiac death.

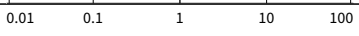
Study or subgroup	Amiodarone n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bardy 2005–SCD-HeFT	75/845	95/847		25.66%	0.79[0.59,1.05]
Biswas 1996	7/46	9/44		2.63%	0.74[0.3,1.82]
Burkart 1990–BASIS	4/98	10/114		1.67%	0.47[0.15,1.44]
Cairns 1991–CAMIATpilot	1/48	4/29		0.46%	0.15[0.02,1.29]
Cairns 1997–CAMIAT	24/606	33/596		8.04%	0.72[0.43,1.2]
Ceremuzynski 1992	10/305	20/308		3.84%	0.5[0.24,1.06]
Doval 1994–GESICA	32/260	39/256		11.23%	0.81[0.52,1.25]
Elizari 2000–GEMICA	12/542	15/531		3.77%	0.78[0.37,1.66]
Garguichevich 1995–EPAMSA	4/66	10/61		1.73%	0.37[0.12,1.12]
Hamer 1989	0/19	4/15		0.26%	0.09[0.01,1.53]
Hockings 1987	4/100	3/100		0.98%	1.33[0.31,5.81]
Julian 1997–EMIAT	33/743	50/743		11.59%	0.66[0.43,1.01]
Navarro-López 1993–SSSD	3/115	5/123		1.07%	0.64[0.16,2.62]
Nicklas 1991	10/49	6/52		2.43%	1.77[0.7,4.5]
Singh 1995–STAT-CHF	64/336	75/338		23.96%	0.86[0.64,1.16]
Sousonis 2014	1/10	0/8		0.22%	2.45[0.11,53.25]
Zehender 1992	1/15	3/15		0.46%	0.33[0.04,2.85]
Total (95% CI)	**4203**	**4180**		**100%**	**0.76[0.66,0.88]**
Total events: 285 (Amiodarone), 381 (Control)					
Heterogeneity: Tau^2=0; Chi^2=14.12, df=16(P=0.59); I^2=0%					
Test for overall effect: Z=3.7(P=0)					



Favours amiodarone — Favours control

Analysis 1.2. Comparison 1 Amiodarone versus placebo or no treatment for primary prevention, Outcome 2 Cardiac mortality.

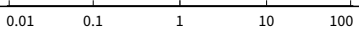
Study or subgroup	Amiodarone n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bardy 2005–SCD-HeFT	162/845	167/847		23.37%	0.97[0.8,1.18]
Biswas 1996	10/46	16/44		2.44%	0.6[0.3,1.17]
Burkart 1990–BASIS	5/98	13/114		1.13%	0.45[0.17,1.21]
Cairns 1991–CAMIATpilot	5/48	5/29		0.85%	0.6[0.19,1.91]
Cairns 1997–CAMIAT	44/606	55/596		7.29%	0.79[0.54,1.15]
Ceremuzynski 1992	19/305	33/308		3.72%	0.58[0.34,1]
Doval 1994–GESICA	76/260	91/256		15.34%	0.82[0.64,1.06]
Elizari 2000–GEMICA	35/542	36/531		5.31%	0.95[0.61,1.49]
Garguichevich 1995–EPAMSA	6/66	14/61		1.41%	0.4[0.16,0.97]
Hamer 1989	4/19	6/15		0.98%	0.53[0.18,1.53]
Hockings 1987	9/100	7/100		1.24%	1.29[0.5,3.32]
Julian 1997–EMIAT	85/743	89/743		12.74%	0.96[0.72,1.26]
Navarro-López 1993–SSSD	4/115	9/123		0.85%	0.48[0.15,1.5]
Nicklas 1991	12/49	9/52		1.87%	1.41[0.65,3.06]
Singh 1995–STAT-CHF	109/336	120/338		20.49%	0.91[0.74,1.13]
Sousonis 2014	1/10	0/8		0.12%	2.45[0.11,53.25]
Zehender 1992	3/15	7/15		0.85%	0.43[0.14,1.35]
Total (95% CI)	**4203**	**4180**		**100%**	**0.86[0.77,0.96]**
Total events: 589 (Amiodarone), 677 (Control)					
Heterogeneity: Tau^2=0; Chi^2=16.94, df=16(P=0.39); I^2=5.52%					
Test for overall effect: Z=2.75(P=0.01)					



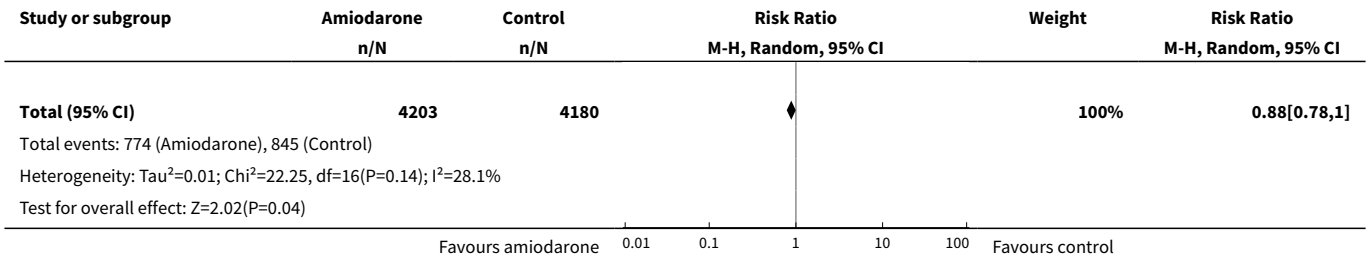
Favours amiodarone — Favours control

Analysis 1.3. Comparison 1 Amiodarone versus placebo or no treatment for primary prevention, Outcome 3 All-cause mortality.

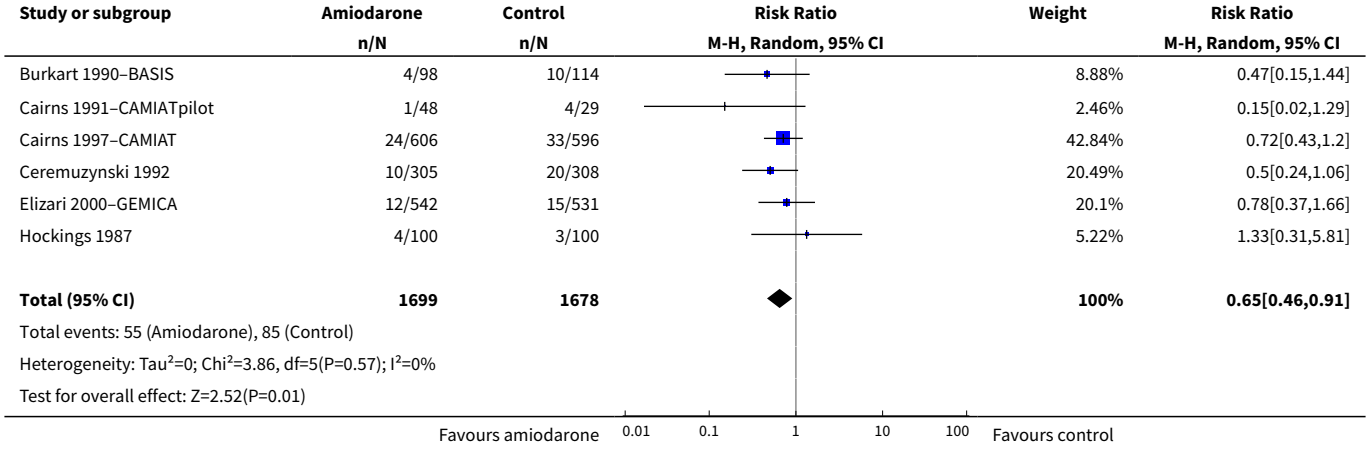
Study or subgroup	Amiodarone n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bardy 2005–SCD-HeFT	240/845	244/847		18.93%	0.99[0.85,1.15]
Biswas 1996	13/46	19/44		3.78%	0.65[0.37,1.16]
Burkart 1990–BASIS	5/98	15/114		1.43%	0.39[0.15,1.03]
Cairns 1991–CAMIATpilot	5/48	6/29		1.15%	0.5[0.17,1.5]
Cairns 1997–CAMIAT	57/606	68/596		8.74%	0.82[0.59,1.15]
Ceremuzynski 1992	21/305	33/308		4.38%	0.64[0.38,1.08]
Doval 1994–GESICA	87/260	106/256		13.83%	0.81[0.65,1.01]
Elizari 2000–GEMICA	62/542	52/531		8.22%	1.17[0.82,1.66]
Garguichevich 1995–EPAMSA	6/66	14/61		1.7%	0.4[0.16,0.97]
Hamer 1989	6/19	6/15		1.64%	0.79[0.32,1.95]
Hockings 1987	16/100	11/100		2.54%	1.45[0.71,2.98]
Julian 1997–EMIAT	103/743	102/743		12.19%	1.01[0.78,1.3]
Navarro-López 1993–SSSD	4/115	9/123		1.04%	0.48[0.15,1.5]
Nicklas 1991	12/49	9/52		2.22%	1.41[0.65,3.06]
Singh 1995–STAT-CHF	131/336	143/338		16.59%	0.92[0.77,1.11]
Sousonis 2014	2/10	0/8		0.17%	4.09[0.22,74.78]
Zehender 1992	4/15	8/15		1.46%	0.5[0.19,1.31]



