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Prophylactic lidocaine for myocardial infarction (Review)

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[Intervention Review]

Prophylactic lidocaine for myocardial infarction

Arturo J Martí-Carvajal[1], Daniel Simancas-Racines[2], Vidhu Anand[3], Shrikant I Bangdiwala[4]

[1]Facultad de Ciencias de la Salud Eugenio Espejo, Universidad UTE (Cochrane Ecuador), Quito, Ecuador. [2]Cochrane Ecuador. Centro de Investigación en Salud Pública y Epidemiología Clínica (CISPEC). Facultad de Ciencias de la Salud Eugenio Espejo, Universidad Tecnológica Equinoccial, Quito, Ecuador. [3]Department of Medicine, University of Minnesota, Minneapolis, MN, USA. [4]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada

Contact: Arturo J Martí-Carvajal, arturo.marti.carvajal@gmail.com.

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ABSTRACT

Background

Coronary artery disease is a major public health problem affecting both developed and developing countries. Acute coronary syndromes include unstable angina and myocardial infarction with or without ST-segment elevation (electrocardiogram sector is higher than baseline). Ventricular arrhythmia after myocardial infarction is associated with high risk of mortality. The evidence is out of date, and considerable uncertainty remains about the effects of prophylactic use of lidocaine on all-cause mortality, in particular, in patients with suspected myocardial infarction.

Objectives

To determine the clinical effectiveness and safety of prophylactic lidocaine in preventing death among people with myocardial infarction.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 3), MEDLINE Ovid (1946 to 13 April 2015), EMBASE (1947 to 13 April 2015) and Latin American Caribbean Health Sciences Literature (LILACS) (1986 to 13 April 2015). We also searched Web of Science (1970 to 13 April 2013) and handsearched the reference lists of included papers. We applied no language restriction in the search.

Selection criteria

We included randomised controlled trials assessing the effects of prophylactic lidocaine for myocardial infarction. We considered all-cause mortality, cardiac mortality and overall survival at 30 days after myocardial infarction as primary outcomes.

Data collection and analysis

We performed study selection, risk of bias assessment and data extraction in duplicate. We estimated risk ratios (RRs) for dichotomous outcomes and measured statistical heterogeneity using I^2. We used a random-effects model and conducted trial sequential analysis.

Main results

We identified 37 randomised controlled trials involving 11,948 participants. These trials compared lidocaine versus placebo or no intervention, disopyramide, mexiletine, tocainide, propafenone, amiodarone, dimethylammonium chloride, aprindine and pirmenol. Overall, trials were underpowered and had high risk of bias. Ninety-seven per cent of trials (36/37) were conducted without an a priori sample size estimation. Ten trials were sponsored by the pharmaceutical industry. Trials were conducted in 17 countries, and intravenous intervention was the most frequent route of administration.

In trials involving participants with proven or non-proven acute myocardial infarction, lidocaine versus placebo or no intervention showed no significant differences regarding all-cause mortality (213/5879 (3.62%) vs 199/5848 (3.40%); RR 1.02, 95% CI 0.82 to 1.27; participants = 11727; studies = 18; I^2 = 15%); low-quality evidence), cardiac mortality (69/4184 (1.65%) vs 62/4093 (1.51%); RR 1.03, 95% CI 0.70 to 1.50; participants = 8277; studies = 12; I^2 = 12%; low-quality evidence) and prophylaxis of ventricular fibrillation (76/5128 (1.48%) vs 103/4987 (2.01%); RR 0.78, 95% CI 0.55 to 1.12; participants = 10115; studies = 16; I^2 = 18%; low-quality evidence). In terms of sinus bradycardia, lidocaine effect is imprecise compared with effects of placebo or no intervention (55/1346 (4.08%) vs 49/1203 (4.07%); RR 1.09, 95% CI 0.66 to 1.80; participants = 2549; studies = 8; I^2 = 21%; very low-quality evidence). In trials involving only participants with proven acute myocardial infarction, lidocaine versus placebo or no intervention showed no significant differences in all-cause mortality (148/2747 (5.39%) vs 135/2506 (5.39%); RR 1.01, 95% CI 0.79 to 1.30; participants = 5253; studies = 16; I^2 = 9%; low-quality evidence). No significant differences were noted between lidocaine and any other antiarrhythmic drug in terms of all-cause mortality and ventricular fibrillation. Data on overall survival 30 days after myocardial infarction were not reported. Lidocaine compared with placebo or no intervention increased risk of asystole (35/3393 (1.03%) vs 14/3443 (0.41%); RR 2.32, 95% CI 1.26 to 4.26; participants = 6826; studies = 4; I^2 = 0%; very low-quality evidence) and dizziness/drowsiness (74/1259 (5.88%) vs 16/1274 (1.26%); RR 3.85, 95% CI 2.29 to 6.47; participants = 2533; studies = 6; I^2 = 0%; low-quality evidence). Overall, safety data were poorly reported and adverse events may have been underestimated. Trial sequential analyses suggest that additional trials may not be needed for reliable conclusions to be drawn regarding these outcomes.

Authors' conclusions

This Cochrane review found evidence of low quality to suggest that prophylactic lidocaine has very little or no effect on mortality or ventricular fibrillation in people with acute myocardial infarction. The safety profile is unclear. This conclusion is based on randomised controlled trials with high risk of bias. However (disregarding the risk of bias), trial sequential analysis suggests that additional trials may not be needed to disprove an intervention effect of 20% relative risk reduction. Smaller risk reductions might require additional higher trials.

PLAIN LANGUAGE SUMMARY

Prophylactic lidocaine for myocardial infarction

Review question
We reviewed the clinical effectiveness and safety of prophylactic lidocaine for myocardial infarction.

Background
Coronary artery disease is a major public health problem that affects both developed and developing countries. Acute coronary syndromes include unstable angina and myocardial infarction with or without ST-segment elevation (electrocardiogram sector is higher than baseline). Ventricular arrhythmia after myocardial infarction is associated with high risk of mortality. The evidence is out of date, and considerable uncertainty remains about the effects of prophylactic lidocaine use on all-cause mortality, in particular, in patients with suspected myocardial infarction.

Study characteristics
We identified 37 trials conducted between 1969 and 1999. The evidence is current up to April 2015. Trials were conducted in Australia, Belgium, Brazil, Canada, Denmark, France, Germany, Italy, New Zealand, Northern Ireland, Norway, Poland, Sweden, Switzerland, The Netherlands, United Kingdom and United States of America and included 11,948 participants. Trials were conducted in pre-hospital and in-hospital settings and included individuals with or without proved acute myocardial infarction. Some trials did not limit results to acute myocardial infarction only. Lidocaine was given by intravenous (bolus and/or infusion) and intramuscular (alone or in combination with intravenous dosage) routes. Overall, trials included small sample sizes and reported low numbers of events. All trials had high risk of bias. Ten trials were sponsored by the pharmaceutical industry.

Key results
In people who had known or suspected heart attack, we found that lidocaine compared with placebo, no intervention or any other antiarrhythmic drug had very small or no effects on death, cardiac death and ventricular fibrillation.

Quality of evidence
Our confidence in the results of this review is low because the included trials that we synthesised were of low quality (overestimation of benefits and underestimation of harms) and were conducted with a small number of participants, leading to imprecision of results.

SUMMARY OF FINDINGS

Summary of findings 1. Lidocaine compared with placebo or no intervention for acute myocardial infarction

Lidocaine compared with placebo or no intervention for acute myocardial infarction

Patient or population: patients with acute myocardial infarction
Settings: pre-hospital and in-hospital
Intervention: lidocaine
Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no intervention	Lidocaine				
All-cause mortality Follow-up: ranging between unknown and 1 month	**34 per 1000**	**35 per 1000** (29 to 42)	**RR 1.02** (0.85 to 1.27)	11727 (18 studies[a])	⊕⊕⊖⊖ **Low** [b,c]	
Cardiac mortality Follow-up: ranging between unknown and 1 month	**15 per 1000**	**16 per 1000** (11 to 23)	**RR 1.03** (0.70 to 1.50)	8277 (12 studies[a])	⊕⊕⊖⊖ **Low** [b,d]	
Overall survival at 30 days after myocardial infarction	See comment	See comment	See comment	See comment	See comment	No trial assessed this outcome
Ventricular fibrillation Electrocardiogram Follow-up: ranging between unknown and 1 month	**21 per 1000**	**16 per 1000** (11 to 23)	**RR 0.78** (0.55 to 1.12)	10115 (16 studies[a])	⊕⊕⊖⊖ **Low** [b,e]	
Adverse events (AEs; adverse drug reaction): asystole Follow-up: ranging between unknown and 1 month	**4 per 1000**	**9 per 1000** (5 to 17)	**RR 2.32** (1.26 to 4.26)	6826 (4 studies[a])	⊕⊖⊖⊖ **Very low** [b,f,g]	
Adverse events (AEs; adverse drug reaction): sinus bradycardia	**41 per 1000**	**44 per 1000** (27 to 73)	**RR 1.09** (0.66 to 1.80)	2549 (8 studies[a])	⊕⊖⊖⊖ **Very low** [b,h,i]	

Follow-up: ranging between unknown and 1 month					
Adverse events (AEs; adverse drug reaction): drowsiness/dizziness Follow-up: ranging between unknown and 1 month	**13 per 1000**	**48 per 1000** (29 to 81)	**RR 3.85** (2.29 to 6.47)	2533 (6 studies[a])	⊕⊕⊖⊖ **Low** [j.k.l]

*The basis for the **assumed risk** (e.g. 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]Trials include participants with proven or unproven acute myocardial infarction.
[b]Downgraded two levels because of limitations in trial design or execution (high attrition bias).
[c]Assumed risk was gotten from control group risk (3.4%).
[d]Assumed risk was gotten from control group risk (1.5%).
[e]Assumed risk was gotten from control group risk (2.1%).
[f]Assumed risk was gotten from control group risk (0.41%).
[g]Downgraded one level because of imprecision (low number of events with an impact on the precision of effect estimates).
[h]Assumed risk was gotten from control group risk (4.1%).
[i]Downgraded one level because of imprecision (low number of events with an impact on the precision of effect estimates).
[j]Downgraded one level because of limitations in trial design or execution (high attrition bias).
[k]Downgraded one level because of imprecision (low number of events with an impact on the precision of effect estimates).
[l]Assumed risk was gotten from control group risk (1.3%).

Summary of findings 2. Lidocaine compared with disopyramide for myocardial infarction

Lidocaine compared with disopyramide for myocardial infarction

Patient or population: patients with myocardial infarction
Settings: in-hospital
Intervention: lidocaine
Comparison: disopyramide

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments

	Assumed risk	Corresponding risk				
	Disopyramide	**Lidocaine**				
All-cause mortality Follow-up: ranging between 12 hours and 24 hours	**70 per 1000**	**98 per 1000** (33 to 291)	**RR 1.39** (0.47 to 4.13)	144 (2 studies)	⊕⊝⊝⊝ **Very low** [a,b,c]	
Cardiac mortality Follow-up: ranging between 12 hours and 24 hours	**41 per 1000**	**42 per 1000** (9 to 200)	**RR 1.02** (0.21 to 4.87)	144 (2 studies)	⊕⊝⊝⊝ **Very low** [a,b,d]	
Overall survival at 30 days after myocardial infarction	See comment	See comment	See comment	See comment	See comment	No trial assessed this outcome
Ventricular fibrillation Follow-up: 12 hours	**79 per 1000**	**26 per 1000** (3 to 242)	**RR 0.32** (0.04 to 2.97)	76 (1 study)	⊕⊝⊝⊝ **Very low** [e,f,g]	
Adverse events (AEs; adverse drug reaction): asystole Follow-up: 12 hours	**26 per 1000**	**9 per 1000** (0 to 209)	**RR 0.33** (0.01 to 7.93)	76 (1 study)	⊕⊝⊝⊝ **Very low** [e,f,h]	
Adverse events (AEs; adverse drug reaction): sinoatrial block Follow-up: 24 hours	**30 per 1000**	**28 per 1000** 2 to 438	**RR 0.94** (0.06 to 14.47)	68 (1 study)	⊕⊝⊝⊝ **Very low** [i,j,k]	
Adverse events (AEs; adverse drug reaction): cardiac blocks (high-degree atrioventricular block and bundle) Follow-up: 24 hours	**152 per 1000**	**86 per 1000** (23 to 330)	**RR 0.57** (0.15 to 2.18)	68 (1 study)	⊕⊝⊝⊝ **Very low** [j,k,l]	

*The basis for the **assumed risk** (e.g. 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]Downgraded one level because of limitations in trial design or execution (high attrition bias).
[b]Downgraded two levels because of imprecision (small sample and very low number of events with an impact on the precision of effect estimates).
[c]Assumed risk was gotten from control group risk (7%).
[d]Assumed risk was gotten from control group risk (4.1%).
[e]Downgraded one level because of limitations in trial design.
[f]Downgraded two levels because of imprecision (small sample and very low number of events with an impact on the precision of effect estimates).
[g]Assumed risk was gotten from control group risk (7.9%).
[h]Assumed risk was gotten from control group risk (2.6%).
[i]Downgraded one level because of limitations in trial design or execution (high attrition bias).
[j]Downgraded two levels because of imprecision (small sample and very low number of events with an impact on the precision of effect estimates).
[k]Assumed risk was gotten from control group risk (3%).
[l]Assumed risk was gotten from control group risk (15.2%).

Summary of findings 3. Lidocaine compared with tocainide for myocardial infarction

Lidocaine compared with tocainide for myocardial infarction						
Patient or population: patients with myocardial infarction **Settings:** in-hospital **Intervention:** lidocaine **Comparison:** tocainide						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Tocainide	**Lidocaine**				
All-cause mortality Follow-up: 48 hours	**62 per 1000**	**77 per 1000** (5 to 1000)	**RR 1.23** (0.08 to 17.83)	29 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	
Cardiac mortality Follow-up: 48 hours	**62 per 1000**	**77 per 1000** (5 to 1000)	**RR 1.23** (0.08 to 17.83)	29 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	
Overall survival at 30 days after myocardial infarction	See comment	See comment	See comment	See comment	See comment	Neither Keefe 1986 nor Rehnqvist 1983 assessed this outcome
Ventricular fibrillation	See comment	See comment	See comment	See comment	See comment	Keefe 1986 reported no participants with VF. Rehnqvist 1983 did not mention this outcome

Adverse events (AEs; adverse drug reaction): any adverse event	**444 per 1000**	**751 per 1000** (476 to 1000)	**RR 1.69** (1.07 to 2.68)	69 (2 studies)	⊕⊖⊖⊖ **Very low** [a,b,d]	As the result of severe inconsistencies regarding reporting data on adverse events, we preferred to show the evidence using this approach

*The basis for the **assumed risk** (e.g. 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]Downgraded one level because of limitations in trial design and execution of trials.
[b]Downgraded two levels because of imprecision (small sample and very low number of events with an impact on the precision of effect estimates).
[c]Assumed risk was gotten from control group risk (6.3%).
[d]Assumed risk was gotten from control group risk (44.4%).

Summary of findings 4. Lidocaine compared with mexiletine for myocardial infarction

Lidocaine compared with mexiletine for myocardial infarction

Patient or population: patients with myocardial infarction
Settings: in-hospital
Intervention: lidocaine
Comparison: mexiletine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Mexiletine	Lidocaine				
All-cause mortality Follow-up: 48 hours	**83 per 1000**	**28 per 1000** (1 to 621)	**RR 0.33** (0.01 to 7.45)	24 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	
Cardiac mortality	**83 per 1000**	**28 per 1000** (1 to 621)	**RR 0.33** (0.01 to 7.45)	24 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	

Follow-up: 48 hours						
Overall survival at 30 days after myocardial infarction	See comment	See comment	See comment	See comment	See comment	Neither Horowitz 1981 nor Rolli 1981 assessed this outcome
Ventricular fibrillation Follow-up: 48 hours	See comment	See comment	**RR 3.00** (0.13 to 67.06)	24 (1 study)	⊕⊖⊖⊖ **Very low** [a,b]	No events in the control group
Adverse events (AEs; adverse drug reaction): atrioventricular block Follow-up: 48 hours	**83 per 1000**	**28 per 1000** (1 to 621)	**RR 0.33** (0.01 to 7.45)	24 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	
Adverse events (AEs; adverse drug reaction): composite neurological adverse event (confusion, vertigo, nystagmus, vomiting and diplopia) Follow-up: between 3 hours and 48 hours[d]	**459 per 1000**	**289 per 1000** (74 to 1000)	**RR 0.63** (0.16 to 2.47)	74 (2 studies)	⊕⊖⊖⊖ **Very low** [a,b,e]	

*The basis for the **assumed risk** (e.g. 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]Downgraded one level because of limitations in the trial design.
[b]Downgraded two levels because of imprecision (small sample and very low number of events with an impact on the precision of effect estimates).
[c]Assumed risk was gotten from control group risk (8.3%).
[d] Horowitz 1981 and Rolli 1981 used 'composite neurological adverse' terms for reporting this adverse event.
[e]Assumed risk was gotten from control group risk (45.9%).