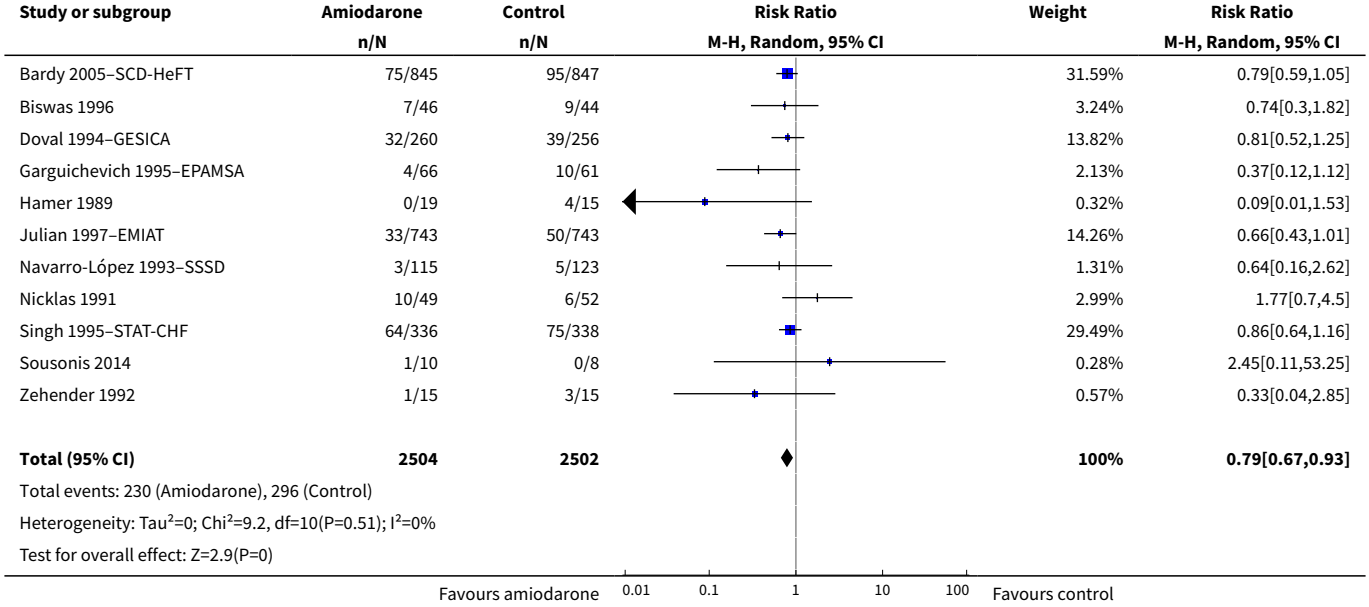
Favours amiodarone — Favours control



Analysis 1.4. Comparison 1 Amiodarone versus placebo or no treatment for primary prevention, Outcome 4 Sudden cardiac death subgroup post- AMI patients.



Analysis 1.5. Comparison 1 Amiodarone versus placebo or no treatment for primary prevention, Outcome 5 Sudden cardiac death subgroup heart failure.



Analysis 1.6. Comparison 1 Amiodarone versus placebo or no treatment for primary prevention, Outcome 6 All-cause mortality subgroup post-AMI.

Study or subgroup	Amiodarone n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Burkart 1990–BASIS	5/98	15/114		8.26%	0.39[0.15,1.03]
Cairns 1991–CAMIATpilot	5/48	6/29		6.88%	0.5[0.17,1.5]
Cairns 1997–CAMIAT	57/606	68/596		26.95%	0.82[0.59,1.15]
Ceremuzynski 1992	21/305	33/308		18.73%	0.64[0.38,1.08]
Elizari 2000–GEMICA	62/542	52/531		26.22%	1.17[0.82,1.66]
Hockings 1987	16/100	11/100		12.96%	1.45[0.71,2.98]
Total (95% CI)	**1699**	**1678**		**100%**	**0.84[0.61,1.16]**
Total events: 166 (Amiodarone), 185 (Control)					
Heterogeneity: Tau^2=0.07; Chi^2=9.67, df=5(P=0.09); I^2=48.3%					
Test for overall effect: Z=1.06(P=0.29)					

Favours amiodarone — Favours control

Analysis 1.7. Comparison 1 Amiodarone versus placebo or no treatment for primary prevention, Outcome 7 All-cause mortality subgroup heart failure.

Study or subgroup	Amiodarone n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bardy 2005–SCD-HeFT	240/845	244/847		28.85%	0.99[0.85,1.15]
Biswas 1996	13/46	19/44		4.14%	0.65[0.37,1.16]
Doval 1994–GESICA	87/260	106/256		18.64%	0.81[0.65,1.01]
Garguichevich 1995–EPAMSA	6/66	14/61		1.79%	0.4[0.16,0.97]
Hamer 1989	6/19	6/15		1.73%	0.79[0.32,1.95]
Julian 1997–EMIAT	103/743	102/743		15.83%	1.01[0.78,1.3]
Navarro-López 1993–SSSD	4/115	9/123		1.09%	0.48[0.15,1.5]
Nicklas 1991	12/49	9/52		2.36%	1.41[0.65,3.06]
Singh 1995–STAT-CHF	131/336	143/338		23.84%	0.92[0.77,1.11]
Sousonis 2014	2/10	0/8		0.17%	4.09[0.22,74.78]
Zehender 1992	4/15	8/15		1.54%	0.5[0.19,1.31]
Total (95% CI)	**2504**	**2502**		**100%**	**0.9[0.8,1.01]**
Total events: 608 (Amiodarone), 660 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=12.52, df=10(P=0.25); I^2=20.14%					
Test for overall effect: Z=1.75(P=0.08)					

Favours amiodarone — Favours control

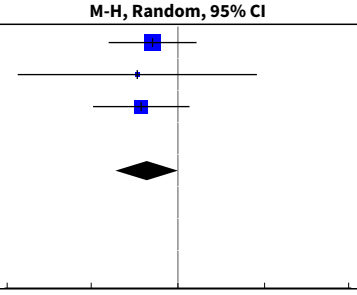
Comparison 2. Amiodarone versus other antiarrhythmics for primary prevention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sudden cardiac death	3	540	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.19, 1.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Cardiac mortality	3	540	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.20, 0.86]
3 All-cause mortality	3	540	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.18, 0.76]

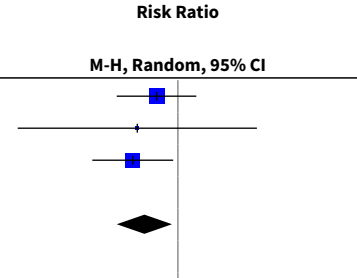
Analysis 2.1. Comparison 2 Amiodarone versus other antiarrhythmics for primary prevention, Outcome 1 Sudden cardiac death.

Study or subgroup	Amiodarone n/N	Other antiarrhythmics n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Burkart 1990–BASIS	4/98	8/100		50.92%	0.51[0.16,1.64]
Fournier 1989	0/48	1/49		6.88%	0.34[0.01,8.15]
Navarro-López 1993–SSSD	3/115	9/130		42.2%	0.38[0.1,1.36]
Total (95% CI)	**261**	**279**		**100%**	**0.44[0.19,1]**
Total events: 7 (Amiodarone), 18 (Other antiarrhythmics)					
Heterogeneity: Tau^2=0; Chi^2=0.14, df=2(P=0.93); I^2=0%					
Test for overall effect: Z=1.95(P=0.05)					



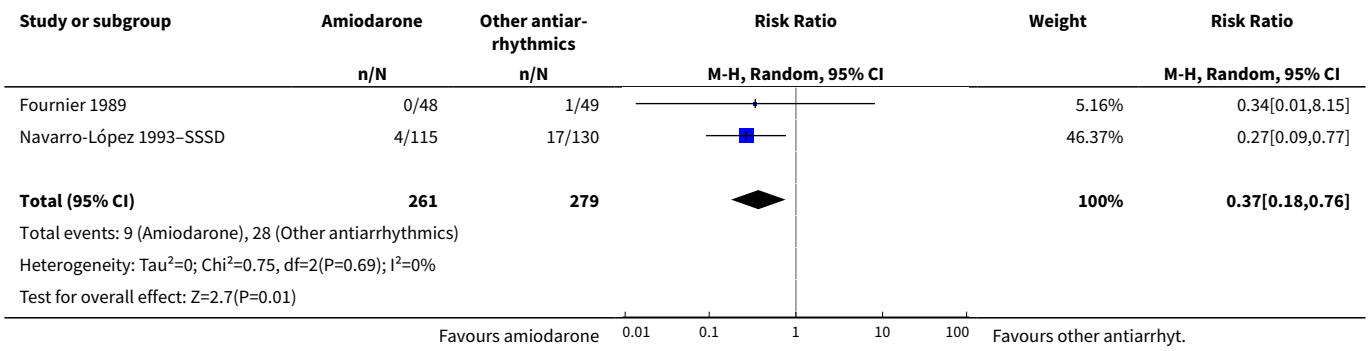
Analysis 2.2. Comparison 2 Amiodarone versus other antiarrhythmics for primary prevention, Outcome 2 Cardiac mortality.

Study or subgroup	Amiodarone n/N	Other antiarrhythmics n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Burkart 1990–BASIS	5/98	9/100		48.09%	0.57[0.2,1.63]
Fournier 1989	0/48	1/49		5.33%	0.34[0.01,8.15]
Navarro-López 1993–SSSD	4/115	15/130		46.59%	0.3[0.1,0.88]
Total (95% CI)	**261**	**279**		**100%**	**0.41[0.2,0.86]**
Total events: 9 (Amiodarone), 25 (Other antiarrhythmics)					
Heterogeneity: Tau^2=0; Chi^2=0.69, df=2(P=0.71); I^2=0%					
Test for overall effect: Z=2.38(P=0.02)					



Analysis 2.3. Comparison 2 Amiodarone versus other antiarrhythmics for primary prevention, Outcome 3 All-cause mortality.