Summary of findings 5. Lidocaine compared with propafenone for myocardial infarction

Lidocaine compared with propafenone for myocardial infarction
Patient or population: patients with myocardial infarction **Settings:** in-hospital

Intervention: lidocaine
Comparison: propafenone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Propafenone	Lidocaine				
All-cause mortality	See comment	See comment	See comment	See comment	See comment	No trial assessed this outcome
Cardiac mortality	See comment	See comment	See comment	See comment	See comment	No trial assessed this outcome
Overall survival at 30 days after myocardial infarction	See comment	See comment	See comment	See comment	See comment	No trial assessed this outcome
Ventricular fibrillation Follow-up: 24 hours	See comment	See comment	**RR 3.00** (0.14 to 65.90)	20 (1 study)	⊕⊖⊖⊖ **Very low** [a,b]	Control group had no event
Adverse events (AEs; adverse drug reaction): heart failure Follow-up: 24 hours	See comment	See comment	**RR 6.38** (0.32 to 127.77)	64 (1 study)	⊕⊖⊖⊖ **Very low** [a,b]	Control group had no event
Adverse events (AEs; adverse drug reaction): bilateral bundle branch block Follow-up: 24 hours	**28 per 1000**	**12 per 1000** (1 to 279)	**RR 0.43** (0.02 to 10.06)	64 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	
Adverse events (AEs; adverse drug reaction): neuropsychiatric disturbances Follow-up: 24 hours	See comment	See comment	**RR 6.95** (0.86 to 55.94)	84 (2 studies)	⊕⊖⊖⊖ **Very low** [a,b]	Control group had no event

*The basis for the **assumed risk** (e.g. 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]Downgraded one level because of limitations in trial design and execution of the trial.
[b]Downgraded two levels because of imprecision (small sample and very low number of events with an impact on the precision of effect estimates).
[c]Assumed risk was gotten from control group risk (2.8%).

Summary of findings 6. Lidocaine compared with amiodarone for myocardial infarction

Lidocaine compared with amiodarone for myocardial infarction

Patient or population: patients with myocardial infarction
Settings: in-hospital
Intervention: lidocaine
Comparison: amiodarone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Amiodarone	Lidocaine				
All-cause mortality Follow-up: not stated	See comment	See comment	See comment	See comment	See comment	Capucci 1985 did not assess this outcome
Cardiac mortality Follow-up: not stated	See comment	See comment	See comment	See comment	See comment	Capucci 1985 did not assess this outcome
Overall survival at 30 days after myocardial infarction	See comment	See comment	See comment	See comment	See comment	Capucci 1985 did not assess this outcome
Ventricular fibrillation Follow-up: not stated	See comment	See comment	**RR 3.44** (0.18 to 46.11)	25 (1 study)	⊕⊖⊖⊖ **Very low** [a,b]	No ventricular fibrillation in control group
Bradycardia Follow-up: not stated	**100 per 1000**	**23 per 1000** (1 to 512)	**RR 0.23** (0.01 to 5.12)	25 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	
Hypotension Follow-up: not stated	**200 per 1000**	**28 per 1000** (2 to 520)	**RR 0.14** (0.01 to 2.60)	25 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,d]	
Diplopia plus sleepiness Follow-up: not stated	See comment	See comment	**RR 2.06** (0.09 to 46.11)	25 (1 study)	⊕⊖⊖⊖ **Very low** [a,b]	No diplopia in control group

*The basis for the **assumed risk** (e.g. 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]Downgraded one level because of limitations in trial design.
[b]Downgraded two levels because of imprecision (small sample and very low number of events with an impact on the precision of effect estimates).
[c]Assumed risk was gotten from control group risk (10%).
[d]Assumed risk was gotten from control group risk (20%).

Summary of findings 7. Lidocaine compared with dimethylammonium for myocardial infarction

Lidocaine compared with dimethylammonium for myocardial infarction

Patient or population: patients with myocardial infarction
Settings: in-hospital
Intervention: lidocaine
Comparison: dimethylammonium

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Dimethylammonium	Lidocaine				
All-cause mortality Follow-up: unclear	See comment	See comment	See comment	See comment	See comment	Bergdahl 1978 did not assess this outcome
Cardiac mortality Follow-up: unclear	See comment	See comment	See comment	See comment	See comment	Bergdahl 1978 did not assess this outcome
Overall survival at 30 days after myocardial infarction	See comment	See comment	See comment	See comment	See comment	Bergdahl 1978 did not assess this outcome

Ventricular fibrillation Follow-up: unclear	See comment	See comment	See comment	See comment	See comment	Bergdahl 1978 did not assess this outcome
Hypotension Follow-up: unclear	**312 per 1000**	**266 per 1000** (88 to 809)	**RR 0.85** (0.28 to 2.59)	31 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	
Tachycardia Follow-up: unclear	**500 per 1000**	**30 per 1000** (0 to 500)	**RR 0.06** (0.00 to 1.0)	31 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,d]	
Bradycardia Follow-up: unclear	**62 per 1000**	**22 per 1000** (1 to 505)	**RR 0.35** (0.02 to 8.08)	31 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,e]	

*The basis for the **assumed risk** (e.g. 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]Downgraded one level because of limitations in trial design or execution (high attrition bias).
[b]Downgraded two levels because of imprecision (small sample and very low number of events with an impact on the precision of effect estimates).
[c]Assumed risk was gotten from control group risk (31.3%).
[d]Assumed risk was gotten from control group risk (50%).
[e]Assumed risk was gotten from control group risk (6.3%).

Summary of findings 8. Lidocaine compared with aprindine for myocardial infarction

Lidocaine compared with aprindine for myocardial infarction

Patient or population: patients with myocardial infarction
Settings: in-hospital
Intervention: lidocaine
Comparison: aprindine

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				

	Aprindine	Lidocaine				
All-cause mortality Follow-up: 3 days	See comment	See comment	See comment	See comment	See comment	Depaepe 1974 did not assess this outcome
Cardiac mortality Follow-up: 3 days	See comment	See comment	See comment	See comment	See comment	Depaepe 1974 did not assess this outcome
Overall survival at 30 days after myocardial infarction	See comment	See comment	See comment	See comment	See comment	Depaepe 1974 did not assess this outcome
Ventricular fibrillation Follow-up: 3 days	See comment	See comment	See comment	See comment	See comment	Depaepe 1974 did not mention this outcome
Coma Follow-up: 3 days	See comment	See comment	**RR 3.00** (0.13 to 67.06)	24 (1 study)	⊕⊖⊖⊖ **Very low** [a,b]	No coma in control group
Seizures Follow-up: 3 days	See comment	See comment	**RR 5.00** (0.27 to 94.34)	24 (1 study)	⊕⊖⊖⊖ **Very low** [a,b]	No seizures in control group
Agitation Follow-up: 3 days	**167 per 1000**	**33 per 1000** (2 to 628)	**RR 0.20** (0.01 to 3.77)	24 (1 study)	⊕⊖⊖⊖ **Very low** [a,b,c]	

*The basis for the **assumed risk** (e.g. 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]Downgraded one level because of limitations in trial design.
[b]Downgraded two levels because of imprecision (small sample and very low number of events with an impact on the precision of effect estimates).
[c]Assumed risk was gotten from control group risk (16.7%).

Summary of findings 9. Lidocaine compared with pirmenol for myocardial infarction

Lidocaine compared with pirmenol for myocardial infarction

Patient or population: patients with myocardial infarction
Settings: in-hospital
Intervention: lidocaine
Comparison: pirmenol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no intervention	Lidocaine				
All-cause mortality Follow-up: 24 hours	See comment	See comment	See comment	See comment	See comment	Cuendet 1988 did not assess this outcome
Cardiac mortality Follow-up: 24 hours	See comment	See comment	See comment	See comment	See comment	Cuendet 1988 did not assess this outcome
Overall survival at 30 days after myocardial infarction	See comment	See comment	See comment	See comment	See comment	Cuendet 1988 did not assess this outcome
Ventricular fibrillation Follow-up: 24 hours.	See comment	See comment	See comment	See comment	See comment	Cuendet 1988 did not assess this outcome
Safety (AEs; adverse drug reaction): any adverse event Follow-up: 24 hours	**500 per 1000**	**555 per 1000** (235 to 1000)	**RR 1.11** (0.47 to 2.60)	19 (1 study[a])	⊕⊖⊖⊖ **Very low** [b,c,d]	

*The basis for the **assumed risk** (e.g. 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]Trial includes participants with proven or unproven acute myocardial infarction.
[b]Downgraded one level because of limitations in the trial design.

[c]Downgraded two levels because of imprecision (very small sample size and very low number of events with an impact on the precision of effect estimates).
[d]Assumed risk was gotten from control group risk (50%).

BACKGROUND

See Appendix 1 for a medical and epidemiological glossary.

Description of the condition

Coronary artery disease is a major public health problem (Gaziano 2006; Leys 2001; Manson 1996; Watkins 2004) that affects both developed and developing countries (Braunwald 2001; Gaziano 2006). The burden of coronary artery disease depends on several modifiable and non-modifiable risk factors and varies by geographical region (Alter 2008; Bainey 2009; Giannakoulas 2009; Goldenberg 2008; Gorter 2007; Goyal 2006; Kerr 2008; Lloyd-Williams 2008; Steptoe 2007). The epidemiology of coronary artery disease has been reviewed widely, as have methods of prevention (Labarthe 1998; Manson 1996).

Acute coronary syndromes include unstable angina and myocardial infarction with or without ST-segment elevation (electrocardiogram sector is higher than baseline) (Kolansky 2009). Acute myocardial infarction is the most important clinical entity of acute coronary syndromes; its definition is based on troponin elevation together with ischaemic symptoms, typical electrocardiogram changes or imaging evidence of loss of viable myocardium (Thygesen 2008). The epidemiology and burden of acute myocardial infarction have been described widely (al-Adsani 2000; Cabadés 2007; Ljung 2006; Manson 1996; Pop 2004; Rich 2006; Roger 2007).

The most frequent complications of acute myocardial infarction are cardiac arrhythmias, conduction abnormalities and left ventricular systolic dysfunction (heart failure). Of these, ventricular arrhythmias are associated with the worst prognosis for people with acute myocardial infarction (Henkel 2006; Hreybe 2009; Khairy 2003; Piccini 2008; Rahimi 2006; Singla 2008; Velazquez 2004; Weir 2006; Wolfe 1991). Ventricular arrhythmias after myocardial infarction are associated with high risk of mortality (Henkel 2006). Between 3% and 10% of uncomplicated acute myocardial infarctions will be affected by ventricular fibrillation (Noneman 1978). Mortality is due mainly to sudden death, which is caused by acute ventricular tachyarrhythmia, often triggered by acute coronary events that may occur in persons without known cardiac disease or in association with structural heart disease (Bayés de Luna 1989 Huikuri 2001). Ventricular fibrillation is the most frequent ventricular tachyarrhythmia, and it usually occurs secondary to ventricular tachyarrhythmia (Bayés de Luna 1989). The presence of arrhythmias in patients with acute myocardial infarction is associated with a poor prognosis (Volpi 1990).

In the era of thrombolysis, early or late primary ventricular fibrillation in patients with first acute myocardial infarction is an independent predictor of in-hospital mortality (Volpi 1998). After adjustment for other variables, patients with ventricular arrhythmias continue to be at significantly higher risk of 30-day or one-year mortality, both of which are significantly increased in patients with sustained ventricular fibrillation or ventricular tachyarrhythmia after myocardial infarction as compared with patients without these arrhythmias (Al-Khatib 2003).

Although different schemes have been used to classify death according to presumed mechanisms, considerable evidence shows that between one-quarter and one-half of cardiac deaths are sudden and are due to arrhythmia (Crystal 2003; Gardner 2000; Goldstein 1986; Koplan 2009; Kuch 2009; Myerburg 1986; Solomon 2005). Thus prevention of sudden death is an important clinical goal (Crystal 2003).

Description of the intervention

Since the 1950s, lidocaine, a local anaesthetic, has been used to control ventricular arrhythmias associated with myocardial infarction and cardiac surgery (Hitchcock 1959). For decades, lidocaine was used as a standard intravenous antiarrhythmic agent to prevent complications such as ventricular tachyarrhythmia and ventricular fibrillation after myocardial infarction (Harrison 1989). The dosage of lidocaine therapy was established by Aps et al., who recommended "a bolus (75-100 mg) followed by 4 mg/min for 30 minutes, 2 mg/min for two hours, and 1 mg/min thereafter" for patients affected with uncomplicated myocardial infarction (Aps 1976). Asystole is associated with lidocaine use (Applebaum 1986; Hill 1973; Manyari-Ortega 1978; Sadikot 1997), although evidence shows that use of lidocaine may not be associated with increased mortality rates (Alexander 1999). Lidocaine does not interact with the autonomic nervous system (Anderson 1984) but causes toxicity of the central nervous system (seizures, tremor, dysarthria, altered levels of consciousness and nystagmus), some of which is associated with high blood levels of lidocaine (Brunton 2008). Lidocaine is also known as lignocaine, but in this review, we use the name lidocaine.

Lidocaine is not used much anymore in high-income countries, but it continues to be used in many low-income countries (Reyes Caorsi 2006), and it is recommended in guidelines on management of patients with myocardial infarction (Anonimous 2006) and patients with ventricular arrhythmias and the prevention of sudden cardiac death (Zipes 2006). Furthermore, many published studies were conducted to explore this issue (Piccini 2011; Tagawa 2008; Takaya 2009).

How the intervention might work

Lidocaine is an antiarrhythmic drug of type IB Vaugham-Williams classification that works by inhibiting rapid sodium channels (a characteristic effect of this class of drugs) (Brunton 2008; Collinsworth 1974). Details of the electrophysiological effects of lidocaine on the heart are presented by Collinsworth 1974. These effects, which were observed in animal studies, briefly include the following: decreased automaticity of pacemaker tissue and sinoatrial node, increased ventricular fibrillation threshold and increased atrioventricular node conduction time according to dosage (Collinsworth 1974). The antiarrhythmic mechanism and efficacy of lidocaine are related to extracellular potassium concentration (Collinsworth 1974). Lidocaine may affect sinus node conduction or function (Klein 1975; Lippestad 1971).

Why it is important to do this review

Numerous randomised controlled trials were conducted to assess the clinical effectiveness and safety of lidocaine in preventing ventricular tachyarrhythmia and ventricular fibrillation among patients with myocardial infarction. In general, lidocaine used to reduce rates of ventricular tachyarrhythmia and ventricular fibrillation is beneficial but is associated with adverse effects (hypotension, neurological complications and other problems) that might be related to dosage. However, five systematic reviews used meta-analysis to verify no evidence of benefit in reducing the mortality rate (De Silva 1981; Hine 1989; MacMahon 1988; Sadowski

1999; Teo 1993). These reviews, published between 1981 and 1999, are now more than 10 years out of date. An update of the evidence is required for the following reasons.

- Reviews consistently reported high clinical heterogeneity between trials but did not report tools used to assess risk of bias (De Silva 1981; Hine 1989; MacMahon 1988; Sadowski 1999; Teo 1993).
- Currently, the I^2 statistic is the favoured method for assessing statistical heterogeneity (Higgins 2003), although previously the Chi^2 test was applied (De Silva 1981; Hine 1989; MacMahon 1988; Sadowski 1999; Teo 1993).
- Different summary measures such as Peto odds ratios (MacMahon 1988), odds ratios (Sadowski 1999) and risk differences (Hine 1989) showed no significant differences between non-surrogate clinical outcomes such as death. Use of risk ratio as a summary statistic for meta-analysis with binary data may have revealed significant differences in mortality (Deeks 2002). Only De Silva 1981 used risk ratios, but the endpoint was incidence of ventricular fibrillation.
- Systematic reviews did not conduct sensitivity analyses (trials with low risk of bias vs trials with high risk of bias).
- Overall, the main outcome was a surrogate marker: ventricular extrasystole/ventricular fibrillation. Although choosing a surrogate marker is not strictly inappropriate, this is not currently recommended (Schünemann 2009).
- We did not include trials comparing lidocaine versus any other antiarrhythmic drug. These trials should be included because indirectness is a reason for reducing confidence in the evidence (Guyatt 2008).
- Hine 1989 excluded trials that were not published in the English language. This decision may have led to oversampling of statistically significant studies (i.e. language bias) (Borenstein 2009).
- MacMahon 1988 and Teo 1993 did not include trials of cross-over design. De Silva 1981, Hine 1989 and Sadowski 1999 included cross-over trials; however, they did not report the methods used for analysis.

In addition, lidocaine is used in low-income countries (Anonimous 2006; Reyes Caorsi 2006).

In conclusion, the evidence is out of date and considerable uncertainty remains about the effects of prophylactic lidocaine use in all-cause mortality, in particular, in patients with suspected acute myocardial infarction. This Cochrane review seeks to update current knowledge and resolve uncertainties. The research question is this: "What is the clinical effectiveness and safety of prophylactic lidocaine for preventing death in people with acute myocardial infarction?"

OBJECTIVES

To determine the clinical effectiveness and safety of prophylactic lidocaine in preventing death among people with acute myocardial infarction.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials irrespective of design (parallel and cross-over) or publication status (unpublished or published as an article, an abstract or a letter). We applied no language, country or sample size limitations and included trials conducted in a hospital or community setting, or both. We also applied no limits with respect to period of follow-up, pre-hospital or in-hospital setting, lidocaine use or bolus with or without infusion.

Types of participants

Adults (≥ 18 years) with acute myocardial infarction. We applied no restrictions by definition of acute myocardial infarction.

Types of interventions

As acute myocardial infarction requires different medical and non-medical treatments (i.e. primary intervention), lidocaine is considered a complementary intervention. Thus, for the purpose of this review, eligible trials compared the same primary interventions with and without lidocaine.

Intervention

Lidocaine. We applied no restrictions by route of administration (intravenous, intra-muscular or both) or dose.

Comparison

Placebo. Standard care or antiarrhythmic drug alone or in any combination.

Types of outcome measures

Primary outcomes

- All-cause mortality.
- Cardiac mortality.
- Overall survival at 30 days after myocardial infarction (MI), which was defined as the proportion of survivors in a group. The proportion of persons in a specified group alive at the beginning of the time interval who survive to the end of the interval (Porta 2008).

Secondary outcomes

- Ventricular fibrillation: assessed by counting how many participants developed this arrhythmia.
- Adverse events: numbers and types of adverse events defined as any untoward medical occurrences not necessarily having a causal relationship with treatment. We reported separately on adverse events that led to treatment discontinuation and those that did not lead to treatment discontinuation. We defined a serious adverse event according to the International Conference on Harmonisation (ICH) Guidelines (ICH-GCP 1997) as any event that at any dose resulted in death, was life-threatening, required in-patient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or was a congenital anomaly/birth defect, and any important medical event that may have jeopardised the patient or required intervention to prevent it. We considered all other adverse events as non-serious.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases to find reports of relevant randomised controlled trials.

- Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 3 of 12).
- MEDLINE (Ovid, 1946 to Week 1 April 2015).
- EMBASE Classic and EMBASE (Ovid, 1947 to 10 April 2015).
- Latin American Caribbean Health Sciences Literature (LILACS) (13 April 2015).
- Web of Science (Thomson Reuters, 1970 to 13 April 2015).

We used Cochrane sensitive-maximising RCT filters to search MEDLINE and EMBASE (Lefebvre 2011). Appendix 2 shows the search strategies.

Searching other resources

We searched the Clinical Trials Search Portal of the World Health Organization (http://apps.who.int/trialsearch/) for ongoing and unpublished trials.

We also searched the following websites.

- http://www.excelenciaclinica.es.
- Scirus (www.scirus.com).
- http://www.evidence.nhs.uk/.

We checked the reference lists of all trials identified by the above methods, and we imposed no language restrictions.

Data collection and analysis

We summarised data using standard methodologies of The Cochrane Collaboration (Higgins 2011).

Selection of studies

Two review authors (AM-C, DS-R) independently assessed each reference identified by the search against the inclusion criteria. Through discussion, we resolved disagreements that arose. We retrieved in full references that appeared to meet the inclusion criteria for further independent assessment by two review authors.

Data extraction and management

One review author (AM-C) independently extracted data from included trials using a spreadsheet data extraction form; the other review author (DS-R) checked entered data for accuracy. We extracted the following data: eligibility criteria, demographics (age, sex, country), characteristics of included patients (treatment setting, lidocaine use (dosage, administration route)), types of control comparison treatments and outcomes. We discussed discrepancies between review authors to reach final consensus and used a pre-formed sheet (Zavala 2006).

Assessment of risk of bias in included studies

Three review authors (AM-C, DS-R, VA) independently assessed the risk of bias of each included trial using the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions,* Section 5.1.0 (Higgins 2011; Lundh 2012; Savović 2012; Wood 2008). Two review authors (of AM-C, DS-R, VA) checked the assessment. Review authors discussed discrepancies and achieved consensus.

The definition of each classification is given below.

Generation of allocation sequence

- Low risk of bias: if the allocation sequence was generated by a computer or a random number table, drawing of lots, tossing of a coin, shuffling of cards or throwing dice.
- Unclear risk of bias: if the trial was described as randomised but the method used for allocation sequence generation was not described.
- High risk of bias: if a system involving dates, names or admittance numbers was used for allocation of participants. These studies are known as quasi-randomised and were excluded from the review when beneficial effects were assessed.

Allocation concealment

- Low risk of bias: if allocation of participants involved a central independent unit, an on-site locked computer, identical-appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
- Unclear risk of bias: if the trial was described as randomised but the method used to conceal the allocation was not described.
- High risk of bias: if the allocation sequence was known to investigators who assigned participants, or if the study was quasi-randomised. The latter studies were excluded from the review when beneficial effects were assessed.

Blinding (or masking)

We assessed each trial (as low, unclear or high risk) with regard to the following levels of blinding.

- Blinding of clinician (person delivering treatment) to treatment allocation.
- Blinding of participant to treatment allocation.
- Blinding of outcome assessor to treatment allocation.

Incomplete outcome data

- Low risk of bias: if numbers of and reasons for dropouts and withdrawals in all intervention groups were described, or if it was specified that no dropouts or withdrawals occurred.
- Unclear risk of bias: if the report gave the impression that no dropouts or withdrawals occurred, but this was not specifically stated.
- High risk of bias: if numbers of or reasons for dropouts and withdrawals were not described.

We further examined the percentage of dropouts overall in each trial and per randomisation arm, and we evaluated from published information whether intention-to-treat analysis was performed or could be performed.

Selective outcome reporting

- Low risk of bias: if pre-defined or clinically relevant and reasonably expected outcomes were reported on.
- Unclear risk of bias: if not all pre-defined or clinically relevant and reasonably expected outcomes were reported on or were

not reported on fully, or if it was unclear whether data on these outcomes were recorded.
- High risk of bias: if one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

Other bias

- Low risk of bias: if the trial appeared to be free of other components that could put it at risk of bias.
- Unclear risk of bias: if the trial may or may not be free of other components that could put it at risk of bias.
- High risk of bias: if other factors in the trial could put it at risk of bias.

Overall risk of bias

We made explicit judgements about whether randomised controlled trials were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed risk of bias as high if any of the above domains were unclear or had high risk of bias.

Trials that showed adequate generation of allocation sequence, allocation concealment, blinding and handling of incomplete outcome data, and no selective outcome reporting, and that were without other risks of bias were considered trials with low risk of bias. We explored the impact of the risk of bias by undertaking subgroup analyses.

One review author (AM-C) entered the information using RevMan 2011 software. Two review authors (DS-R, VA) checked the entered data.

Measures of treatment effect

For each binary outcome such as all-cause mortality, cardiac mortality, ventricular fibrillation, adverse events and adverse drug reactions, we calculated the risk ratio (RR) with 95% confidence interval (CI).

We would have attempted to assess time-to-event outcomes and overall survival at 30 days by using the hazard ratio (HR) with 95% CI if included trials had reported this outcome. This will be done in future updates if trials report this outcome.

We planned to include cross-over trials, but none were available. If cross-over trials become available in the future, we will use the inverse variance method to pool data from these trials and will apply the Becker-Balagtas marginal estimated odds ratio to summarise ventricular fibrillation (Elbourne 2002).

Dealing with missing data

We assessed the percentage of dropouts for each included trial and for each intervention group, and we evaluated whether an intention-to-treat (ITT) analysis had been performed or could have been performed from available published information.

To undertake an ITT analysis, we sought data from trial authors on numbers of participants in treatment groups, irrespective of compliance and whether or not participants were later thought to be ineligible or otherwise excluded from treatment or lost to follow-up. If this information was not forthcoming, we undertook a complete participant analysis, knowing that it may be biased.

Assessment of heterogeneity

We quantified statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across trials due to heterogeneity rather than to sampling error (Higgins 2003). We considered statistical heterogeneity to be present if I^2 was greater than 50% (Higgins 2011).

Assessment of reporting biases

We assessed publication bias and other bias by using a funnel plot (Sterne 2011). We assessed publication bias for all-cause mortality and ventricular fibrillation using Comprehensive Meta-Analysis software (CMA 2005).

Data synthesis

We used random-effects methods to determine pool estimates and 95% confidence intervals.

Trial sequential analysis

Meta-analysis of cumulative data may run the risk of random errors ('play of chance') due to sparse data and repetitive analyses of cumulative data (Brok 2008; Brok 2009; Thorlund 2009; Thorlund 2010; Thorlund 2011a; Wetterslev 2008; Wetterslev 2009). To assess risks of random error in our cumulative meta-analyses, we conducted diversity-adjusted trial sequential analyses based on the proportion with the outcome in the control group; an a priori set relative risk reduction of 20%; alpha of 5% and beta of 20%; and squared diversity in the meta-analysis (CTU 2011; Thorlund 2009; Thorlund 2011b).

Subgroup analysis and investigation of heterogeneity

Despite statistical heterogeneity less than 50% for primary outcomes, we conducted the following pre-planned subgroup analyses.

- Route of administration of lidocaine (intravenous vs intramuscular).
- Pre-hospital setting lidocaine use versus In-hospital setting lidocaine use.
- Doses of lidocaine.

We were not able to conduct subgroup analysis by age and gender; congestive heart failure, cardiogenic shock or bradycardia/atrioventricular block before randomisation.

We performed subgroup analyses for primary outcomes.

We had planned to conduct meta-regression analyses. However, we did not use this approach because we found low statistical heterogeneity in meta-analyses for primary outcomes.

Furthermore, we conducted the following post hoc subgroup analyses (undertaken after results of the studies had been compiled).

- Acute myocardial infarction patients only.
- Trials without suspicion of industry bias versus trials with suspicion of industry bias.

Sensitivity analysis

We would have used the following procedures (and will apply these in future updates, if possible) in conducting sensitivity analysis to compare trials having 'low risk of bias' versus trials having 'high risk of bias' (Higgins 2011). As all included trials were rated as having high risk of bias, we were not able to conduct sensitivity analysis as planned.

We conducted a sensitivity analysis in the following way.

- Repeating the analysis while taking attrition bias into consideration (best-worst case scenario and worst-best case scenario).

'Summary of findings' tables

We used the principles of the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system (Guyatt 2008; Guyatt 2008b) in our review to assess the quality of the body of evidence associated with specific outcomes (all-cause mortality, cardiac mortality, overall survival at 30 days after myocardial infarction, ventricular fibrillation, adverse events) and constructed a 'Summary of findings (SoF)' table using GRADE software. The GRADE approach is used to appraise the quality of a body of evidence according to the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Assessment of the quality of a body of evidence considers within-study risk of bias (methodological quality), directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

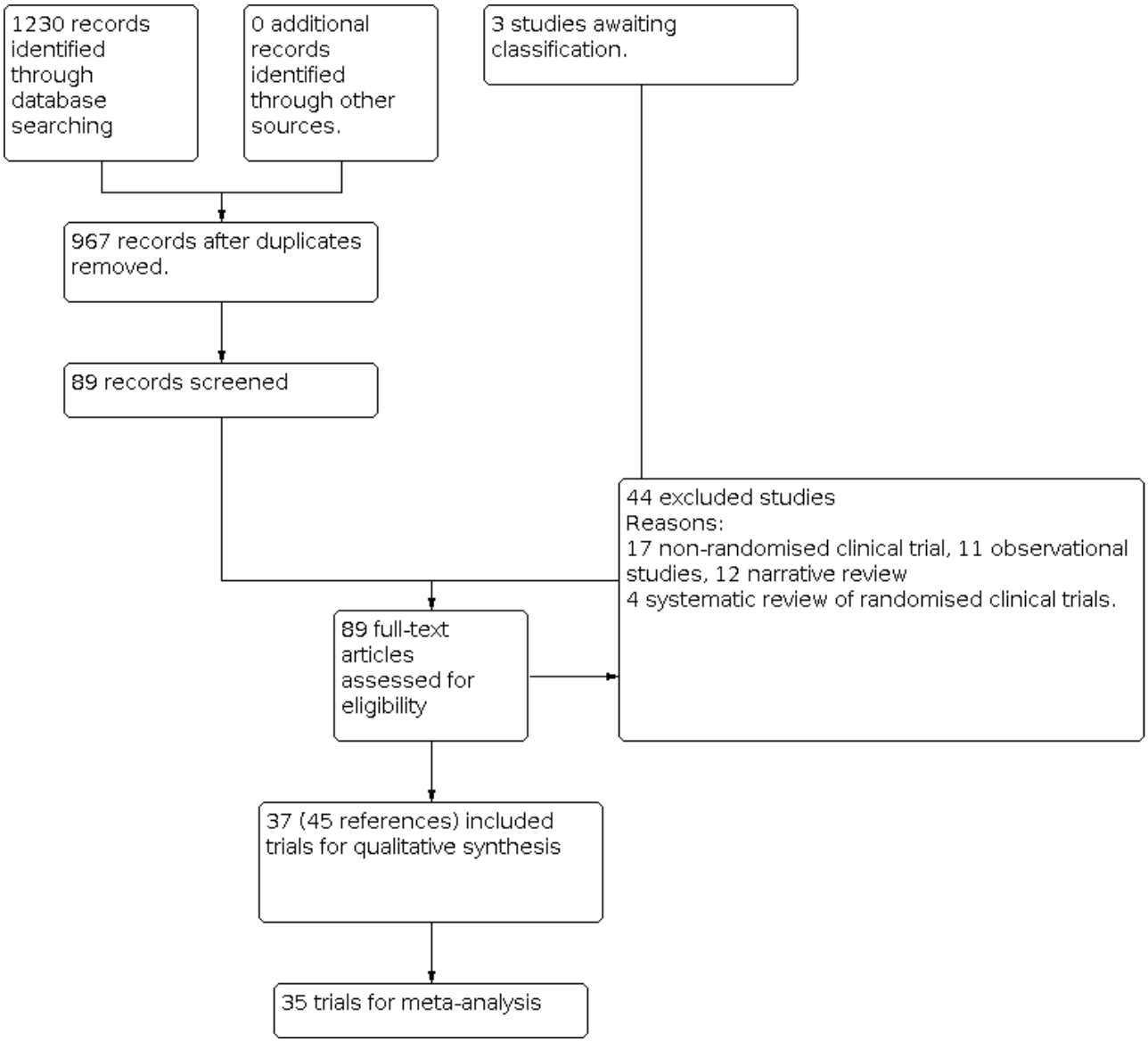
RESULTS

Description of studies

Results of the search

We identified 1230 references by using our search strategies. Thirty-seven trials (45 references) involving 11,948 participants met our inclusion criteria (ALIT 1985; Baker 1971; Bennett 1970; Bergdahl 1978; Capucci 1985; Chopra 1971; Cuendet 1988; Darby 1972; Depaepe 1974; Dunn 1985; Hargarten 1990; Horowitz 1981; Keefe 1986; Kostuk 1969; Kuck 1985; Lie 1974; Lie 1978; NNLIT 1992; O'Brien 1973; Pedersen 1986; Pharand 1995; Pitt 1971; Poprawski 1987; Rademaker 1986; Rehnqvist 1983; Rehnqvist 1984; Rolli 1981; Ronnevik 1987; Rossi 1976; Sadowski 1999; Sandler 1976; Sbarbaro 1979; Solimene 1983; Touboul 1988; Valentine 1974; Wennerblom 1982; Wyse 1988). See Figure 1 for details.

Figure 1. Study flow diagram.



Included studies

Tables of Characteristics of included studies show detailed descriptions of the studies.

Lidocaine and populations assessed in included trials

The 37 randomised controlled trials reported comparisons between lidocaine and several different control interventions.

Twenty-four trials compared lidocaine versus placebo (without or with co-interventions). Comparisons included saline solution (Chopra 1971; Dunn 1985; Lie 1978; NNLIT 1992; Rossi 1976; Sandler 1976; Valentine 1974; Wennerblom 1982) and 5% dextrose solution (Baker 1971; Kostuk 1969; Lie 1974; O'Brien 1973; Pharand 1995; Pitt 1971; Poprawski 1987). Characteristics of controls were not sufficiently described in ALIT 1985; Bennett 1970; Darby 1972; Hargarten 1990; Kuck 1985; Rademaker 1986; Sadowski 1999; Solimene 1983; and Wyse 1988.

Thirteen trials compared lidocaine versus another antiarrhythmic drug (with or without co-interventions). Comparisons included disopyramide (Horowitz 1981; Pedersen 1986; Ronnevik 1987; Sbarbaro 1979), amiodarone (Capucci 1985), dimethylammonium chloride (Bergdahl 1978), pirmenol (Cuendet 1988), mexiletine (Rolli 1981), aprindine (Depaepe 1974), propafenone (Rehnqvist 1984; Touboul 1988) and tocainide (Keefe 1986; Rehnqvist 1983).