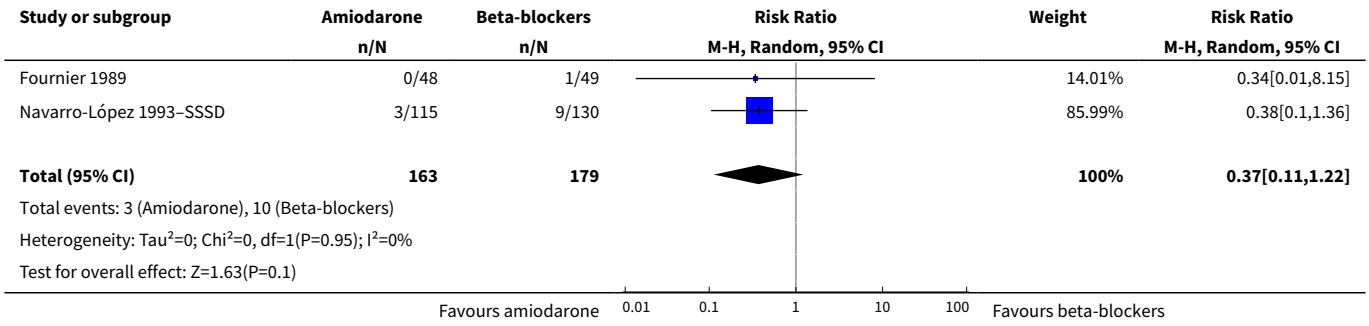
Study or subgroup	Amiodarone n/N	Other antiarrhythmics n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Burkart 1990–BASIS	5/98	10/100		48.47%	0.51[0.18,1.44]



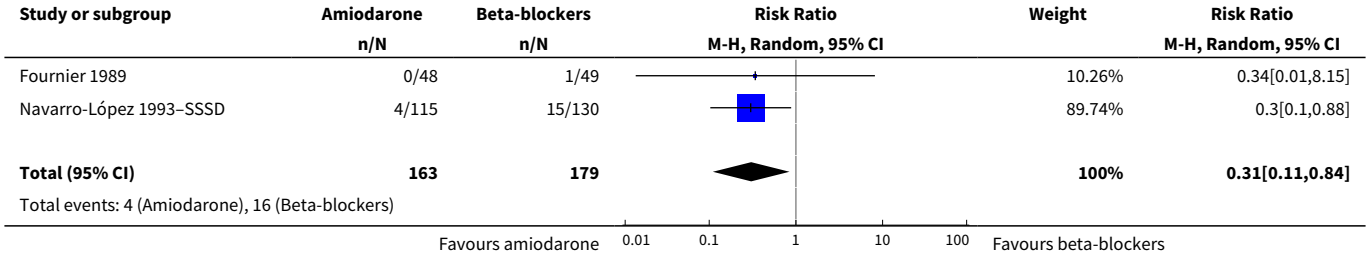
Comparison 3. Amiodarone versus beta-blockers for primary prevention

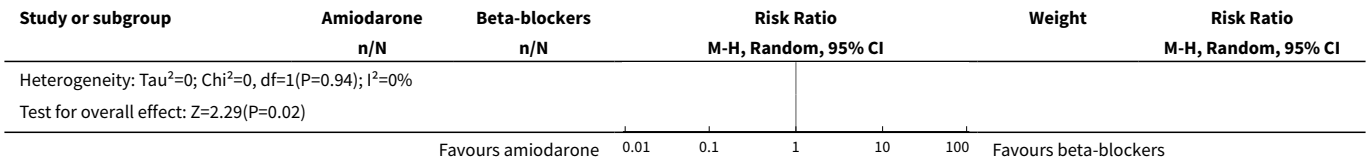
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sudden cardiac death	2	342	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.11, 1.22]
2 Cardiac mortality	2	342	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.11, 0.84]
3 All-cause mortality	2	342	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.10, 0.75]

Analysis 3.1. Comparison 3 Amiodarone versus beta-blockers for primary prevention, Outcome 1 Sudden cardiac death.

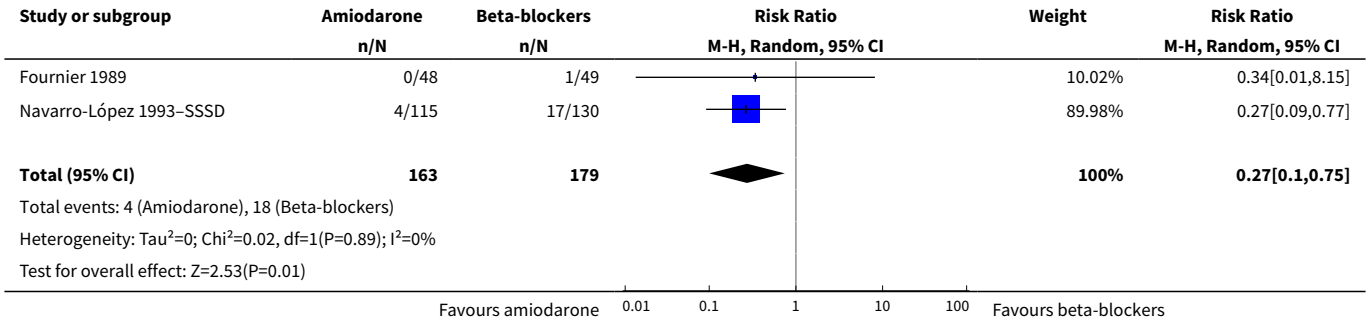


Analysis 3.2. Comparison 3 Amiodarone versus beta-blockers for primary prevention, Outcome 2 Cardiac mortality.





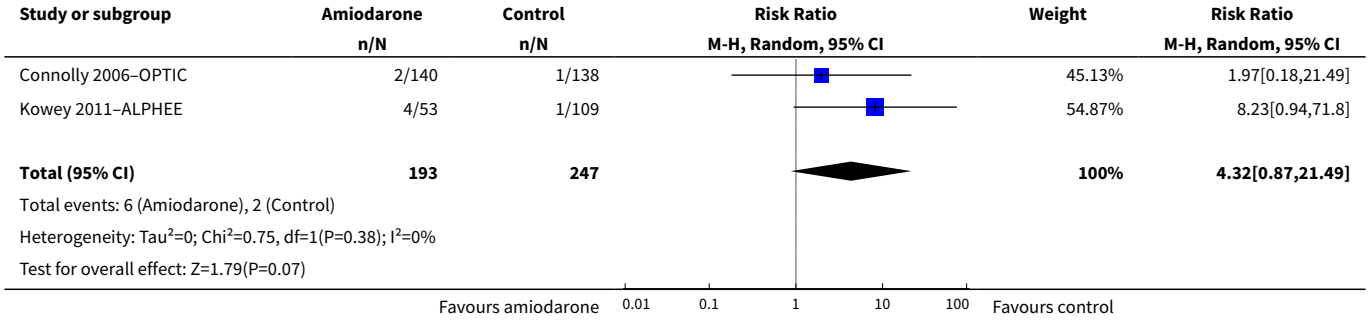
Analysis 3.3. Comparison 3 Amiodarone versus beta-blockers for primary prevention, Outcome 3 All-cause mortality.



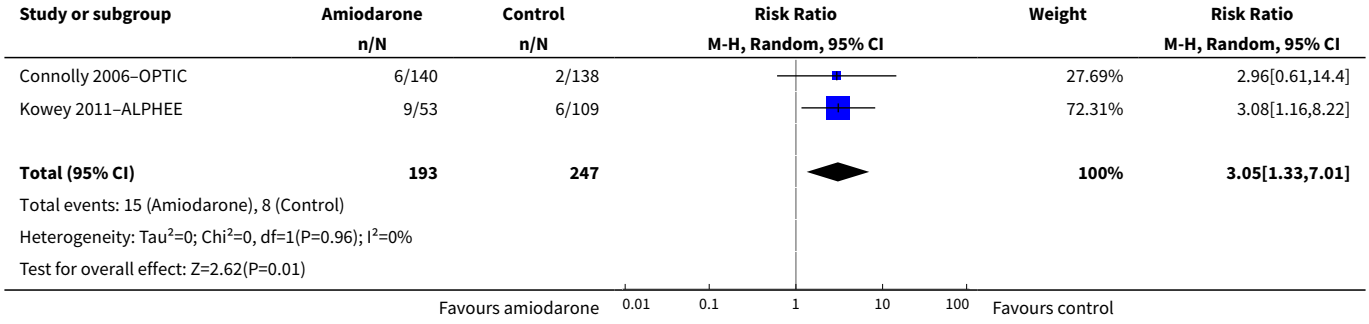
Comparison 4. Amiodarone versus placebo or no treatment for secondary prevention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sudden cardiac death	2	440	Risk Ratio (M-H, Random, 95% CI)	4.32 [0.87, 21.49]
2 All-cause mortality	2	440	Risk Ratio (M-H, Random, 95% CI)	3.05 [1.33, 7.01]

Analysis 4.1. Comparison 4 Amiodarone versus placebo or no treatment for secondary prevention, Outcome 1 Sudden cardiac death.



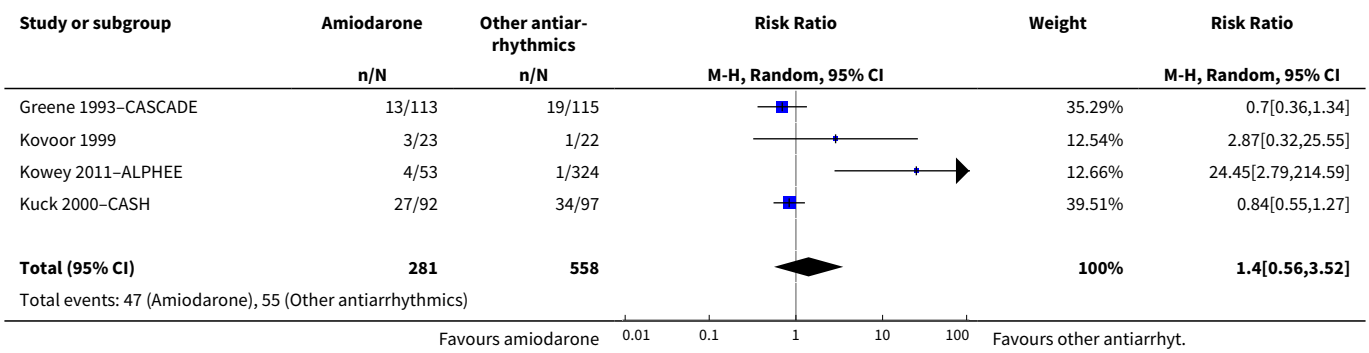
Analysis 4.2. Comparison 4 Amiodarone versus placebo or no treatment for secondary prevention, Outcome 2 All-cause mortality.