Co-interventions used most often in experimental and control groups were lidocaine (Baker 1971; Horowitz 1981; Pharand 1995; Pitt 1971), oxygen (Bergdahl 1978; Keefe 1986), hydromorphone or pentazocine (Bergdahl 1978), defibrillation (Capucci 1985; Lie 1974; NNLIT 1992; Valentine 1974), electroversion (Horowitz 1981; Solimene 1983), mexiletine (Horowitz 1981), pacemaker (Pitt 1971), subcutaneous heparin (Keefe 1986; Poprawski 1987), nitroglycerin (Keefe 1986; Poprawski 1987; Sadowski 1999), morphine sulphate (Keefe 1986), furosemide (Keefe 1986; Ronnevik 1987), intracoronary thrombolysis (Kuck 1985; NNLIT 1992; Sadowski 1999), digitalis (Ronnevik 1987) and atropine (Sandler

1976; Wennerblom 1982). Twenty trials did not report use of a co-intervention (ALIT 1985; Bennett 1970; Chopra 1971; Cuendet 1988; Darby 1972; Depaepe 1974; Dunn 1985; Hargarten 1990; Kostuk 1969; Lie 1978; O'Brien 1973; Pedersen 1986; Rademaker 1986; Rehnqvist 1983; Rehnqvist 1984; Rolli 1981; Rossi 1976; Sbarbaro 1979; Touboul 1988; Wyse 1988).

Twenty-six trials used intravenous lidocaine (Baker 1971; Bennett 1970; Bergdahl 1978; Capucci 1985; Chopra 1971; Cuendet 1988; Depaepe 1974; Hargarten 1990; Horowitz 1981; Keefe 1986; Kostuk 1969; Kuck 1985; Lie 1974; O'Brien 1973; Pedersen 1986; Pharand 1995; Pitt 1971; Poprawski 1987; Rademaker 1986; Rehnqvist 1984; Rolli 1981; Ronnevik 1987; Sadowski 1999; Sbarbaro 1979; Solimene 1983; Wyse 1988, six used intramuscular lidocaine (ALIT 1985; Lie 1978; Rossi 1976; Sandler 1976; Valentine 1974; Wennerblom 1982) and three used intravenous and intramuscular lidocaine (Darby 1972; Dunn 1985; NNLIT 1992). Two studies used intravenous and oral routes (Rehnqvist 1983; Touboul 1988).

The follow-up period varied between trials: one hour (ALIT 1985; Lie 1978), two hours (Sbarbaro 1979), three hours (Chopra 1971; Dunn 1985; NNLIT 1992; Wennerblom 1982), 12 hours (Pedersen 1986; Solimene 1983), 24 hours (Cuendet 1988; Rehnqvist 1983; Rehnqvist 1984; Ronnevik 1987; Touboul 1988; Wyse 1988), 48 hours (Baker 1971; Bennett 1970; Darby 1972; Horowitz 1981; Keefe 1986; Kostuk 1969; Lie 1974; O'Brien 1973; Pharand 1995; Pitt 1971; Rademaker 1986; Sadowski 1999), 72 hours (Depaepe 1974), 504 hours (Rossi 1976) and 720 hours (Valentine 1974). Four trials did not report follow-up (Capucci 1985; Hargarten 1990; Poprawski 1987; Sandler 1976), and for three trials, the follow-up period was unclear (Bergdahl 1978; Kuck 1985; Rolli 1981).

Diagnostic criteria for myocardial infarction varied among included trials. Five trials used World Health Organization criteria (Baker 1971; Poprawski 1987; Rolli 1981; Sandler 1976; Valentine 1974); nine trials used Lawrie's criteria (ALIT 1985; Bennett 1970; Capucci 1985; Dunn 1985; Kuck 1985; Pedersen 1986; Rehnqvist 1983; Sadowski 1999; Wennerblom 1982); and 15 trials used clinical signs, electrocardiograms and laboratory enzymes alone or in combination (Chopra 1971; Depaepe 1974; Hargarten 1990; Keefe 1986; Lie 1974; Lie 1978; Pharand 1995; Pitt 1971; Rademaker 1986; Rehnqvist 1984; Ronnevik 1987; Rossi 1976; Solimene 1983; Touboul 1988; Wyse 1988). Eight trials had unclear diagnostic criteria or did not report them (Bergdahl 1978; Cuendet 1988; Darby 1972; Horowitz 1981; Kostuk 1969; NNLIT 1992; O'Brien 1973; Sbarbaro 1979).

Included trials were conducted in participants with proved or suspected myocardial infarction. Seventeen trials included participants with confirmed acute myocardial infarction (Baker 1971; Bennett 1970; Capucci 1985; Chopra 1971; Darby 1972; Depaepe 1974; Keefe 1986; Kostuk 1969; Kuck 1985; Lie 1974; Lie 1978; O'Brien 1973; Pitt 1971; Rehnqvist 1984; Rossi 1976; Solimene 1983; Touboul 1988), and 20 trials included participants with acute myocardial infarction or suspected acute myocardial infarction (ALIT 1985; Bergdahl 1978; Cuendet 1988; Dunn 1985; Hargarten 1990; Horowitz 1981; NNLIT 1992; Pedersen 1986; Pharand 1995; Poprawski 1987; Rademaker 1986; Rehnqvist 1983; Rolli 1981; Ronnevik 1987; Sadowski 1999; Sandler 1976; Sbarbaro 1979; Valentine 1974; Wennerblom 1982; Wyse 1988).

Three trials were conducted in a pre-hospital setting (ALIT 1985; NNLIT 1992; Wennerblom 1982), 31 in a hospital setting (Baker 1971; Bergdahl 1978; Depaepe 1974; Capucci 1985; Chopra 1971; Cuendet 1988; Darby 1972; Horowitz 1981; Keefe 1986; Kostuk 1969; Kuck 1985; Lie 1974; Lie 1978; O'Brien 1973; Pedersen 1986; Pharand 1995; Pitt 1971; Poprawski 1987; Rademaker 1986; Rehnqvist 1983; Rehnqvist 1984; Rolli 1981; Ronnevik 1987; Rossi 1976; Sadowski 1999; Sandler 1976; Sbarbaro 1979; Solimene 1983; Touboul 1988; Valentine 1974; Wyse 1988) and three in both settings (Bennett 1970; Dunn 1985; Hargarten 1990).

Thirty-one trials reported participants' age. Overall, the mean age of participants was older than 50 years (ALIT 1985; Baker 1971; Bennett 1970; Bergdahl 1978; Capucci 1985; Chopra 1971; Cuendet 1988; Depaepe 1974; Dunn 1985; Hargarten 1990; Horowitz 1981; Keefe 1986; Kuck 1985; Lie 1974; Lie 1978; NNLIT 1992; Pedersen 1986; Pharand 1995; Pitt 1971; Poprawski 1987; Rademaker 1986; Rehnqvist 1983; Rehnqvist 1984; Rolli 1981; Ronnevik 1987; Sadowski 1999; Sandler 1976; Touboul 1988; Valentine 1974; Wennerblom 1982; Wyse 1988). Six trials did not report participants' age (Darby 1972; Kostuk 1969; O'Brien 1973; Rossi 1976; Sbarbaro 1979; Solimene 1983). Thirty-one trials reported the percentage of included male participants, which was 75.06 ± 11.58 (minimum 50, maximum 95, median 76) (ALIT 1985; Baker 1971; Bennett 1970; Bergdahl 1978; Capucci 1985; Chopra 1971; Cuendet 1988; Darby 1972; Depaepe 1974; Dunn 1985; Hargarten 1990; Horowitz 1981; Keefe 1986; Kuck 1985; Lie 1974; Lie 1978; NNLIT 1992; Pharand 1995; Pitt 1971; Poprawski 1987; Rademaker 1986; Rehnqvist 1983; Rehnqvist 1984; Rolli 1981; Ronnevik 1987; Sadowski 1999; Sandler 1976; Touboul 1988; Valentine 1974; Wennerblom 1982; Wyse 1988), and six trials did not report the gender of participants (Kostuk 1969; O'Brien 1973; Pedersen 1986; Rossi 1976; Sbarbaro 1979; Solimene 1983).

Trial locations

Included trials were conducted between 1969 and 1999 in 17 countries: three in Australia (Horowitz 1981; Pitt 1971; Valentine 1974), one in Belgium (Depaepe 1974), one in Brazil (Solimene 1983), four in Canada (Chopra 1971; Kostuk 1969; Rademaker 1986; Wyse 1988), one in Denmark (Pedersen 1986), one in France (Touboul 1988), one in Germany (Kuck 1985), three in Italy (Capucci 1985; Rolli 1981; Rossi 1976), one in New Zealand (O'Brien 1973), one in Northern Ireland (Dunn 1985), two in Norway (NNLIT 1992; Ronnevik 1987), two in Poland (Poprawski 1987; Sadowski 1999), four in Sweden (Bergdahl 1978; Rehnqvist 1983; Rehnqvist 1984; Wennerblom 1982), one in Switzerland (Cuendet 1988), three in The Netherlands (ALIT 1985; Lie 1974; Lie 1978), four in the United Kingdom (Baker 1971; Bennett 1970; Darby 1972; Sandler 1976) and four in the United States of America (Hargarten 1990; Keefe 1986; Pharand 1995; Sbarbaro 1979).

Trial methods

The mean sample size was 357.22 ± 994.08 (minimum 19, maximum 6024, median 150). One trial reported sample size estimation a priori (NNLIT 1992). Thirty-six trials were conducted without sample size estimated a priori (ALIT 1985; Baker 1971; Bennett 1970; Bergdahl 1978; Capucci 1985; Chopra 1971; Cuendet 1988; Darby 1972; Depaepe 1974; Dunn 1985; Hargarten 1990; Horowitz 1981; Keefe 1986; Kostuk 1969; Kuck 1985; Lie 1974; Lie 1978; O'Brien 1973; Pedersen 1986; Pharand 1995; Pitt 1971; Poprawski 1987; Rademaker 1986; Rehnqvist 1983; Rehnqvist 1984; Rolli 1981; Ronnevik 1987; Rossi 1976; Sadowski 1999; Sandler 1976; Sbarbaro

1979; Solimene 1983; Touboul 1988; Valentine 1974; Wennerblom 1982; Wyse 1988).

Thirty-six trials used a parallel study design (ALIT 1985; Baker 1971; Bennett 1970; Bergdahl 1978; Capucci 1985; Chopra 1971; Cuendet 1988; Darby 1972; Depaepe 1974; Dunn 1985; Hargarten 1990; Horowitz 1981; Keefe 1986; Kostuk 1969; Kuck 1985; Lie 1974; Lie 1978; NNLIT 1992; O'Brien 1973; Pedersen 1986; Pharand 1995; Pitt 1971; Poprawski 1987; Rademaker 1986; Rehnqvist 1983; Rehnqvist 1984; Rolli 1981; Ronnevik 1987; Rossi 1976; Sadowski 1999; Sandler 1976; Solimene 1983; Touboul 1988; Valentine 1974; Wennerblom 1982; Wyse 1988). Thirty-two trials used two comparison groups (ALIT 1985; Baker 1971; Bergdahl 1978; Capucci 1985; Chopra 1971; Darby 1972; Depaepe 1974; Dunn 1985; Hargarten 1990; Horowitz 1981; Keefe 1986; Kostuk 1969; Kuck 1985; Lie 1974; Lie 1978; NNLIT 1992; O'Brien 1973; Pedersen 1986; Pharand 1995; Pitt 1971; Poprawski 1987; Rademaker 1986; Rehnqvist 1983; Rehnqvist 1984; Rolli 1981; Ronnevik 1987; Rossi 1976; Sadowski 1999; Solimene 1983; Valentine 1974; Wennerblom 1982; Wyse 1988), two trials three comparison groups (Bennett 1970; Touboul 1988) and two trials four comparison groups (Sandler 1976; Sbarbaro 1979). One trial had a cross-over design (Sbarbaro 1979).

Excluded studies

We excluded 43 studies for the following reasons: non-randomised controlled trials (Bernard 1972; Bertini 1993; Bleifeld 1973; Church 1972; Diederich 1979; Fehmers 1972; Garratt 1998; Gonzalez 1977; Leone 1991; Miller 1973; Mogensen 1971; Riabokon' 1980; Ryden 1973; Singh 1976; Szeplaki 1973; Szeplaki 1976; Wojtala 1982), systematic reviews of randomised controlled trials (De Silva 1981; Hine 1989; MacMahon 1988; Teo 1993), observational studies (Beloev 1983; Campbell 1978; Destuelles 1969; Egre 1981; Gianelly 1967; Mazur 1982; Pentecost 1981; Ruano 1989; Shih 1995; Wyman 2004) and narrative reviews (Antman 1992; Bernard 1970; Campbell 1980; Campbell 1983; Formichev 1995; Goodman 1979; Iosava 1982; Jaffe 1992; Lechleitner 1987; Noneman 1978; Oltmanns 1979; Ribner 1979). See the Characteristics of excluded studies table.

Studies awaiting classification

Three references were considered as 'Studies awaiting classification' (Bolinska 1971; Hopperstead 1980; Knight 1973). See Characteristics of studies awaiting classification for details. These three studies lacked an abstract indicating whether they were randomised trials. We were not able to find the addresses of study authors and were not able to find their full-text articles.

Risk of bias in included studies

See Figure 2 and Figure 3 for details.

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

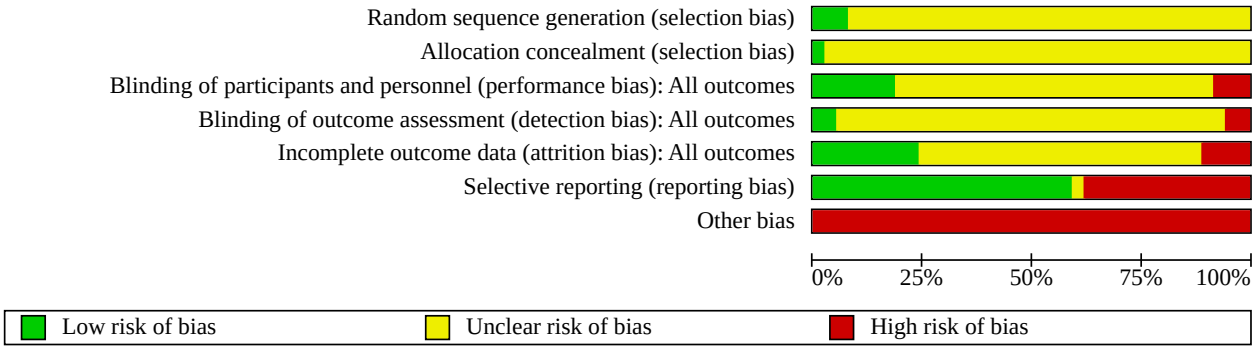


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

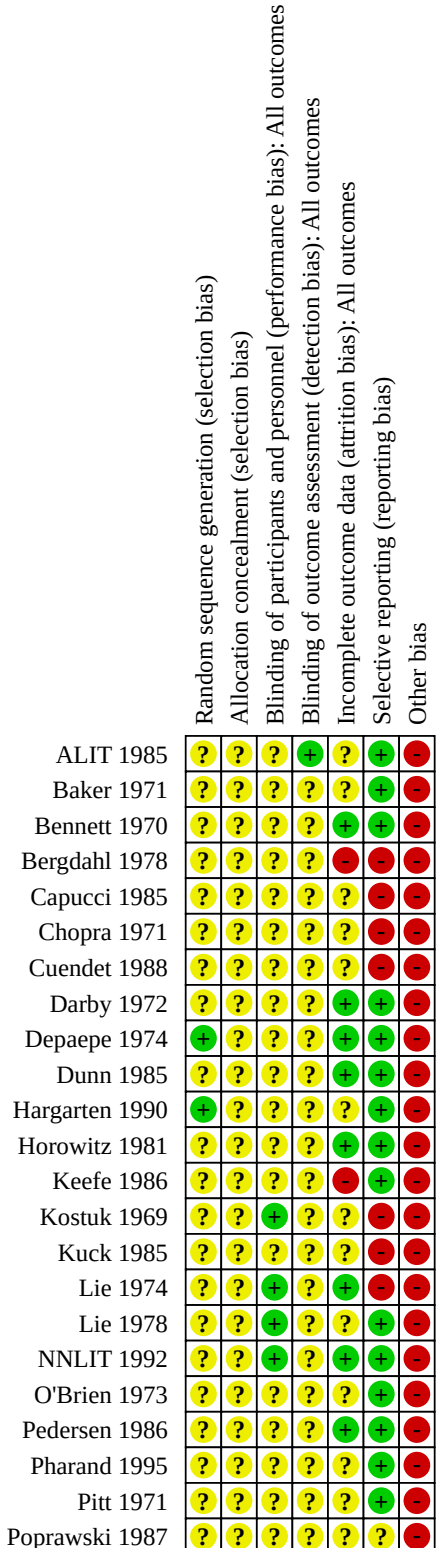
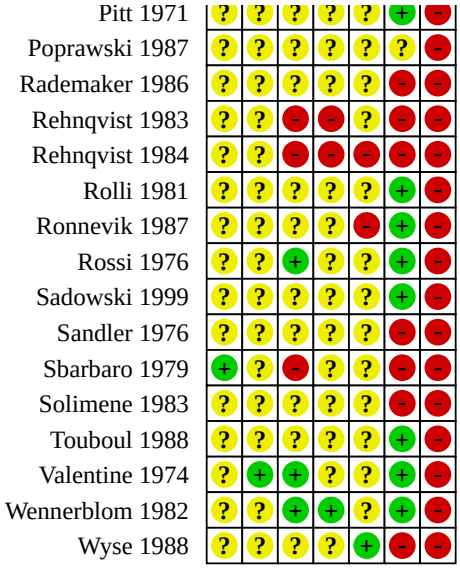


Figure 3. (Continued)



Allocation

Random sequence generation

Risk of bias arising from the method of generation of the allocation sequence was considered low in three trials (Depaepe 1974; Hargarten 1990; Sbarbaro 1979). Thirty-four studies had an unclear risk of bias for this domain (ALIT 1985; Baker 1971; Bennett 1970; Bergdahl 1978; Capucci 1985; Chopra 1971; Cuendet 1988; Darby 1972; Dunn 1985; Horowitz 1981; Keefe 1986; Kostuk 1969; Kuck 1985; Lie 1974; Lie 1978; NNLIT 1992; O'Brien 1973; Pedersen 1986; Pharand 1995; Pitt 1971; Poprawski 1987; Rademaker 1986; Rehnqvist 1983; Rehnqvist 1984; Rolli 1981; Ronnevik 1987; Rossi 1976; Sadowski 1999; Sandler 1976; Solimene 1983; Touboul 1988; Valentine 1974; Wennerblom 1982; Wyse 1988).