Comparison 5. Amiodarone versus other antiarrhythmics for secondary prevention

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Sudden cardiac death	4	839	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.56, 3.52]
2 Cardiac mortality	2	273	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.49, 1.21]
3 All-cause mortality	5	898	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.75, 1.42]
4 Sudden cardiac death sub-group with ICD	1	377	Risk Ratio (M-H, Random, 95% CI)	24.45 [2.79, 214.59]
5 Sudden cardiac death sub-group without ICD	2	234	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.45, 2.05]
6 All-cause mortality subgroup with ICD	1	377	Risk Ratio (M-H, Random, 95% CI)	1.96 [0.98, 3.93]
7 All-cause mortality subgroup without ICD	3	293	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.72, 1.31]

Analysis 5.1. Comparison 5 Amiodarone versus other antiarrhythmics for secondary prevention, Outcome 1 Sudden cardiac death.



Study or subgroup	Amiodarone	Other antiarrhythmics	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Heterogeneity: Tau²=0.51; Chi²=10.79, df=3(P=0.01); I²=72.2%					
Test for overall effect: Z=0.72(P=0.47)					

Favours amiodarone — Favours other antiarrhyt.

Analysis 5.2. Comparison 5 Amiodarone versus other antiarrhythmics for secondary prevention, Outcome 2 Cardiac mortality.

Study or subgroup	Amiodarone	Other antiarrhythmics	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Greene 1993–CASCADE	23/113	32/115		92.87%	0.73[0.46,1.17]
Kovoor 1999	3/23	2/22		7.13%	1.43[0.26,7.78]
Total (95% CI)	**136**	**137**		**100%**	**0.77[0.49,1.21]**
Total events: 26 (Amiodarone), 34 (Other antiarrhythmics)					
Heterogeneity: Tau²=0; Chi²=0.57, df=1(P=0.45); I²=0%					
Test for overall effect: Z=1.15(P=0.25)					

Favours amiodarone — Favours other antiarrhyt.

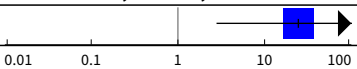
Analysis 5.3. Comparison 5 Amiodarone versus other antiarrhythmics for secondary prevention, Outcome 3 All-cause mortality.

Study or subgroup	Amiodarone	Other antiarrhythmics	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Harper 1989	4/30	5/29		6.2%	0.77[0.23,2.6]
Greene 1993–CASCADE	27/113	34/115		31.16%	0.81[0.52,1.25]
Kovoor 1999	4/23	2/22		3.71%	1.91[0.39,9.41]
Kuck 2000–CASH	40/92	44/97		42.68%	0.96[0.7,1.32]
Kowey 2011–ALPHEE	9/53	28/324		16.25%	1.96[0.98,3.93]
Total (95% CI)	**311**	**587**		**100%**	**1.03[0.75,1.42]**
Total events: 84 (Amiodarone), 113 (Other antiarrhythmics)					
Heterogeneity: Tau²=0.03; Chi²=5.46, df=4(P=0.24); I²=26.73%					
Test for overall effect: Z=0.21(P=0.84)					

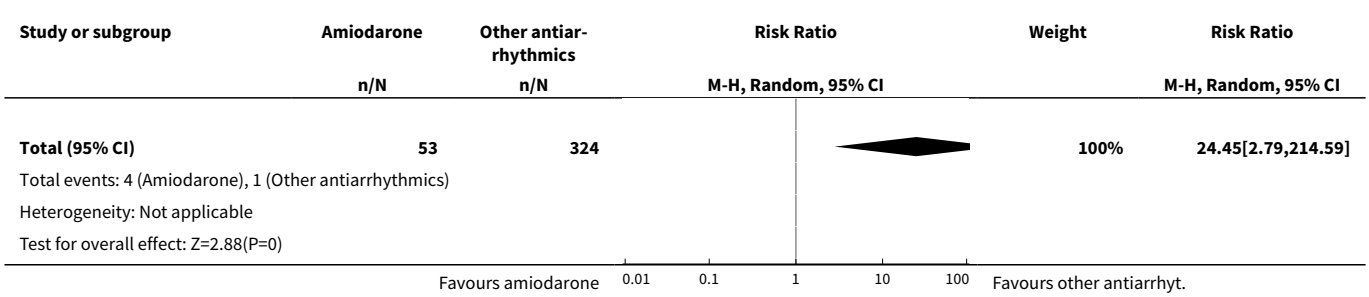
Favours amiodarone — Favours other antiarrhyt.

Analysis 5.4. Comparison 5 Amiodarone versus other antiarrhythmics for secondary prevention, Outcome 4 Sudden cardiac death subgroup with ICD.

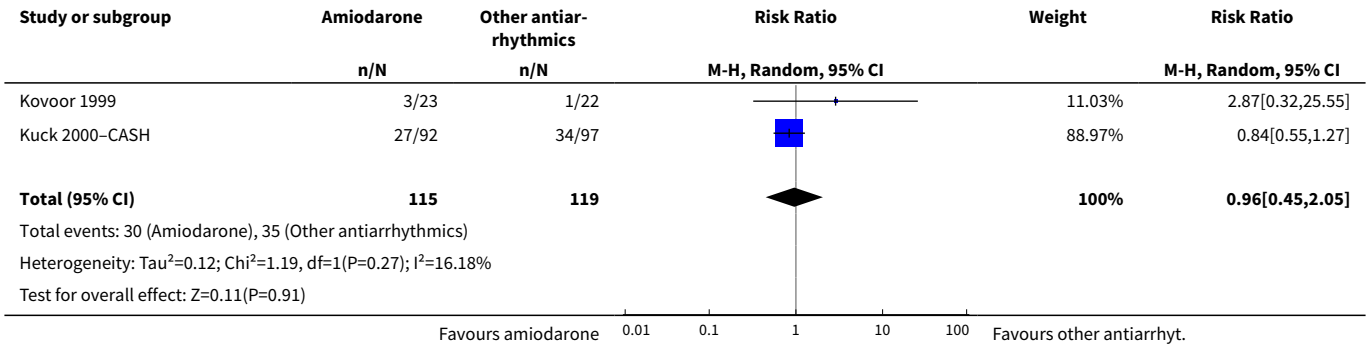
Study or subgroup	Amiodarone	Other antiarrhythmics	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Kowey 2011–ALPHEE	4/53	1/324		100%	24.45[2.79,214.59]



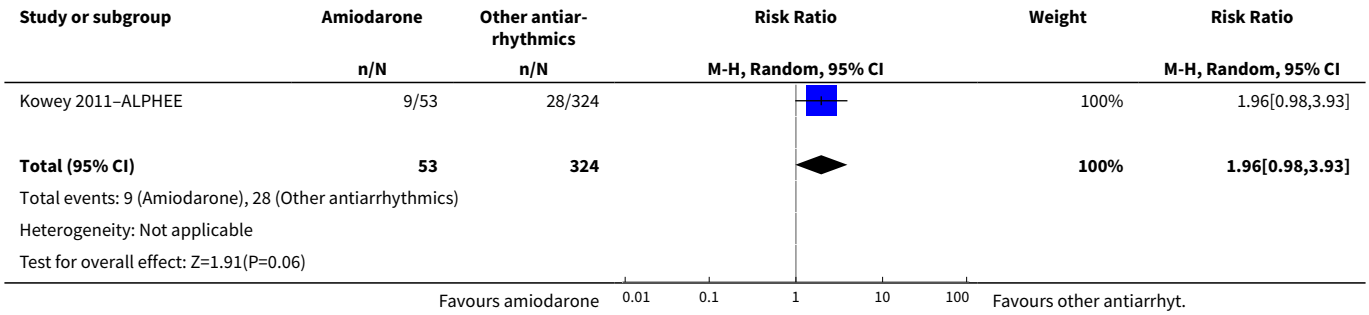
Favours amiodarone — Favours other antiarrhyt.



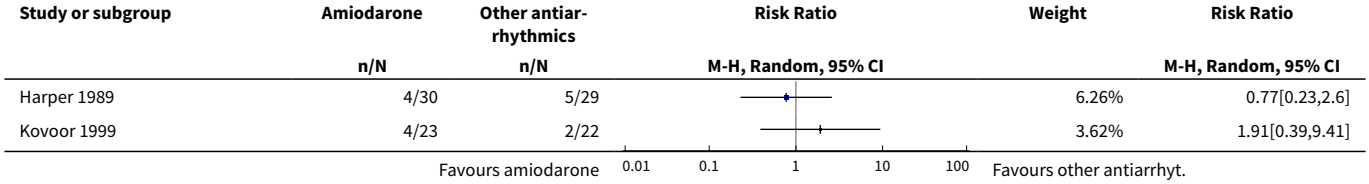
Analysis 5.5. Comparison 5 Amiodarone versus other antiarrhythmics for secondary prevention, Outcome 5 Sudden cardiac death subgroup without ICD.