Allocation concealment

Risk of bias arising from the method of allocation concealment was considered low in one trial (Valentine 1974). Thirty-six trials had unclear risk of bias for this domain (ALIT 1985; Baker 1971; Bennett 1970; Bergdahl 1978; Capucci 1985; Chopra 1971; Cuendet 1988; Darby 1972; Depaepe 1974; Dunn 1985; Hargarten 1990; Horowitz 1981; Keefe 1986; Kostuk 1969; Kuck 1985; Lie 1974; Lie 1978; NNLIT 1992; O'Brien 1973; Pedersen 1986; Pharand 1995; Pitt 1971; Poprawski 1987; Rademaker 1986; Rehnqvist 1983; Rehnqvist 1984; Rolli 1981; Ronnevik 1987; Rossi 1976; Sadowski 1999; Sandler 1976; Sbarbaro 1979; Solimene 1983; Touboul 1988; Wennerblom 1982; Wyse 1988).

Blinding

Risk of bias due to lack of blinding of participants and personnel was rated as low in seven trials (Kostuk 1969; Lie 1974; Lie 1978; NNLIT 1992; Rossi 1976; Valentine 1974; Wennerblom 1982). Risk of bias of blinding was high in 30 trials (ALIT 1985; Baker 1971; Bennett 1970; Bergdahl 1978; Capucci 1985; Chopra 1971; Cuendet 1988; Darby 1972; Depaepe 1974; Dunn 1985; Hargarten 1990; Horowitz 1981; Keefe 1986; Kuck 1985; O'Brien 1973; Pedersen 1986; Pharand 1995; Pitt 1971; Poprawski 1987; Rademaker 1986; Rehnqvist 1983; Rehnqvist 1984; Rolli 1981; Ronnevik 1987; Sadowski 1999; Sandler 1976; Sbarbaro 1979; Solimene 1983; Touboul 1988; Wyse 1988).

In two trials, outcome assessment was clearly reported as blinded and detection bias was considered low (ALIT 1985; Wennerblom 1982). Blinding was unclear or was not performed in 35 trials and risk of detection bias was considered high (Baker 1971; Bennett 1970; Bergdahl 1978; Capucci 1985; Chopra 1971; Cuendet 1988; Darby 1972; Depaepe 1974; Dunn 1985; Hargarten 1990; Horowitz 1981; Keefe 1986; Kostuk 1969; Kuck 1985; Lie 1974; Lie 1978; NNLIT 1992; O'Brien 1973; Pedersen 1986; Pharand 1995; Pitt 1971; Poprawski 1987; Rademaker 1986; Rehnqvist 1983; Rehnqvist 1984; Rolli 1981; Ronnevik 1987; Rossi 1976; Sadowski 1999; Sandler 1976; Sbarbaro 1979; Solimene 1983; Touboul 1988; Valentine 1974; Wyse 1988).

Incomplete outcome data

Risk of attrition bias was rated as low in nine trials (Bennett 1970; Darby 1972; Depaepe 1974; Dunn 1985; Horowitz 1981; Lie 1974; NNLIT 1992; Pedersen 1986; Wyse 1988). Risk of attrition bias was rated as high in 28 trials (ALIT 1985; Baker 1971; Bergdahl 1978; Capucci 1985; Chopra 1971; Cuendet 1988; Hargarten 1990; Keefe 1986; Kostuk 1969; Kuck 1985; Lie 1978; O'Brien 1973; Pharand 1995; Pitt 1971; Poprawski 1987; Rademaker 1986; Rehnqvist 1983; Rehnqvist 1984; Rolli 1981; Ronnevik 1987; Rossi 1976; Sadowski 1999; Sandler 1976; Sbarbaro 1979; Solimene 1983; Touboul 1988; Valentine 1974; Wennerblom 1982).

Selective reporting

Risk of selective outcome reporting bias was rated as low in 22 trials (ALIT 1985; Baker 1971; Bennett 1970; Darby 1972; Depaepe 1974; Dunn 1985; Hargarten 1990; Horowitz 1981; Keefe 1986; Lie 1978; NNLIT 1992; O'Brien 1973; Pedersen 1986; Pharand 1995; Pitt 1971; Rolli 1981; Ronnevik 1987; Rossi 1976; Sadowski 1999; Touboul 1988; Valentine 1974; Wennerblom 1982) and high in 15 trials (Bergdahl 1978; Capucci 1985; Chopra 1971; Cuendet 1988; Kostuk 1969; Kuck 1985; Lie 1974; Poprawski 1987; Rademaker

1986; Rehnqvist 1983; Rehnqvist 1984; Sandler 1976; Sbarbaro 1979; Solimene 1983; Wyse 1988).

Other potential sources of bias

Risk of other bias was rated as high in all trials because of bias in presentation of data, design bias or industry bias (ALIT 1985; Baker 1971; Bennett 1970; Bergdahl 1978; Capucci 1985; Chopra 1971; Cuendet 1988; Darby 1972; Depaepe 1974; Dunn 1985; Hargarten 1990; Horowitz 1981; Keefe 1986; Kostuk 1969; Kuck 1985; Lie 1974; Lie 1978; NNLIT 1992; O'Brien 1973; Pedersen 1986; Pharand 1995; Pitt 1971; Poprawski 1987; Rademaker 1986; Rehnqvist 1983; Rehnqvist 1984; Rolli 1981; Ronnevik 1987; Rossi 1976; Sadowski 1999; Sandler 1976; Sbarbaro 1979; Solimene 1983; Touboul 1988; Valentine 1974; Wennerblom 1982; Wyse 1988).

Ten trials had potential industry bias (Bennett 1970; Bergdahl 1978; Chopra 1971; Depaepe 1974; Keefe 1986; Lie 1974; Pitt 1971; Rademaker 1986; Rossi 1976; Sbarbaro 1979).

Accordingly, all trials were considered as having high risk of bias.

Effects of interventions

See: **Summary of findings 1** Lidocaine compared with placebo or no intervention for acute myocardial infarction; **Summary of findings 2** Lidocaine compared with disopyramide for myocardial infarction; **Summary of findings 3** Lidocaine compared with tocainide for myocardial infarction; **Summary of findings 4** Lidocaine compared with mexiletine for myocardial infarction; **Summary of findings 5** Lidocaine compared with propafenone for myocardial infarction; **Summary of findings 6** Lidocaine compared with amiodarone for myocardial infarction; **Summary of findings 7** Lidocaine compared with dimethylammonium for myocardial infarction; **Summary of findings 8** Lidocaine compared with aprindine for myocardial infarction; **Summary of findings 9** Lidocaine compared with pirmenol for myocardial infarction

Primary outcomes

All-cause mortality

Lidocaine versus placebo or no intervention

Meta-analysis of 18 trials involving participants with proven or non-proven acute myocardial infarction, comparing lidocaine versus placebo or no intervention, showed no significant differences in all-cause mortality (213/5879 (3.62%) vs 199/5848 (3.40%); RR 1.02, 95% CI 0.82 to 1.27; participants = 11727; I^2 = 15%; P value = 0.86; low-quality evidence) (ALIT 1985; Baker 1971; Bennett 1970; Chopra 1971; Darby 1972; Dunn 1985; Hargarten 1990; Lie 1974; Lie 1978; NNLIT 1992; O'Brien 1973; Pharand 1995; Pitt 1971; Poprawski 1987; Rossi 1976; Sadowski 1999; Valentine 1974; Wennerblom 1982). See Analysis 1.1. A funnel plot revealed no evidence of publication bias for this outcome (Figure 4). Trial sequential analysis shows that 14 trials provided evidence that lidocaine is not able to induce a 20% RR reduction in all-cause mortality compared with placebo or no intervention, if we disregard risks of bias (Figure 5).

Figure 4. Funnel plot on all-cause mortality in 18 lidocaine vs placebo or no intervention trials Funnel plot of data from the meta-analysis evaluating the effects of lidocaine compared with placebo for preventing all-cause mortality in patients with proven or not proven acute myocardial infarction (18 trials). This figure shows low risk of publication bias. Individual circles represent point estimates of the included randomised controlled trials. The pattern of distribution simulates an inverted funnel. Larger trials are closer and upper to the pooled estimate. Effect sizes of smaller trials are lower and are more or less symmetrically distributed around the pooled estimate.

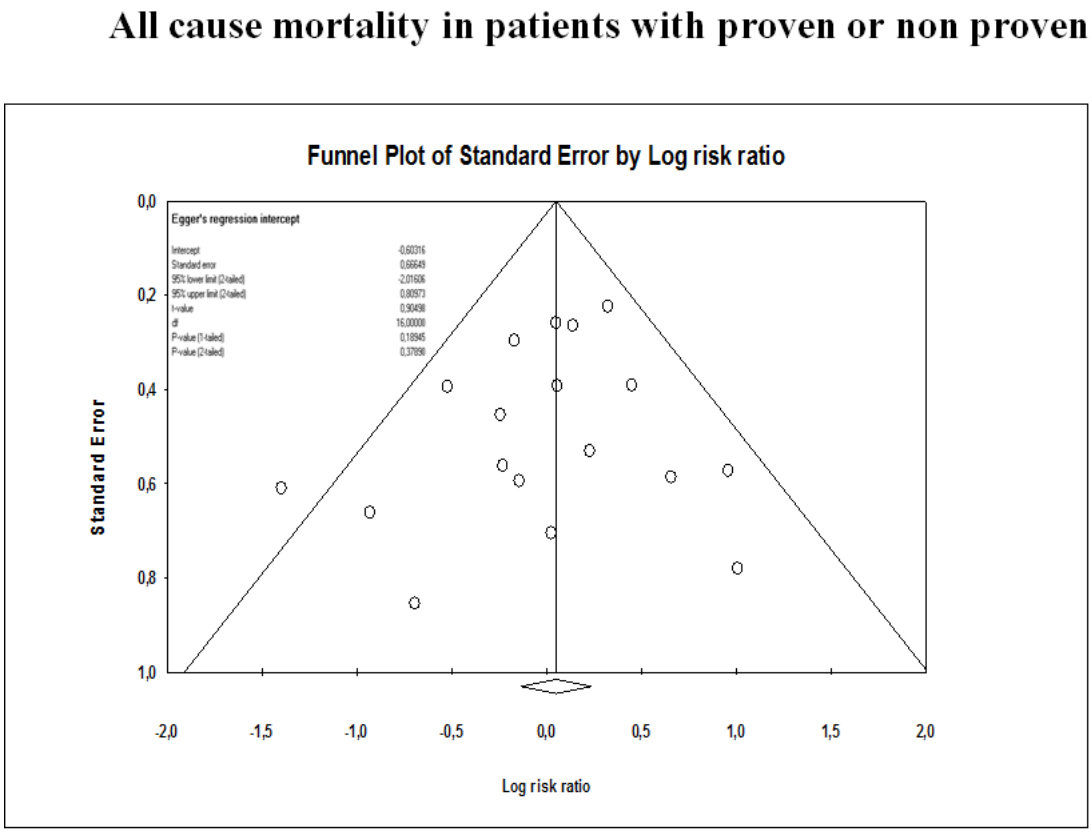
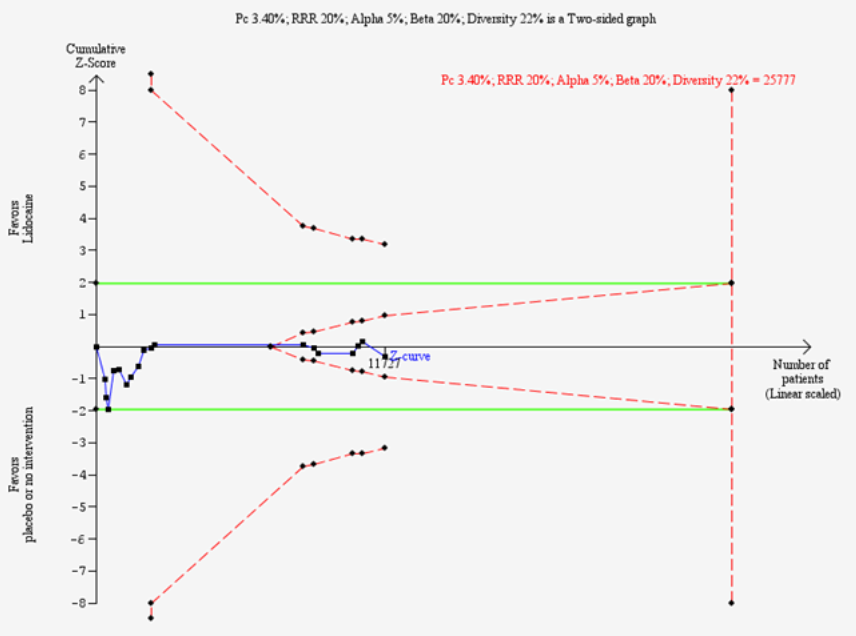


Figure 5. Trial sequential analysis on all-cause mortality in 18 lidocaine vs placebo or no intervention trials
Trial sequential analysis of lidocaine vs placebo or no intervention on all-cause mortality in participants with or without proven myocardial infarction based on the diversity-adjusted required information size (DARIS) of 25,777 participants. This DARIS was calculated on the basis of a proportion of participants with suspected myocardial infarction of 3.40% in the control group; RRR of 20% in the experimental intervention group; alpha (α) of 5%; beta (β) of 20%; and diversity of 22%. The cumulative Z-curve (blue line) did not cross the conventional alpha 5% boundaries (green lines) at any time. After the 14th trial, the cumulative Z-curve crosses the trial sequential monitoring boundary for futility. Accordingly, although only 45.5% (11,727/25,777) of the DARIS has been obtained, we can reject an intervention effect of 20% or larger. This implies that no additional trials may be needed to disprove an intervention effect of 20% relative risk reduction if bias can be ignored. Smaller risk reductions may require additional trials with larger sample sizes.

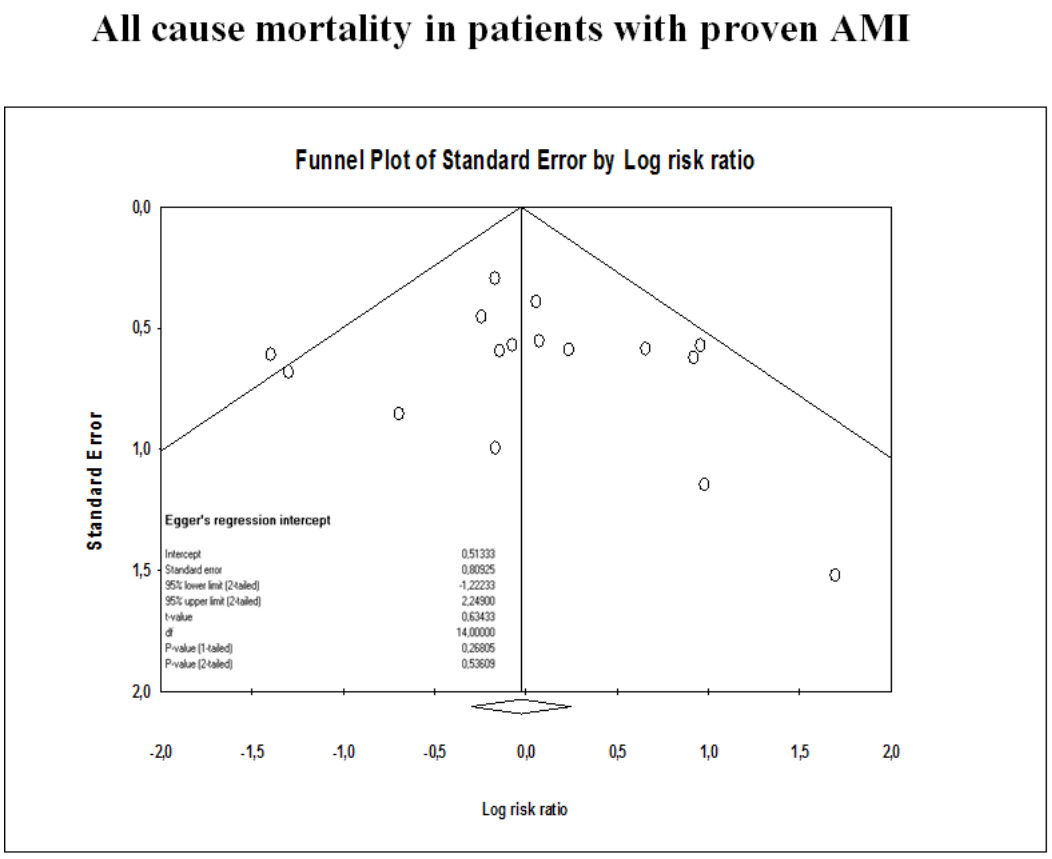


Heterogeneity for this critical endpoint was low, as conveyed by I^2 values. However, because of the large number of trials and the importance of determining the effect of prophylactic lidocaine on all-cause mortality in individuals with proven acute myocardial infarction, we conducted many subgroup analyses for this population.

Subgroup analyses involving acute myocardial infarction patients only

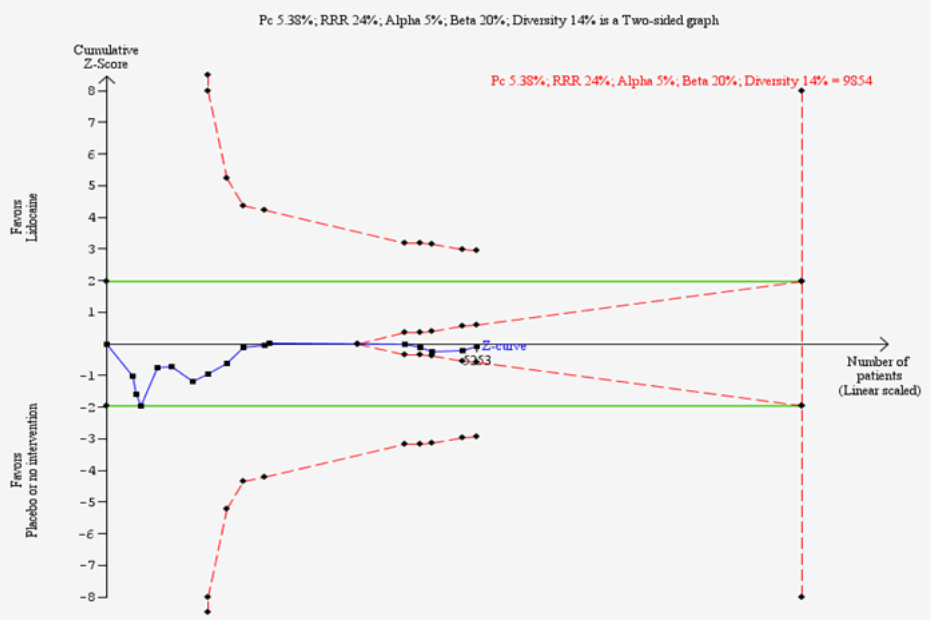
Meta-analysis of 16 trials comparing lidocaine versus placebo or no intervention revealed no differences regarding all-cause mortality (148/2747 (5.38%) vs 135/2506 (5.38%); RR 1.01, 95% CI 0.79 to 1.30; participants = 5253; I^2 = 9%; P value = 0.92) (ALIT 1985; Baker 1971; Bennett 1970; Chopra 1971; Darby 1972; Dunn 1985; Hargarten 1990; Lie 1974; Lie 1978; O'Brien 1973; Pharand 1995; Pitt 1971; Poprawski 1987; Rossi 1976; Valentine 1974; Wennerblom 1982). See Analysis 1.2. Figure 6 shows no evidence of publication bias outcome.

Figure 6. Funnel plot on all-cause mortality in participants with proven acute myocardial infarction in 16 lidocaine vs placebo or no intervention trials Funnel plot of data from the meta-analysis of effects of lidocaine compared with placebo for preventing all-cause mortality in individuals with proven acute myocardial infarction (16 trials). This figure shows low risk of publication bias. The circles show point estimates of the included randomised controlled trials. The pattern of distribution simulates an inverted funnel. Each half of the funnel plot includes eight trials. Larger trials are closer and upper to the pooled estimate. Effect sizes of the smaller trials are lower and are more or less symmetrically distributed around the pooled estimate. The right half of the funnel plot (near the bottom corner) shows two smaller trials with higher standard error and far of the point estimate.



Trial sequential analysis shows that 13 trials provided evidence that lidocaine is not able to induce a 25% RR reduction in all-cause mortality among participants with myocardial infarction compared with placebo or no intervention, if we disregard risks of bias (Figure 7).

Figure 7. Trial sequential analysis on all-cause mortality among participants with myocardial infarction in 16 lidocaine vs placebo or no intervention trials Trial sequential analysis of lidocaine vs placebo or no intervention on all-cause mortality in participants with myocardial infarction based on the diversity-adjusted required information size (DARIS) of 9854 participants. This DARIS was calculated on the basis of a proportion of participants with mortality by myocardial infarction of 5.38% in the control group; post hoc selected RRR of 25% in the experimental intervention group; alpha (α) of 5%; beta (β) of 20%; and diversity of 14%. The cumulative Z-curve (blue line) did not cross the conventional alpha 5% boundaries (green lines). After the 12th trial, the cumulative Z-curve crossed the trial sequential monitoring boundary for futility. Accordingly, although only 53.30% (5253/9854) of the DARIS has been obtained, we can reject an intervention effect of 25% or larger. Had we calculated the DARIS on the basis of a more realistic RRR like 20% (as we had planned) or less, the obtained information would represent a smaller part of the DARIS. Accordingly, the boundaries for futility would not have been crossed in such scenarios. Therefore, risk reduction of 20% or less may require additional trials with larger sample sizes.



Subgroup analysis of trials according to administration route of lidocaine

Meta-analysis of nine trials administering lidocaine by the intravenous route showed no significant differences regarding all-cause mortality when lidocaine was compared with placebo or with no intervention (92/1100 (8.36%) vs 70/942 (7.43%); RR 1.16, 95% CI 0.82 to 1.63; participants = 2042; I^2 = 14%; P value = 0.40) (Baker 1971; Bennett 1970; Chopra 1971; Hargarten 1990; Lie 1974; O'Brien 1973; Pharand 1995; Pitt 1971; Poprawski 1987). Meta-analysis of five trials administering lidocaine by the intramuscular route showed no significant differences regarding all-cause mortality when lidocaine was compared with placebo or with no intervention (41/1436 (2.85%) vs 53/1368 (3.87%); RR 0.77, 95% CI 0.50 to 1.17; participants = 2804; I^2 = 4%; P value = 0.22) (ALIT 1985; Lie 1978; Rossi 1976; Valentine 1974; Wennerblom 1982). Meta-analysis of two trials administering lidocaine by the intramuscular route showed no significant differences regarding all-cause mortality when lidocaine was compared with placebo or with no intervention (15/211 (7.11%) vs 12/196 (6.12%); RR 1.17, 95% CI 0.56 to 2.42; participants = 407; I^2 = 0%; P value = 0.68) (Darby 1972; Dunn 1985). Tests for subgroup differences showed no significant differences (I^2 = 16.3%; P value = 0.92). See Analysis 1.3.

Subgroup analysis of trials with infusion administration only compared with trials with bolus and infusion administrations

Meta-analysis of three trials administering lidocaine by infusion showed no significant differences regarding all-cause mortality only when lidocaine was compared with placebo or with no intervention (16/229 (6.98%) vs 22/237 (9.28%); RR 0.85, 95% CI 0.33 to 2.17; participants = 466; I^2 = 40%; P value = 0.73) (Baker 1971; Pharand 1995; Pitt 1971). Meta-analysis of six trials administering lidocaine by both bolus and infusion approaches revealed no significant differences regarding all-cause mortality when lidocaine was compared with placebo or with no intervention (76/871 (8.72%) vs 48/705 (6.81%); RR 1.30, 95% CI 0.92 to 1.83; participants = 1576; I^2 = 0%; P value = 0.14) (Bennett 1970; Chopra 1971; Hargarten 1990; Lie 1974; O'Brien 1973; Poprawski 1987). Tests for subgroup differences showed no significant differences (I^2 = 0%; P value = 0.40). See Analysis 1.4.

Subgroup analysis according to bolus lidocaine dose

One trial found no significant differences in all-cause mortality when lidocaine administered by bolus up to 50 mg was compared with placebo or with no intervention (7/39 (17.95%) vs 4/43 (9.30%); RR 1.93, 95% CI 0.61 to 6.09; participants = 82; P value = 0.26) (Chopra 1971). One bolus of 60 mg of lidocaine does not produce statistically significant differences when compared with to placebo or with no intervention in terms of all-cause mortality (25/249 (10.04%) vs 8/125 (6.4%); RR 1.57, 95% CI 0.73 to 3.38; participants = 374; P value = 0.25) (Bennett 1970). Meta-analysis of two trials comparing a bolus of 75 mg of lidocaine versus placebo or no intervention showed no significant differences regarding all-cause mortality (34/240 (14.17%) vs 24/232 (10.34%); RR 1.49, 95% CI 0.70 to 3.16; participants = 472; I^2 = 42%; P value = 0.30) (O'Brien 1973; Poprawski 1987). One trial found no statistically significant differences in all-cause mortality when lidocaine administered by bolus at a dose of 100 mg was compared with placebo or with no intervention (8/107 (7.48%) vs 10/105 (9.52%); RR 0.79, 95% CI 0.32 to 1.91; participants = 212; P value = 0.59) (Lie 1974). At a dose of 1 mg/kg, lidocaine did not significantly affect all-cause mortality when compared with placebo or no intervention (2/236 (0.85%) vs 2/200 (1%); RR 0.85, 95% CI 0.12 to 5.96; participants = 436; P value = 0.87) (Hargarten 1990). Tests for subgroup differences showed no significant differences (I^2 = 0%; P value = 0.70). See Analysis 1.5.

Subgroup analysis according to number of lidocaine boluses at any dose

Meta-analysis of four trials assessing one bolus of lidocaine at any dose versus placebo or no intervention showed no statistically significant differences regarding all-cause mortality (51/549 (9.29%) vs 26/419 (6.20%); RR 1.47, 95% CI 0.90 to 2.38; participants = 968; I^2 = 5%; P value = 0.12) (Bennett 1970; Chopra 1971; Lie 1974; O'Brien 1973). Administration of two boluses at any dose of lidocaine versus placebo or no intervention did not significantly affect all-cause mortality in participants with acute myocardial infarction (27/322 (8.38%) vs 22/286 (7.69%); RR 1.19, 95% CI 0.72 to 1.95; participants = 608; I^2 = 0%; P value = 0.49) (Hargarten 1990; Poprawski 1987). See Analysis 1.6.

Subgroup analysis according to intravenous infusion dose of lidocaine

Meta-analysis of three trials comparing infusion of lidocaine between 1 mg/min and 1.5 mg/min versus placebo or no intervention showed no significant differences regarding all-cause mortality (32/370 (8.64%) vs 14/248 (5.64%); RR 1.45, 95% CI 0.71 to 2.95; participants = 618; I^2 = 11%; P value = 0.31) (Baker 1971; Bennett 1970; Pharand 1995). Meta-analysis of six trials comparing infusion of lidocaine between 2 mg/min and 3 mg/min versus placebo or no intervention also showed no statistically significant differences regarding all-cause mortality (60/730 (8.21%) vs 56/694 (8.1%); RR 1.08, 95% CI 0.72 to 1.62; participants = 1424; I^2 = 20%; P value = 0.72) (Chopra 1971; Hargarten 1990; Lie 1974; O'Brien 1973; Pitt 1971; Poprawski 1987). See Analysis 1.7.

Subgroup analysis according to clinical setting

Meta-analysis of two trials performed in a pre-hospital setting showed no statistically significant differences regarding all-cause mortality when lidocaine was compared with placebo or with no intervention (12/1034 (1.16%) vs 11/955 (1.15%); RR 1.00, 95% CI 0.46 to 2.19; participants = 1989; I^2 = 0%; P value = 1.00) (ALIT 1985; Wennerblom 1982). Meta-analysis of 11 trials performed in a hospital setting also showed no statistically significant differences regarding all-cause mortality when lidocaine was compared with placebo or with no intervention (106/1120 (9.46%) vs 113/1130 (10%); RR 0.95, 95% CI 0.69 to 1.32; participants = 2250; I^2 = 30%; P value = 0.77) (Baker 1971; Chopra 1971; Darby 1972; Lie 1974; Lie 1978; O'Brien 1973; Pharand 1995; Pitt 1971; Poprawski 1987; Rossi 1976; Valentine 1974). Meta-analysis of three trials performed in both pre-hospital and hospital settings similarly showed no significant differences in all-cause mortality when lidocaine was compared with placebo or with no intervention (30/593 (5.1%) vs 11/421 (2.61%); RR 1.53, 95% CI 0.77 to 3.02; participants = 1014; I^2 = 0%; P value = 0.22) (Bennett 1970; Dunn 1985; Hargarten 1990). Tests for subgroup differences showed no significant differences (I^2 = 0%; P value = 0.47). See Analysis 1.8.

Subgroup analysis of trials without risk of industry bias compared with trials with risk of industry bias

Meta-analysis of 11 trials without risk of industry bias showed no significant differences in all-cause mortality when lidocaine was compared with placebo or with no intervention (96/2145 (4.48%) vs 79/1972 (4.01%); RR 1.09, 95% CI 0.82 to 1.44; participants = 4117; I^2 = 0%; P value = 0.54) (ALIT 1985; Baker 1971; Darby 1972; Dunn 1985; Hargarten 1990; Lie 1978; O'Brien 1973; Pharand 1995; Poprawski 1987; Valentine 1974; Wennerblom 1982). Meta-analysis of five trials at risk of industry bias showed no significant differences in all-cause mortality when lidocaine was compared with placebo or with no intervention (52/602 (8.64%) vs 56/534 (10.49%); RR 0.84, 95% CI 0.44 to 1.58; participants = 1136; I^2 = 58%; P value = 0.58) (Bennett 1970; Chopra 1971; Lie 1974; Pitt 1971; Rossi 1976). Tests for subgroup differences showed no significant differences (I^2 = 0%; P value = 0.45). See Analysis 1.9.

Sensitivity analyses taking attrition into consideration

Of the 18 trials (11,727 participants) combined for this outcome, three trials (17% (3/18)) reported exact numbers of participants with missing events in the intervention and control groups (Bennett 1970; Darby 1972; NNLIT 1992). Two trials involving 614 participants reported information for this outcome overall (Dunn 1985; Lie 1974). Thirteen trials did not report information for this outcome in any comparison group (ALIT 1985; Baker 1971; Chopra 1971; Hargarten 1990; Lie 1978; O'Brien 1973; Pharand 1995; Pitt 1971; Poprawski 1987; Rossi 1976; Sadowski 1999; Valentine 1974; Wennerblom 1982). Thus, three trials reported missing data

for intervention groups and control groups involving 6.60% of participants (774/11,727). Furthemore, these three trials involved 18.8% of events in the experimental group (40/213) and 13.6% of events in the control group (27/199).

'Best-worse case' scenario

In a best-worst case scenario analysis, we found no statistically significant differences in proportions of all-cause mortality (40/448 (8.93%) vs 48/326 (14.72%); RR 0.57, 95% CI 0.30 to 1.08; participants = 774; I^2 = 49%; P value < 0.08).

'Worst-best case' scenario

In a worst-best case scenario analysis, we found no statistically significant differences in proportions of all-cause mortality (100/448 (22.32%) vs 27/326 (8.28%); RR 2.20, 95% CI 1.02 to 4.73; participants = 774; I^2 = 67%; P value = 0.04).

See Analysis 1.10.

Lidocaine versus disopyramide

Meta-analysis of two trials comparing lidocaine versus disopyramide showed no significant differences in terms of all-cause mortality (7/73 (9.59%) vs 5/71 (7.04%); RR 1.39, 95% CI 0.47 to 4.13; participants = 144; I^2 = 0%; P value = 0.55; very-low-quality evidence) (Pedersen 1986; Ronnevik 1987). See Analysis 2.1.