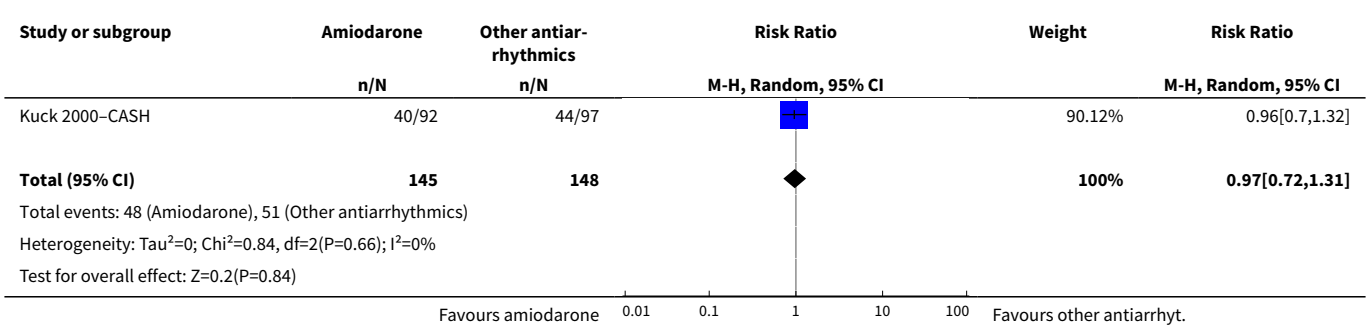


Analysis 5.6. Comparison 5 Amiodarone versus other antiarrhythmics for secondary prevention, Outcome 6 All-cause mortality subgroup with ICD.



Analysis 5.7. Comparison 5 Amiodarone versus other antiarrhythmics for secondary prevention, Outcome 7 All-cause mortality subgroup without ICD.

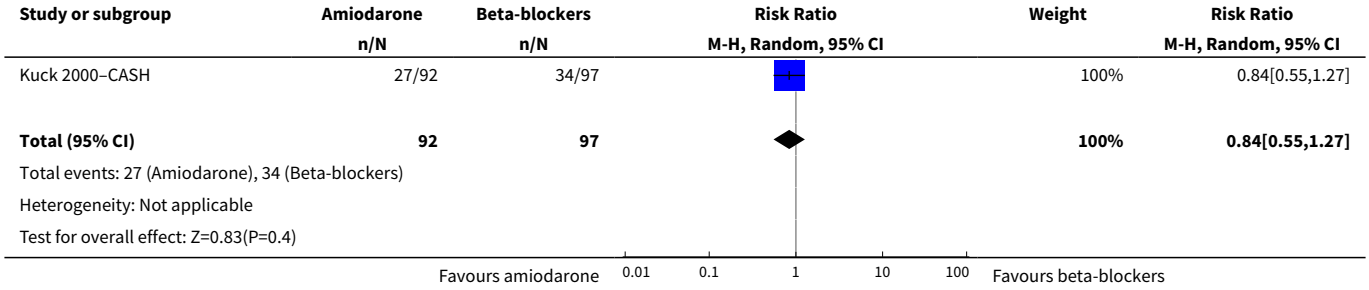




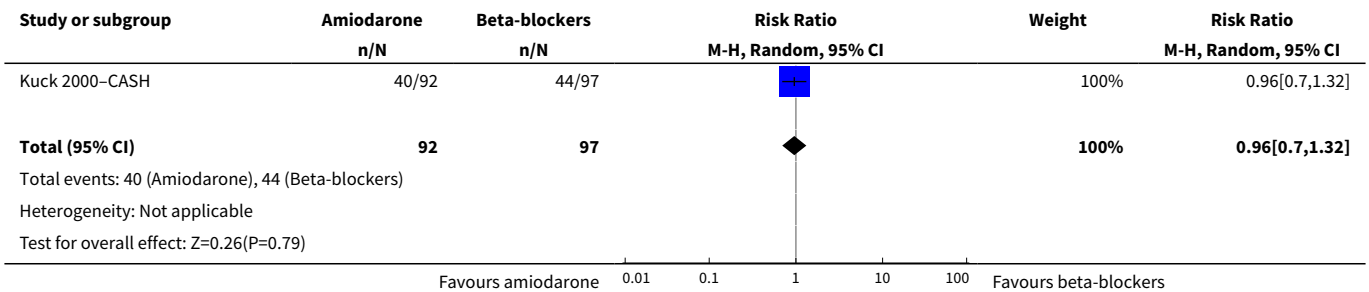
Comparison 6. Amiodarone versus beta-blockers for secondary prevention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sudden cardiac death	1	189	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.55, 1.27]
2 All-cause mortality	1	189	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.70, 1.32]

Analysis 6.1. Comparison 6 Amiodarone versus beta-blockers for secondary prevention, Outcome 1 Sudden cardiac death.



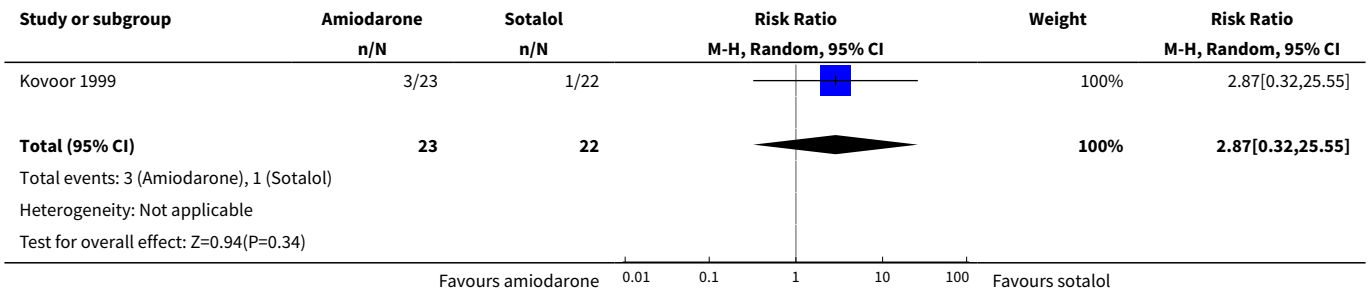
Analysis 6.2. Comparison 6 Amiodarone versus beta-blockers for secondary prevention, Outcome 2 All-cause mortality.



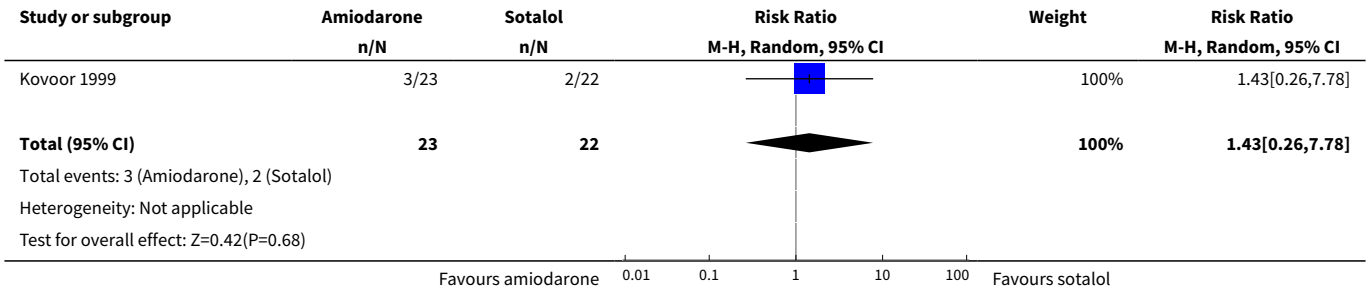
Comparison 7. Amiodarone versus sotalol for secondary prevention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sudden cardiac death	1	45	Risk Ratio (M-H, Random, 95% CI)	2.87 [0.32, 25.55]
2 Cardiac mortality	1	45	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.26, 7.78]
3 All-cause mortality	2	104	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.41, 2.83]

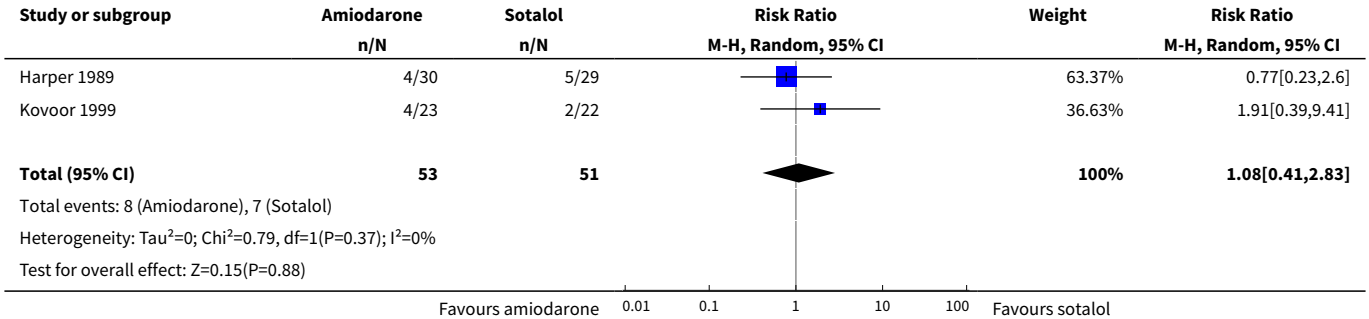
Analysis 7.1. Comparison 7 Amiodarone versus sotalol for secondary prevention, Outcome 1 Sudden cardiac death.



Analysis 7.2. Comparison 7 Amiodarone versus sotalol for secondary prevention, Outcome 2 Cardiac mortality.



Analysis 7.3. Comparison 7 Amiodarone versus sotalol for secondary prevention, Outcome 3 All-cause mortality.

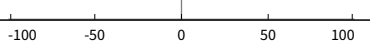


Comparison 8. Amiodarone and quality of life

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life (DASI at 30 months)	1	1160	Mean Difference (IV, Random, 95% CI)	1.20 [-0.56, 2.96]
2 Quality of life (MHI-5 at 30 months)	1	1124	Mean Difference (IV, Random, 95% CI)	2.20 [-0.26, 4.66]

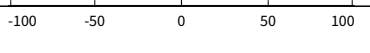
Analysis 8.1. Comparison 8 Amiodarone and quality of life, Outcome 1 Quality of life (DASI at 30 months).

Study or subgroup	Amiodarone N	Amiodarone Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bardy 2005–SCD-HeFT	575	27.1 (15.3)	585	25.9 (15.3)		100%	1.2[-0.56,2.96]
Total ***	**575**		**585**			**100%**	**1.2[-0.56,2.96]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.34(P=0.18)							



Analysis 8.2. Comparison 8 Amiodarone and quality of life, Outcome 2 Quality of life (MHI-5 at 30 months).

Study or subgroup	Amiodarone N	Amiodarone Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Bardy 2005–SCD-HeFT	560	73.2 (20.3)	564	71 (21.7)		100%	2.2[-0.26,4.66]
Total ***	**560**		**564**			**100%**	**2.2[-0.26,4.66]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.76(P=0.08)							



Comparison 9. Amiodarone versus placebo (adverse effects)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hyperthyroidism	8	5972	Risk Ratio (M-H, Random, 95% CI)	4.14 [1.54, 11.17]
2 Hypothyroidism	8	4008	Risk Ratio (M-H, Random, 95% CI)	6.13 [2.46, 15.28]
3 Pulmonary	12	5924	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.15, 2.40]
4 Discontinuation	13	7616	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.26, 1.67]

Analysis 9.1. Comparison 9 Amiodarone versus placebo (adverse effects), Outcome 1 Hyperthyroidism.

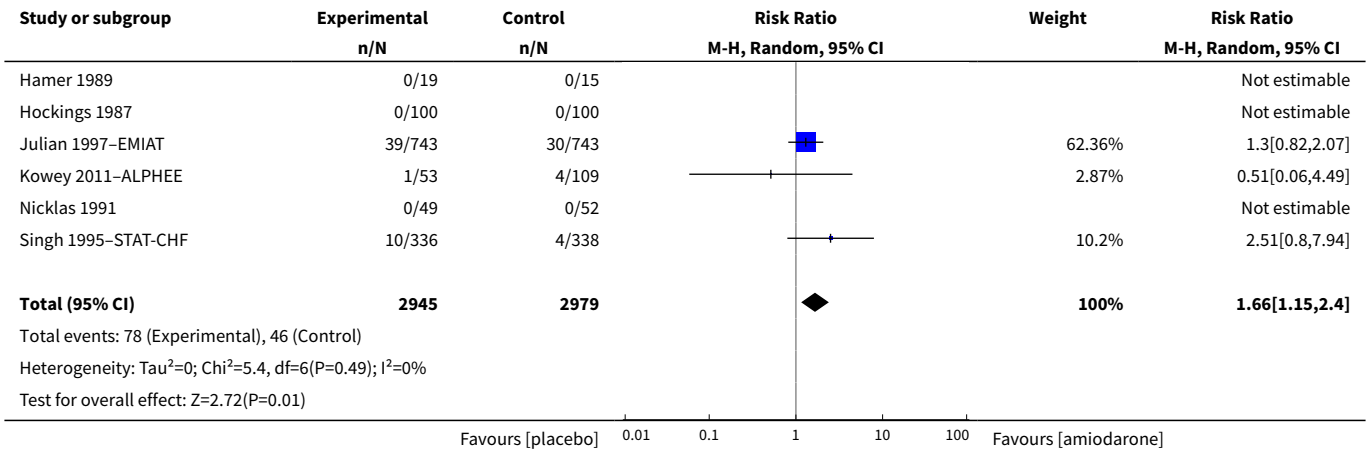
Study or subgroup	Amiodarone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bardy 2005–SCD-HeFT	51/845	0/847		8.12%	103.24[6.38,1670.19]
Cairns 1991–CAMIATpilot	23/48	5/29		19.38%	2.78[1.19,6.5]
Cairns 1997–CAMIAT	4/606	4/596		15.71%	0.98[0.25,3.91]
Ceremuzynski 1992	11/305	1/308		11.54%	11.11[1.44,85.51]
Hamer 1989	8/14	0/14		8.21%	17[1.07,268.84]
Hockings 1987	3/100	0/100		7.53%	7[0.37,133.78]
Julian 1997–EMIAT	12/743	4/743		17.49%	3[0.97,9.26]
Singh 1995–STAT-CHF	2/336	2/338		12.03%	1.01[0.14,7.1]
Total (95% CI)	**2997**	**2975**		**100%**	**4.14[1.54,11.17]**
Total events: 114 (Amiodarone), 16 (Placebo)					
Heterogeneity: Tau^2=1.13; Chi^2=18.9, df=7(P=0.01); I^2=62.95%					
Test for overall effect: Z=2.81(P=0)					

Analysis 9.2. Comparison 9 Amiodarone versus placebo (adverse effects), Outcome 2 Hypothyroidism.

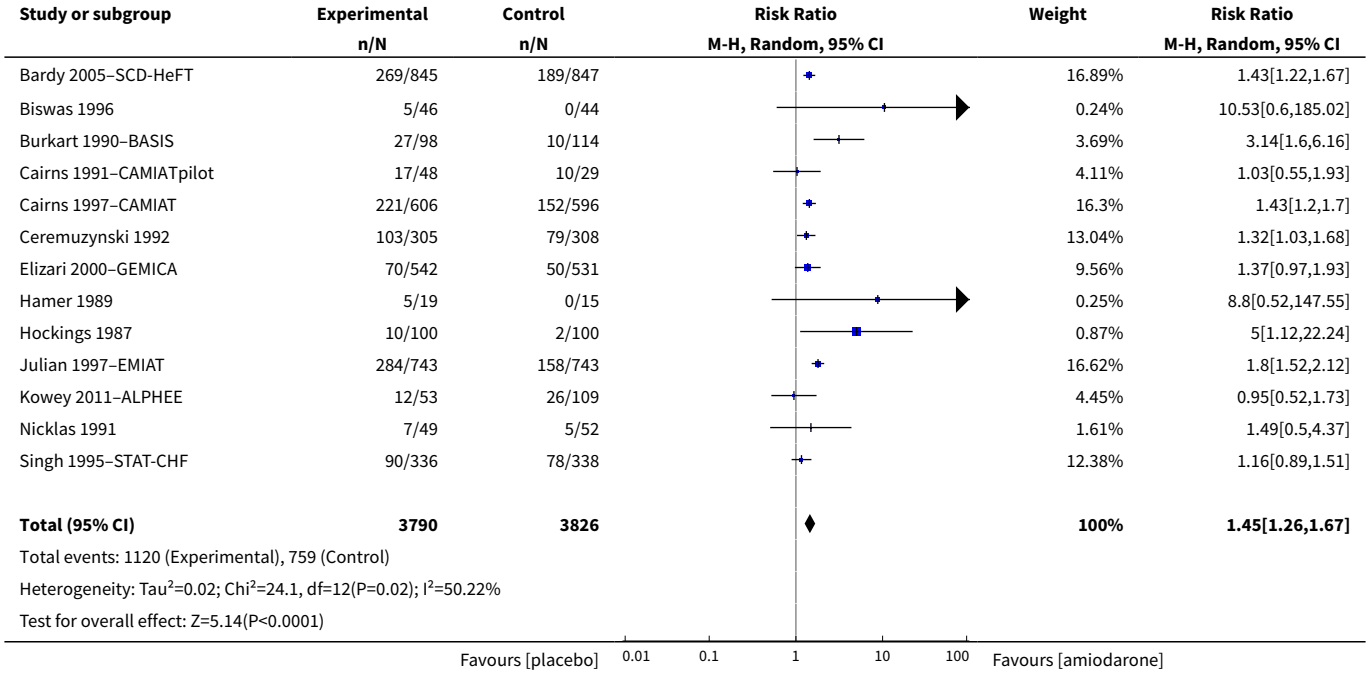
Study or subgroup	Amiodarone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Cairns 1991–CAMIATpilot	12/48	0/29		9.53%	15.31[0.94,249.19]
Cairns 1997–CAMIAT	20/606	1/596		16.73%	19.67[2.65,146.1]
Elizari 2000–GEMICA	2/108	2/73		17.68%	0.68[0.1,4.69]
Hamer 1989	2/14	0/14		8.62%	5[0.26,95.61]
Hockings 1987	5/100	1/100		15.17%	5[0.59,42.04]
Julian 1997–EMIAT	11/743	0/743		9.3%	23[1.36,389.59]
Kowey 2011–ALPHEE	4/51	1/109		14.75%	8.55[0.98,74.57]
Singh 1995–STAT-CHF	2/336	0/338		8.21%	5.03[0.24,104.37]
Total (95% CI)	**2006**	**2002**		**100%**	**6.13[2.46,15.28]**
Total events: 58 (Amiodarone), 5 (Placebo)					
Heterogeneity: Tau^2=0.25; Chi^2=8.18, df=7(P=0.32); I^2=14.46%					
Test for overall effect: Z=3.89(P<0.0001)					

Analysis 9.3. Comparison 9 Amiodarone versus placebo (adverse effects), Outcome 3 Pulmonary.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Biswas 1996	0/46	0/44			Not estimable
Burkart 1990–BASIS	0/98	0/114			Not estimable
Cairns 1991–CAMIATpilot	3/48	1/29		2.75%	1.81[0.2,16.62]
Cairns 1997–CAMIAT	23/606	7/596		19.18%	3.23[1.4,7.47]
Ceremuzynski 1992	1/305	0/308		1.32%	3.03[0.12,74.07]
Elizari 2000–GEMICA	1/542	0/531		1.32%	2.94[0.12,71.99]



Analysis 9.4. Comparison 9 Amiodarone versus placebo (adverse effects), Outcome 4 Discontinuation.