Sensitivity analyses taking attrition into consideration

Pedersen 1986 and Ronnevik 1987 reported the exact numbers of participants with missing events in lidocaine and disopyramide groups.

'Best-worse case' scenario

In a best-worst case scenario analysis, we found no significant differences in proportions of participants for all-cause mortality (7/73 (9.59%) vs 12/71 (16.90%); RR 0.49, 95% CI 0.08 to 3.02; participants = 144; I^2 = 62%; P value = 0.44).

'Worst-best case' scenario

In a worst-best case scenario analysis, we found no significant differences in proportions of participants for all-cause mortality (15/73 (20.54%) vs 5/71 (7.04%); RR 2.75, 95% CI 1.05 to 7.20; participants = 144; I^2 = 0%; P value = 0.04).

See Analysis 2.2.

Lidocaine versus tocainide

One trial comparing lidocaine versus tocainide showed no significant differences in risk of all-cause mortality (1/13 (7.6%) vs 1/16 (6.25%); RR 1.23, 95% CI 0.08 to 17.83; participants = 29; P value = 0.88; very-low-quality evidence) (Keefe 1986). See Analysis 3.1.

Sensitivity analyses taking attrition into consideration

Keefe 1986 reported the exact numbers of participants with missing events in lidocaine and tocainide groups.

'Best-worse case' scenario

In a best-worst case scenario analysis, we found no statistically significant differences in proportions of participants for all-cause mortality (1/13 (7.7%) vs 2/16 (12.5%); RR 0.62, 95% CI 0.06 to 6.05; participants = 29; P value = 0.68).

'Worst-best case' scenario

In a worst-best case scenario analysis, we found no statistically significant differences in proportions of participants for all-cause mortality (2/13 (15.4%) vs 1/16 (6.25%); RR 2.46, 95% CI 0.25 to 24.21; participants = 29; P value = 0.44).

See Analysis 3.2.

Lidocaine versus mexiletine

No significant differences in risk of all-cause mortality were noted between lidocaine and mexiletine (0/12 (0%) vs 1/12 (8.33%); RR 0.33, 95% CI 0.01 to 7.45; participants = 24; P value = 0.49; very-low-quality evidence) (Horowitz 1981). See Analysis 4.1.

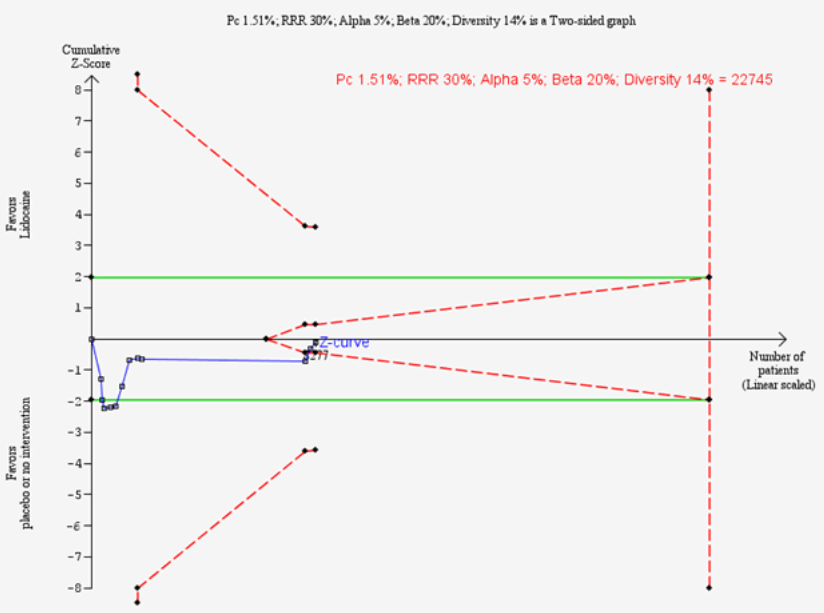
Cardiac mortality

Lidocaine versus placebo or no intervention

Meta-analysis of 12 trials showed no significant differences regarding cardiac mortality in participants with or without proved acute myocardial infarction when lidocaine was compared with placebo or with no intervention (69/4184 (1.65%) vs 62/4093 (1.51%); RR 1.03, 95% CI 0.70 to 1.50; participants = 8277; I^2 = 12%; P value = 0.90; low-quality evidence) (ALIT 1985; Baker 1971; Bennett 1970; Chopra 1971; Darby 1972; Lie 1974; Lie 1978; NNLIT 1992; Pharand 1995; Pitt 1971; Valentine 1974; Wennerblom 1982). See Analysis 1.11.

Figure 7 shows no evidence of publication bias outcome. Trial sequential analysis shows 11 trials provided evidence showing that lidocaine is not able to induce a 30% RR reduction in cardiac mortality compared with placebo or with no intervention, if we disregard risks of bias (Figure 8).

Figure 8. Trial sequential analysis on cardiac mortality in 12 lidocaine vs placebo or no intervention trials
Trial sequential analysis of lidocaine vs placebo or no intervention on cardiac mortality in participants with or without proven myocardial infarction based on the diversity-adjusted required information size (DARIS) of 22,745 participants. This DARIS was calculated on the basis of a proportion of participants with cardiac mortality among those with suspected myocardial infarction of 1.51% in the control group; post hoc selected RRR of 30% in the experimental intervention group; alpha (α) of 5%; beta (β) of 20%; and diversity of 14%. The cumulative Z-curve (blue line) crossed the conventional alpha of 5% (green line) after 3 trials suggested harm. After 10 trials, however, the cumulative Z-curve (blue line) crossed the trial sequential monitoring boundary for futility. Accordingly, after only 36.4% (8277/22,745) of the DARIS had been obtained, we were able to reject an intervention effect of 30% or larger. Had we calculated the DARIS on the basis of a more realistic RRR like 20% (as originally planned) or less, the obtained evidence would represent a smaller part of the DARIS. Accordingly, boundaries for futility would not have been crossed in such scenarios. Therefore, risk reductions of 20% or less may require additional trials with larger sample sizes.



Subgroup analysis of trials not suspected to be at risk of industry bias versus trials suspected to be at risk of industry bias

Meta-analysis of eight trials without risk of industry bias showed no significant differences regarding cardiac mortality among participants with and those without proved acute myocardial infarction when lidocaine was compared with placebo or with no intervention (35/3681 (0.95%) vs 42/3706 (1.13%); RR 0.85, 95% CI 0.52 to 1.39; participants = 7387; I^2 = 14%; P value = 0.51) (ALIT 1985; Baker 1971; Darby 1972; Lie 1978; NNLIT 1992; Pharand 1995; Valentine 1974; Wennerblom 1982). Meta-analysis of four trials at risk of industry bias showed no significant differences regarding cardiac mortality when lidocaine was compared with placebo or with no intervention (34/503 (6.76%) vs 20/387 (5.16%); RR 1.36, 95% CI 0.77 to 2.39; participants = 890; I^2 = 0%; P value = 0.29) (Bennett 1970; Chopra 1971; Lie 1974; Pitt 1971). Tests for subgroup differences showed no significant differences (I^2 = 34.4%; P value = 0.22). See Analysis 1.12.

Lidocaine versus disopyramide

Regarding cardiac mortality, one meta-analysis of two trials found no significant differences between lidocaine and placebo (3/71 (4.23%) vs 3/73 (4.10%); RR 1.02, 95% CI 0.21 to 4.87; participants = 144; I^2 = 0%; P value = 0.98; very-low-quality evidence) (Pedersen 1986; Ronnevik 1987). See Analysis 2.3.

Lidocaine versus tocainide

One trial comparing lidocaine with tocainide showed no significant differences in risk of cardiac mortality (1/13 (7.7%) vs 1/16 (6.25%); RR 1.23, 95% CI 0.08 to 17.83; participants = 29; P value = 0.88; very-low-quality evidence) (Keefe 1986). See Analysis 3.3.

Lidocaine versus mexiletine

No significant differences in risk of cardiac mortality were noted between lidocaine and mexiletine (0/12 (0%) versus 1/12 (8.33%); (RR 0.33, 95% CI 0.01 to 7.45; participants = 24; P = 0.49, very low quality evidence) (Horowitz 1981). See Analysis 4.2.

Overall survival at 30 days after myocardial infarction

Trials did not assess this outcome.

Secondary outcomes

Ventricular fibrillation

Lidocaine versus placebo or no intervention

Meta-analysis of 16 trials showed no significant differences between lidocaine and placebo or no intervention regarding prophylaxis of ventricular fibrillation in participants with or without proven acute myocardial infarction (76/5128 (1.48%) vs 103/4987 (2.07%); RR 0.78, 95% CI 0.55 to 1.12; participants = 10115; I^2 = 18%; P value = 0.18; low-quality evidence) (ALIT 1985; Baker 1971; Bennett 1970; Chopra 1971; Darby 1972; Dunn 1985; Hargarten 1990; Kuck 1985; Lie 1974; Lie 1978; NNLIT 1992; O'Brien 1973; Poprawski 1987; Sadowski 1999; Solimene 1983; Valentine 1974). See Analysis 1.13. Figure 9 shows no evidence of publication bias. Trial sequential analysis reveals that 16 trials provided evidence to show that lidocaine is not able to induce a 30% RR reduction in cardiac mortality compared with placebo or with no intervention, if we disregard risks of bias (Figure 10).

Figure 9. Funnel plot of data from the meta-analysis of effects of lidocaine compared with placebo for preventing ventricular fibrillation in individuals with proven or non-proven acute myocardial infarction (15 trials). This figure shows low risk of publication bias. Circles show point estimates of the included randomised controlled trials. The pattern of distribution simulates an inverted funnel. Trials are symmetrically distributed in each of the halves. Larger trials are closer and upper to the pooled estimate. Effect sizes of the smaller trials are lower and are more or less symmetrically distributed around the pooled estimate.

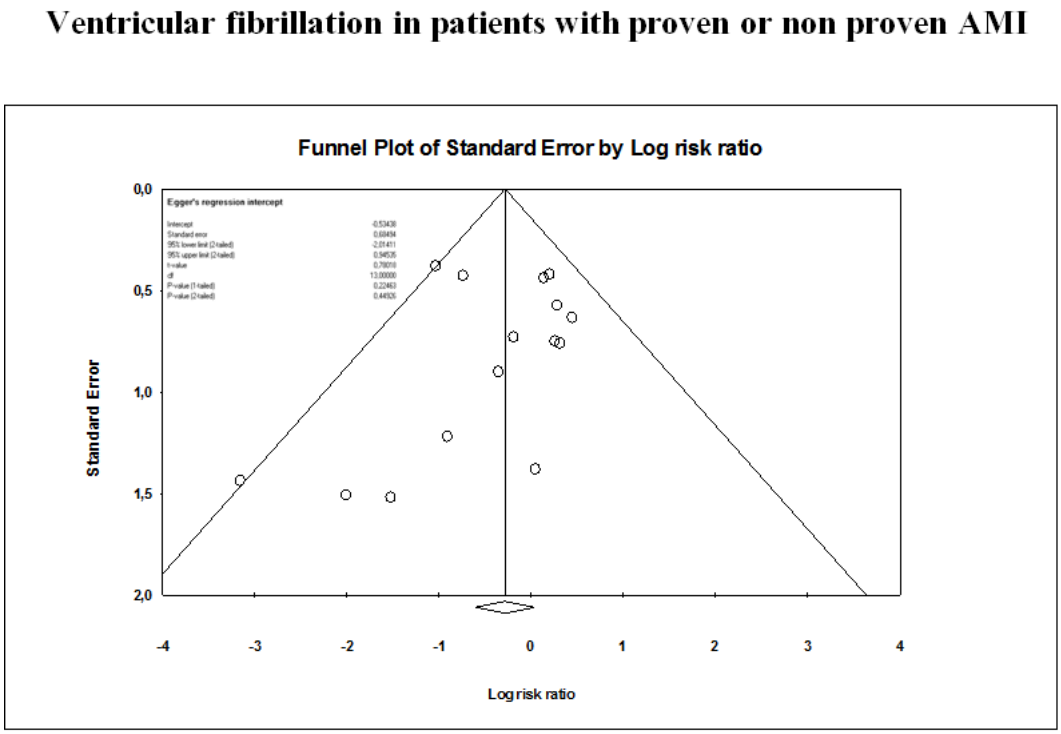
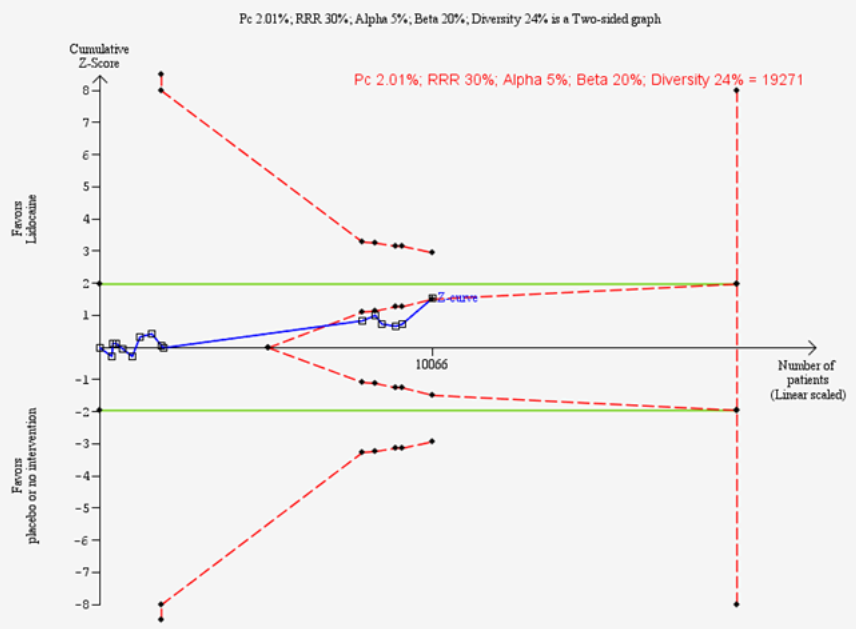


Figure 10. Trial sequential analysis on prevention of ventricular fibrillation in 15 lidocaine vs placebo or no intervention trials Trial sequential analysis of lidocaine vs placebo or no intervention on prevention of ventricular fibrillation in participants with or without proven myocardial infarction based on the diversity-adjusted required information size (DARIS) of 19,271 individuals. This DARIS was calculated on the basis of a proportion of participants with ventricular fibrillation of 2.01% in the control group; post hoc selected RRR of 30% in the experimental intervention group; alpha (α) of 5%; beta (β) of 20%; and diversity of 24%. The cumulative Z-curve (blue line) did not cross conventional alpha 5% boundaries (green lines). After the 10th trial, the cumulative Z-curve crosses the trial sequential monitoring boundary for futility. Accordingly, after only 52.2% (10,066/19,271) of the DARIS had been obtained, we were able to reject an intervention effect of 30% or larger. Had we calculated the DARIS on the basis of a more realistic RRR like 20% (as originally planned) or less, the obtained evidence would represent a smaller portion of the DARIS. Accordingly, the boundaries for futility would not have been crossed in such scenarios. Therefore, risk reductions of 20% or less may require additional trials with larger sample sizes.



Lidocaine versus disopyramide

One trial comparing lidocaine versus disopyramide provided very-low-quality evidence regarding ventricular fibrillation (1/38 (2.6%) vs 3/38 (7.9%); RR 0.33, 95% CI 0.04 to 3.06; participants = 76; P value = 0.33) (Pedersen 1986). See Analysis 2.4.

Lidocaine versus tocainide

Two trials assessed this comparison (Keefe 1986; Rehnqvist 1983). However, Keefe 1986 reported that no participants experienced ventricular fibrillation. On the other hand, Rehnqvist 1983 did not mention this outcome.

Lidocaine versus mexiletine

No significant differences in risk of ventricular fibrillation were noted between comparison groups (1/12 (8.33%) vs 0/12 (0%); RR 3.00, 95% CI 0.13 to 67.06; participants = 24; P value = 0.49; very-low-quality evidence) (Horowitz 1981). See Analysis 4.3.

Lidocaine versus amiodarone

No significant differences in risk of ventricular fibrillation were noted between comparison groups (2/15 (13.33%) vs 0/10 (0%); RR 3.44, 95% CI 0.18 to 64.88; participants = 25; P value = 0.41; very-low-quality evidence) (Capucci 1985). See Analysis 6.1.

Lidocaine versus propafenone

No significant differences in risk of ventricular fibrillation were noted between comparison groups (1/10 (1%) vs 0/10 (0%); RR 3.00, 95% CI 0.14 to 65.90; participants = 20; P value = 0.49; low-quality evidence) (Rehnqvist 1984). See Analysis 5.1.