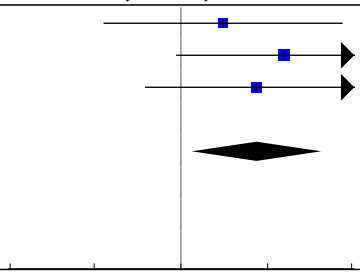
Comparison 10. Amiodarone versus other antiarrhythmics (adverse effects)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Hyperthyroidism	3	514	Risk Ratio (M-H, Random, 95% CI)	7.43 [1.33, 41.57]
2 Hypothyroidism	4	886	Risk Ratio (M-H, Random, 95% CI)	7.77 [1.85, 32.68]
3 Pulmonary	6	1296	Risk Ratio (M-H, Random, 95% CI)	2.30 [0.36, 14.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Discontinuation	8	1438	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.84, 1.33]

Analysis 10.1. Comparison 10 Amiodarone versus other antiarrhythmics (adverse effects), Outcome 1 Hyperthyroidism.

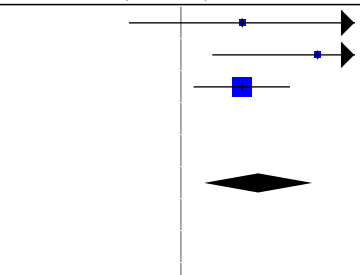
Study or subgroup	Amiodarone n/N	Other antiarrhythmics n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Fournier 1989	1/48	0/49		29.4%	3.06[0.13,73.34]
Greene 1993–CASCADE	7/113	0/115		36.5%	15.26[0.88,264.13]
Kuck 2000–CASH	3/92	0/97		34.1%	7.38[0.39,140.87]
Total (95% CI)	**253**	**261**		**100%**	**7.43[1.33,41.57]**
Total events: 11 (Amiodarone), 0 (Other antiarrhythmics)					
Heterogeneity: Tau^2=0; Chi^2=0.57, df=2(P=0.75); I^2=0%					
Test for overall effect: Z=2.28(P=0.02)					



Favours [other antiarrhy] Favours [amiodarone]

Analysis 10.2. Comparison 10 Amiodarone versus other antiarrhythmics (adverse effects), Outcome 2 Hypothyroidism.

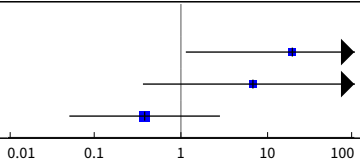
Study or subgroup	Amiodarone n/N	Other antiarrhythmics n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Fournier 1989	2/48	0/49		18.97%	5.1[0.25,103.58]
Greene 1993–CASCADE	18/113	0/115		21.41%	37.65[2.3,617.33]
Kowey 2011–ALPHEE	4/51	5/321		59.62%	5.04[1.4,18.13]
Kuck 2000–CASH	0/92	0/97			Not estimable
Total (95% CI)	**304**	**582**		**100%**	**7.77[1.85,32.68]**
Total events: 24 (Amiodarone), 5 (Other antiarrhythmics)					
Heterogeneity: Tau^2=0.47; Chi^2=2.68, df=2(P=0.26); I^2=25.51%					
Test for overall effect: Z=2.8(P=0.01)					



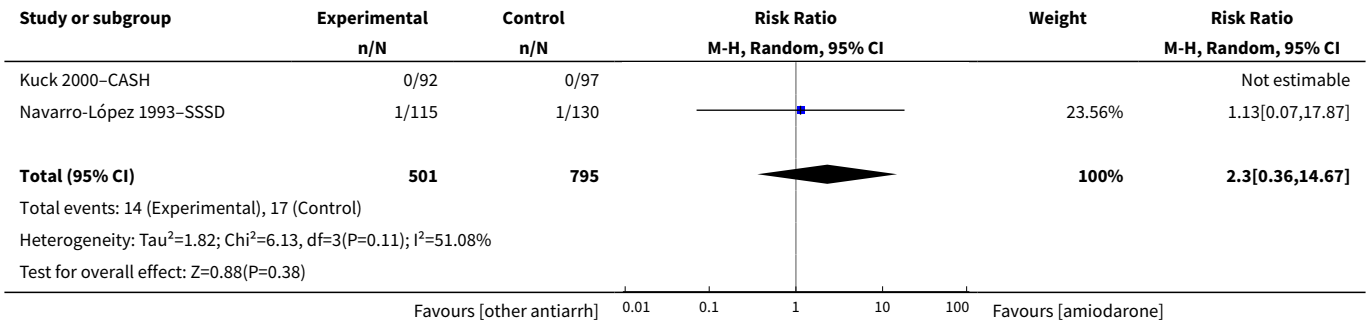
Favours [other antiarrhy] Favours [amiodarone]

Analysis 10.3. Comparison 10 Amiodarone versus other antiarrhythmics (adverse effects), Outcome 3 Pulmonary.

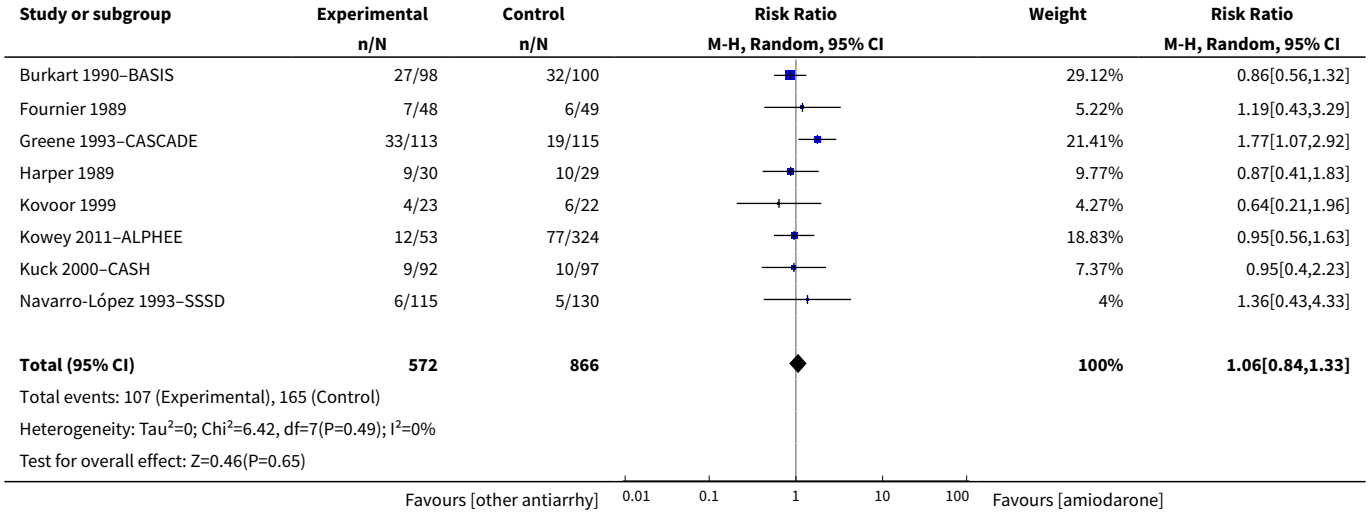
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Burkart 1990–BASIS	0/98	0/100			Not estimable
Greene 1993–CASCADE	9/113	0/115		22.93%	19.33[1.14,328.28]
Harper 1989	3/30	0/29		22.18%	6.77[0.37,125.65]
Kowey 2011–ALPHEE	1/53	16/324		31.33%	0.38[0.05,2.82]



Favours [other antiarrh] Favours [amiodarone]



Analysis 10.4. Comparison 10 Amiodarone versus other antiarrhythmics (adverse effects), Outcome 4 Discontinuation.



Comparison 11. Amiodarone versus no treatment (adverse effects)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Hyperthyroidism	3	414	Risk Ratio (M-H, Random, 95% CI)	4.97 [0.60, 41.16]
2 Hypothyroidism	3	414	Risk Ratio (M-H, Random, 95% CI)	12.82 [0.73, 225.33]
3 Pulmonary	2	405	Risk Ratio (M-H, Random, 95% CI)	14.79 [0.85, 256.43]

Analysis 11.1. Comparison 11 Amiodarone versus no treatment (adverse effects), Outcome 1 Hyperthyroidism.

Study or subgroup	Amiodarone n/N	No treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Connolly 2006–OPTIC	2/140	0/138		48.81%	4.93[0.24,101.74]
Garguichevich 1995–EPAMSA	0/57	0/49			Not estimable
Zehender 1992	2/15	0/15		51.19%	5[0.26,96.13]
Total (95% CI)	**212**	**202**		**100%**	**4.97[0.6,41.16]**
Total events: 4 (Amiodarone), 0 (No treatment)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=1.48(P=0.14)					

Favours [no treatment] Favours [amiodarone]

Analysis 11.2. Comparison 11 Amiodarone versus no treatment (adverse effects), Outcome 2 Hypothyroidism.

Study or subgroup	Amiodarone n/N	No treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Connolly 2006–OPTIC	6/140	0/138		100%	12.82[0.73,225.33]
Garguichevich 1995–EPAMSA	0/57	0/49			Not estimable
Zehender 1992	0/15	0/15			Not estimable
Total (95% CI)	**212**	**202**		**100%**	**12.82[0.73,225.33]**
Total events: 6 (Amiodarone), 0 (No treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.74(P=0.08)					

Favours [no treatment] Favours [amiodarone]

Analysis 11.3. Comparison 11 Amiodarone versus no treatment (adverse effects), Outcome 3 Pulmonary.

Study or subgroup	Amiodarone n/N	No treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Connolly 2006–OPTIC	7/140	0/138		100%	14.79[0.85,256.43]
Garguichevich 1995–EPAMSA	0/66	0/61			Not estimable
Total (95% CI)	**206**	**199**		**100%**	**14.79[0.85,256.43]**
Total events: 7 (Amiodarone), 0 (No treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.85(P=0.06)					

Favours [no treatment] Favours [amiodarone]

APPENDICES

Appendix 1. Search strategy

CENTRAL

#1 MeSH descriptor: [Amiodarone] this term only

#2 amiodaron*

#3 cordarex

#4 amiobeta

#5 amiodarex

#6 cordaron*

#7 trangorex

#8 amiohexal

#9 aratac

#10 braxan

#11 corbionax

#12 kordaron

#13 ortacrone

#14 rytmarone

#15 tachydaron

#16 MeSH descriptor: [Benzofurans] this term only

#17 benzofurans

#18 MeSH descriptor: [Diethylamines] this term only

#19 diethylamine*

#20 odobenzoates

#21 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10

#22 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20

#23 #21 or #22

#24 MeSH descriptor: [Death, Sudden] explode all trees

#25 MeSH descriptor: [Death] this term only

#26 MeSH descriptor: [Heart Arrest] explode all trees

#27 MeSH descriptor: [Mortality] explode all trees

#28 death

#29 mortality

#30 MeSH descriptor: [Ventricular Fibrillation] this term only

#31 MeSH descriptor: [Tachycardia, Ventricular] explode all trees

#32 MeSH descriptor: [Cardiopulmonary Resuscitation] explode all trees

#33 heart next arrest

#34 cardiac next arrest

#35 cardiopulmonary next arrest

#36 cardiorespiratory next arrest

#37 ventric* next tachy*

#38 ventric* next fibrillation

#39 #24 or #25 or #26 or #27 or #28 or #29 or #30

#40 #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38

#41 #39 or #40

#42 #23 and #41

MEDLINE OVID

1. exp Death, Sudden/

2. exp Heart Arrest/

3. exp Cardiopulmonary Resuscitation/

4. exp Tachycardia, Ventricular/

5. exp Heart Failure/

6. exp Myocardial Infarction/

7. exp Ventricular Fibrillation/

8. exp Mortality/

9. resuscit$.tw.

10. asystol$.tw.

11. ((cardiac or heart or cardiopulm$ or ventric$) adj10 (tachycard$ or arrest or fibrillat$ or flutt$ or arrhythm$)).tw.

12. exp Death/

13. death.tw.

14. mortality.tw.

15. or/1-14

16. Amiodarone/

17. amiodaro$.tw.

18. cordarex.tw.

19. amiobeta.tw.

20. amiodarex.tw.

21. cordarone.tw.

22. trangorex.tw.

23. miohexal.tw.

24. aratac.tw.

25. braxan.tw.

26. corbionax.tw.

27. kordaron.tw.

28. ortacrone.tw.

29. rytmarone.tw.

30. tachydaron.tw.

31. benzofurans.tw.

32. diethylamines.tw.

33. iodobenzoate.tw.

34. or/16-33

35. 34 and 15

36. randomized controlled trial.pt.

37. controlled clinical trial.pt.

38. randomized.ab.

39. placebo.ab.

40. drug therapy.fs.

41. randomly.ab.

42. trial.ab.

43. groups.ab.

44. 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43

45. animals/ not humans/

46. 44 not 45

47. 35 and 46

EMBASE OVID

1. sudden death/

2. heart death/

3. heart arrest/

4. resuscitation/

5. exp heart ventricle arrhythmia/

6. exp heart failure/

7. exp heart infarction/

8. mortality/

9. exp survival/

10. death/

11. (death or mortality).tw.

12. resuscit$.tw.

13. asystol$.tw.

14. ((cardiac or heart or cardiopulm$ or ventric$) adj10 (tachycard$ or arrest or fibrillat$ or flutt$ or arrhythm$)).tw.

15. or/1-14

16. amiodarone/

17. amiodaro$.tw.

18. cordarex.tw.

19. amiobeta.tw.

20. amiodarex.tw.

21. cordarone.tw.

22. trangorex.tw.

23. miohexal.tw.

24. aratac.tw.

25. braxan.tw.

26. corbionax.tw.

27. kordaron.tw.

28. ortacrone.tw.

29. rytmarone.tw.

30. tachydaron.tw.

31. benzofurans.tw.

32. diethylamines.tw.

33. iodobenzoate.tw.

34. or/16-33

35. 15 and 34

36. controlled clinical trial/

37. random$.tw.

38. randomized controlled trial/

39. follow-up.tw.

40. double blind procedure/

41. placebo$.tw.

42. placebo/

43. factorial$.ti,ab.

44. (crossover$ or cross-over$).ti,ab.

45. (double$ adj blind$).ti,ab.

46. (singl$ adj blind$).ti,ab.

47. assign$.ti,ab.

48. allocat$.ti,ab.

49. volunteer$.ti,ab.

50. Crossover Procedure/

51. Single Blind Procedure/

52. or/36-51

53. (exp animals/ or nonhuman/) not human/

54. 52 not 53

55. 35 and 54

CINAHL Plus with Full Text

S19 S15 and S18

S18 S16 or S17

S17 TI (randomi* or randomly or placebo* or trial) or AB (randomi* or randomly or placebo* or trial)

S16 (MH "Clinical Trials+")

S15 S10 and S14

S14 S11 or S12 or S13

S13 (MH "Amiodarone")

S12 AB (amiodaron* or cordarex or amiobeta or amiodarex or cordarona* or trangorex or miohexal or aratac or braxan or corbionax or kordaron or ortacrone or rytmarone or tachydaron or benzofurans or diethylamines or iodobenzoate)

S11 TI (amiodaron* or cordarex or amiobeta or amiodarex or cordarona* or trangorex or miohexal or aratac or braxan or corbionax or kordaron or ortacrone or rytmarone or tachydaron or benzofurans or diethylamines or iodobenzoate)

S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9

S9 AB ((cardiac or heart or cardiopulm* or ventric*) and (tachycard* or arrest or fibrillat* or flutt* or arrhythm*))

S8 TI ((cardiac or heart or cardiopulm* or ventric*) and (tachycard* or arrest or fibrillat* or flutt* or arrhythm*))

S7 TI (asystol* or resuscit*) or AB (asystol* or resuscit*)

S6 (MH "Mortality")

S5 (MH "Arrhythmia, Ventricular+")

S4 (MH "Resuscitation, Cardiopulmonary+")

S3 (MH "Death")

S2 (MH "Death, Sudden")

S1 (MH "Heart Arrest+")

LILACS (only English)

amiodaron$ or cordarex or amiobeta or amiodarex or cordaron$ or trangorex or amiohexal or aratac or braxan or corbionax or kordaron or ortacrone or rytmarone or tachydaron or benzofurans or diethylamine$ or odobenzoates [Words] and death or mortality or arrest or tachy$ or fibrillation$ [Words]

LILACS (including Spanish and Portuguese)

Amiodarona [MH] or amiodaron$ or cordarex or amiobeta or amiodarex or cordaron$ or trangorex or amiohexal or aratac or braxan or corbionax or kordaron or ortacrone or rytmarone or tachydaron or benzofurans or diethylamine$ or odobenzoates or atlansil or ritmocardyl [Palabras] and death or muerte or morte or mortality or mortalidad$ or arrest or paro or parada or asistolia or tachy$ or taqui $ or fibrillation$ or fibrilación or fibrilação [Palabras]

WHAT'S NEW

Date	Event	Description
30 August 2016	Amended	Some discordances with total number of studies between abstract and main text were corrected

CONTRIBUTIONS OF AUTHORS

Searching for trials: JCC/FL/GR
Handsearching: JCC/FB
Obtaining copies of trials: JCC
Selecting which trials to include (2 + 1 arbiter): JCC/RC + LML
Extracting data from trials (2 people): JCC/RC
Entering data into RevMan: RC/GR
Carrying out the analysis: RC/JCC/GR
Interpreting the analysis: JCC/RC/GR/LML
Drafting the final review: JCC/RC/FB/FL/GR/LML
Updating the review: JCC/RC

DECLARATIONS OF INTEREST

Juan Carlos Claro declares having received funding from a grant (FONIS (Fondo Nacional de Investigación y Desarrollo en Salud) project SA11I2195). This project was presented to CONICYT (Comisión Nacional de Investigación Científica y Tecnológica) in the year 2008 in order to receive some funding while carrying out the review, as the Government understood the research question addressed a pertinent issue for low- and middle-income countries like Chile.
Luz M Letelier declares having received a clinical research grant from FONIS (Fondo Nacional de Investigación y Desarrollo en Salud).
Roberto Candia: none known.
Gabriel Rada: none known.
Fernando Baraona: none known.
Francisco Larrondo: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Proyecto FONIS SA11I2195 2011, Chile.

  The main authors won a grant from the National Comission for Scientific and Technological Investigation (CONICYT)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We initially defined reduced LVEF as < 35%. However, we included studies with LVEF as low as 30%. A number of primary studies included participants with that LVEF, and we were not able to obtain individual patient data regarding solely those with LVEF < 35%.

We had initially stated that we would include participants with previous myocardial infarction (> 30 days prior to study). However, not a single study in the primary prevention setting included post-MI participants of over 30 days. All of the studies included participants from 24 h post-MI onwards. We thought that due to amiodarone pharmacodynamics, it would take more than three weeks to obtain plateau plasma levels, so the effect of amiodarone would not be apparent until the first month.

We did not plan to include Summary of Findings tables and GRADE assessment in the review at protocol stage but have done so in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Primary Prevention; *Secondary Prevention; Amiodarone [*therapeutic use]; Anti-Arrhythmia Agents [*therapeutic use]; Cause of Death; Death, Sudden, Cardiac [*prevention & control]; Randomized Controlled Trials as Topic; Vasodilator Agents [therapeutic use]

MeSH check words

Adult; Humans