Adverse events

Cardiovascular adverse events

Lidocaine versus placebo or no intervention

Lidocaine significantly increased the risk of asystole over placebo or no intervention (35/3393 (1.03%) vs 14/3443 (0.41%); RR 2.32, 95% CI 1.26 to 4.26; participants = 6826; I^2 = 0%; very-low-quality evidence) (ALIT 1985; Darby 1972; Dunn 1985; NNLIT 1992). No significant differences were noted between lidocaine and placebo or no intervention regarding sinus bradycardia (55/1346 (4.09%) vs 49/1203 (4.07%); RR 1.09, 95% CI 0.66 to 1.80; participants = 2549; I^2 = 21%; P value = 0.74; very-low-quality evidence) (Bennett 1970; Darby 1972; Dunn 1985; Hargarten 1990; Rademaker 1986; Sandler 1976; Touboul 1988; Wennerblom 1982); bundle branch block (83/853 (9.73%) vs 75/733 (10.23%); RR 1.07, 95% CI 0.80 to 1.44; participants = 1586; I^2 = 0%; P value = 0.64) (Bennett 1970; Darby 1972; Sadowski 1999; Touboul 1988); non-complete atrioventricular block (78/888 (8.79%) vs 75/773 (9.70%); RR 1.01, 95% CI 0.75 to 1.37; participants = 1661; I^2 = 0%%; P value = 0.93) (Bennett 1970; Darby 1972; Sadowski 1999; Sandler 1976); complete atrioventricular block (13/443 (2.93%) vs 5/315 (1.59%); RR 1.77, 95% CI 0.66 to 4.78; participants = 758; I^2 = 0%; P value = 0.26) (Bennett 1970; Darby 1972; Sandler 1976); unknown grade atrioventricular block (66/919 (7.18%) vs 56/808 (6.93%); RR 1.12, 95% CI 0.75 to 1.67; participants = 1727; I^2 = 7%; P value = 0.49) (Bennett 1970; O'Brien 1973; Sadowski 1999; Wennerblom 1982); pulmonary edema (83/868 (9.56%) vs 71/762 (9.32%); RR 1.08, 95% CI 0.80 to 1.46; participants = 1630; I^2 = 0%; P value = 0.51) (Bennett 1970; Darby 1972; Sadowski 1999; Wennerblom 1982); cardiogenic shock (77/868 (8.87%) vs 73/762 (9.58%); RR 1.04, 95% CI 0.77 to 1.41; participants = 1630; I^2 = 0%; P value = 0.79) (Bennett 1970; Darby 1972; Sadowski 1999; Wennerblom 1982); hypotension (87/814 (10.69%) vs 88/885 (9.94%); RR 1.07, 95% CI 0.81 to 1.41; participants = 1699; I^2 = 0%; P value = 0.59) (Darby 1972; NNLIT 1992; Rossi 1976; Sadowski 1999; Wennerblom 1982); cardiac arrest (76/1149 (6.61%) vs 76/1181 (6.43%); RR 1.03, 95% CI 0.77 to 1.39; participants = 2330; I^2 = 0%; P value = 0.85) (Hargarten 1990; Sadowski 1999); and heart failure (134/851 (15.74%) vs 170/800 (21.25%); RR 0.91, 95% CI 0.63 to 1.33; participants = 1751; I^2 = 62%; P value = 0.64) (Dunn 1985; Pharand 1995; Rossi 1976; Sadowski 1999). See Analysis 1.14.

Lidocaine versus disopyramide

No significant differences were noted between lidocaine and disopyramide regarding pulmonary oedema (2/73 (2.73%) vs 4/71 (5.63%); RR 0.62, 95% CI 0.12 to 3.10; participants = 144; I^2 = 0%; P value = 0.56) (Pedersen 1986; Ronnevik 1987); cardiogenic shock (2/38 (5.26%) vs 1/38 (2.63%); RR 2.00, 95% CI 0.19 to 21.14; participants = 76; P value = 0.56) (Pedersen 1986); asystole (0/38 (0%) vs 1/38 (2.63%); RR 0.33, 95% CI 0.01 to 7.93; participants = 76; P value = 0.50; very-low-quality evidence) (Pedersen 1986); sinoatrial block (1/35 (2.85%) vs 1/33 (3.03%); RR 0.94, 95% CI 0.06 to 14.47; participants = 68; P value = 0.97; very-low-quality evidence) (Ronnevik 1987) and cardiac block (high-degree atrioventricular block and bundle branch block) (3/35 (8.57%) vs 5/33 (15.15%); RR 0.57, 95% CI 0.15 to 2.18; participants = 68; P value = 0.51; very-low-quality evidence) (Ronnevik 1987). See Analysis 2.5.

Lidocaine versus tocainide

Meta-analysis of two trials shows increased risk of any adverse event in the lidocaine group compared with the tocainide group (25/33 (75.75%) vs 16/36 (44.44%); RR 1.69, 95% CI 1.07 to 2.68; participants = 69; I^2 = 17%); very-low-quality evidence) (Keefe 1986; Rehnqvist 1983). See Analysis 3.4.

Lidocaine versus mexiletine

No significant differences were noted between lidocaine and mexiletine groups in terms of cardiogenic shock (0/12 (0%) vs 1/12 (8.33%); RR 0.33, 95% CI 0.01 to 7.45; participants = 24; P value = 0.49); incomplete atrioventricular block (0/12 (0%) vs 1/12 (8.33%); RR 0.33, 95% CI 0.01 to 7.45; participants = 24; P value = 0.49) and pulmonary oedema (3/12 (25%) vs 2/12 (16.66%); RR 1.50, 95% CI 0.30 to 7.43; participants = 24; P value = 0.62; very-low-quality evidence) (Horowitz 1981). See Analysis 4.4.

Lidocaine versus propafenone

One trial showed no significant differences between lidocaine and propafenone regarding heart failure (2/28 (7.14%) vs 0/36 (0%); RR 6.38, 95% CI 0.32 to 127.77; participants = 64; P value = 0.23; very-low-quality evidence) and bilateral bundle branch block (0/28 (0%) vs 1/36 (2.78%); RR 0.43, 95% CI 0.02 to 10.06; participants = 64; P value = 0.60; very-low-quality evidence) (Touboul 1988). See Analysis 5.2.

Lidocaine versus amiodarone

Capucci 1985 found no significant differences between lidocaine and amiodarone regarding bradycardia (0/15 (0%) vs 1/10 (10%); RR 0.23, 95% CI 0.01 to 5.12; participants = 25; P value = 0.35; very-low-quality evidence) and hypotension (0/15 (0%) vs 12/10 (20%); RR 0.14, 95% CI 0.01 to 2.60; participants = 25; P value = 0.19; very-low-quality evidence). See Analysis 6.2.

Lidocaine versus dimethylammonium

One trial found no significant differences between lidocaine and dimethylammonium in terms of hypotension (4/15 (26.7%) vs 5/16 (31.25%); RR 0.85, 95% CI 0.28 to 2.59; participants = 31; P value = 0.78; very-low-quality evidence); rise in blood pressure (0/15 (0%) vs 5/16 (31.25%); RR 0.10, 95% CI 0.01 to 1.61; participants = 31; P value = 0.10; very-low-quality evidence); tachycardia (0/15 (0%) vs 8/16 (50%); RR 0.06, 95% CI 0.00 to 1.00; participants = 31; P value = 0.05; very-low-quality evidence); and bradycardia (0/15 (0%) vs 1/16 (6.25%); RR 0.35, 95% CI 0.02 to 8.08; participants = 31; P value = 0.52; very-low-quality evidence) (Bergdahl 1978). See Analysis 7.1.

Neurological adverse events

Lidocaine versus placebo or no intervention

Meta-analysis of three trials showed no significant differences between lidocaine and placebo or no intervention in terms of seizures (4/3248 (0.12%) vs 0/3263 (0%); RR 3.58, 95% CI 0.59 to 21.85; participants = 6481; I^2 = 0%; P value = 0.17) (ALIT 1985; Poprawski 1987; Rademaker 1986). Lidocaine, compared with placebo or with no intervention, increased significantly the risk of dizziness/drowsiness (74/1259 (5.88%) vs 16/1274(1.25%);

RR 3.85, 95% CI 2.29 to 6.47; participants = 2533; I^2 = 0%; low-quality evidence) (Hargarten 1990; Lie 1974; Lie 1978; NNLIT 1992; Pharand 1995; Rademaker 1986). Lidocaine and placebo or no intervention do not differ significantly regarding nausea/vomiting (30/245 (12.24%) vs 24/240 (10%); RR 1.62, 95% CI 0.45 to 5.89; participants = 485; I^2 = 64%; I^2 = 64%; P value = 0.46) (Pharand 1995; Rademaker 1986). Risk of speech disturbances is not statistically significant in the lidocaine group compared with the placebo or no intervention group (16/438 (3.65%) vs 1/431 (0.23%); RR 4.34, 95% CI 1.00 to 18.81; participants = 869; I^2 = 0%; P value = 0.05) (Lie 1974; Pharand 1995; Poprawski 1987; Rademaker 1986). Comparison groups did not differ in terms of confusion (17/3386 (0.50%) vs 6/3423 (0.17%); RR 2.44, 95% CI 0.76 to 7.81; participants = 6809; I^2 = 21%; P value = 0.13) (O'Brien 1973; Pharand 1995; Rademaker 1986) or agitation (3/186 (0.50%) vs 2/186 (0.17%); RR 1.35, 95% CI 0.26 to 7.06; participants = 372; I^2 = 0%; P value = 0.73) (Pharand 1995; Poprawski 1987). Two trials reporting overall neurological adverse events showed no significant differences between comparison groups (22/307 (7.17%) vs 11/295 (3.73%); RR 2.24, 95% CI 0.44 to 11.31; participants = 602; I^2 = 73%; P value = 0.33) (Dunn 1985; Pharand 1995). See Analysis 1.15.

Lidocaine versus disopyramide

No significant differences between comparison groups were noted in risk of confusion (3/35 (8.57%) vs 0/33 (0%); RR 6.61, 95% CI 0.35 to 123.30; participants = 68; P value = 0.21; very-low-quality evidence) (Ronnevik 1987). See Analysis 2.6.

Lidocaine versus mexiletine

Meta-analysis of two trials revealed very-low-quality evidence when lidocaine was compared with mexiletine regarding risk of composite neurological adverse events (nausea/vomiting, confusion, vertigo, nystagmus) (9/37 (24.32%) vs 17/37 (45.94%); RR 0.63, 95% CI 0.16 to 2.47; participants = 74; I^2 = 26%; P value = 0.51) (Horowitz 1981; Rolli 1981). See Analysis 4.4.

Lidocaine versus propafenone

Very-low-quality evidence was found when lidocaine was compared with propafenone regarding mental or neurological symptoms (6/38 (15.78%) vs 0/46 (0%); RR 6.95, 95% CI 0.86 to 55.94; participants = 84; I^2 = 0%; P value = 0.07) (Rehnqvist 1984; Touboul 1988). See Analysis 5.2.

Lidocaine versus amiodarone

No significant differences in risk of diplopia/sleepiness were noted between groups (1/15 (6.67%) vs 0/10 (0%); RR 2.06, 95% CI 0.09 to 46.11; participants = 25; P value = 0.65; very-low-quality evidence) (Capucci 1985). See Analysis 6.2.

Lidocaine versus dimethylammonium

One trial found very-low-quality evidence when lidocaine was compared with dimethylammonium regarding risks of nausea and vomiting (1/15 (6.66%) vs 7/16 (43.75%); RR 0.15, 95% CI 0.02 to 1.10; participants = 31; P value = 0.06); vertigo (1/156.67%) vs 0/16 (0%); RR 3.19, 95% CI 0.14 to 72.69; participants = 31; P value = 0.47) and paraesthesia (0/15 (0%) vs 7/16 (43.75%); RR 0.07, 95% CI 0.00 to 1.14; participants = 31; P value = 0.06) (Bergdahl 1978). See Analysis 7.1.

Lidocaine versus aprindine

Very-low-quality evidence was found when lidocaine was compared with aprindine in terms of coma (1/12 (8.33%) vs 0/12 (0%); RR 3.00, 95% CI 0.13 to 67.06; participants = 24; P value = 0.49); seizures (2/12 (16.67%) vs 0/12 (0%); RR 5.00, 95% CI 0.27 to 94.34; participants = 24; P value = 0.28); agitation (0/12 (0%) vs 2/12 (16.67%); RR 0.20, 95% CI 0.01 to 3.77; participants = 24; P value = 0.28) and disturbances of speech (2/12 (16.67%) vs 0/12 (0%); RR 5.00, 95% CI 0.27 to 94.34; participants = 24, P = 0.28) (Depaepe 1974). See Analysis 8.1.

Lidocaine versus pirmenol

One trial found very-low-quality evidence when lidocaine was compared with pirmenol regarding adverse events (5/9 (55.55%) vs 5/10 (50%); RR 1.11, 95% CI 0.47 to 2.60; participants = 19; P value = 0.81) (Cuendet 1988). See Analysis 9.1.

DISCUSSION

Summary of main results

This Cochrane systematic review on prophylactic lidocaine for myocardial infarction found 37 randomised controlled trials incorporating 11,948 participants. Trials reported comparisons between lidocaine versus placebo or no intervention, as well as versus eight antiarrhythmic drugs (i.e., disopyramide, tocainide, mexiletine, propafenone, amiodarone, dimethylammonium chloride, aprindine and pirmenol). Overall, trials had high risks of bias and were underpowered. Ninety-seven per cent of trials (36/37) did not report an a priori sample size estimation. Drug companies sponsored at least 10 trials, suggesting potential risk of industry bias. Trials were conducted in 17 countries (Australia, Belgium, Brazil, Canada, Denmark, France, Germany, Italy, New Zealand, Northern Ireland, Norway, Poland, Sweden, Switzerland, The Netherlands, United Kingdom and United States of America), in general in pre-hospital and/or hospital settings. Included participants had proven or non-proven acute myocardial infarction.

We were able to meta-analyse data for all-cause mortality. One meta-analysis of 18 trials involved participants with proven or non-proven acute myocardial infarction; investigators compared lidocaine versus placebo or no intervention and found no statistically significant differences between comparison groups (Summary of findings 1). A second meta-analysis combined two trials and compared lidocaine versus disopyramide. Researchers found no significant differences between antiarrhythmic drugs (Summary of findings 2). Non-pooled trials examining lidocaine versus tocainide or mexiletine did not differ significantly in terms of all-cause mortality (Summary of findings 3; Summary of findings 4, respectively).

We were able to meta-analyse data from 12 trials on cardiac mortality, which showed that lidocaine did not result in significant differences in cardiac mortality compared with placebo or no intervention (Summary of findings 1). Meta-analysis of two trials revealed no significant differences between lidocaine and disopyramide in reducing cardiac mortality (Summary of findings 2). Similarly, lidocaine did not differ significantly from tocainide and mexiletine in terms of cardiac mortality (Summary of findings 3; Summary of findings 4, respectively).

Lidocaine compared with placebo or no intervention, disopyramide, mexiletine and propafenone did not significantly reduce the proportions of participants developing ventricular fibrillation (Summary of findings 1; Summary of findings 2; Summary of findings 4; Summary of findings 5).

Lidocaine compared with placebo or no intervention significantly increased risks of asystole, drowsiness and dizziness (Summary of findings 1). No significant differences were noted between lidocaine and disopyramide, tocainide, mexiletine, propafenone, amiodarone, dimethylammonium and aprindine in terms of adverse events - cardiovascular or neurological (Summary of findings 1; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6; Summary of findings 7; Summary of findings 8). However, safety data were poorly reported overall, and adverse events may be underestimated. No trials reported data on overall survival at 30 days after myocardial infarction.

Overall completeness and applicability of evidence

This Cochrane review found evidence suggesting that prophylactic lidocaine for myocardial infarction is not useful in preventing all-cause mortality nor ventricular fibrillation. However, this conclusion is based on randomised controlled trials with high risk of bias. Furthermore, the safety profile of lidocaine is unclear from data reported in the included trials.

We conducted subgroup analyses of participants with proven acute myocardial infarction including administration route, infusion administration only compared with bolus and infusion administrations, bolus lidocaine dose, number of lidocaine boluses at any dose, intravenous infusion doses of lidocaine and clinical setting. Furthermore, we performed sensitivity analyses that included trials without risk of industry bias versus trials with risk of industry bias, while taking attrition into consideration. Both types of analyses were conducted for all-cause mortality. Results show consistency and are based on data from trials that included a broad range of participants with different co-morbidities, for whom different treatment approaches were provided. Although these aspects could be considered as a threat to applicability, consistency in results derived from our analyses shows that the included trials may represent a broad spectrum of patients with low and high risk of mortality.

We tried to identify all published and unpublished data, as well as ongoing studies, to warrant confidence in the completeness of data gathered in the review. However, we cannot rule out that calculated effects are overestimated as the result of poor methodological quality (design, analysis) and small sample size of randomised controlled trials. Furthermore, we cannot rule out an underestimation of safety findings.

Figure 5, Figure 7, Figure 8 and Figure 10 seem to present overly optimistic considerations regarding which intervention effects can be proved or disproved; these illustrations show that lidocaine could have effects that would be not only statistically significant but clinically significant as well. However, much larger trials are needed to prove or disprove these effects.

Quality of the evidence

Grades of Recommendation, Assessment, Development and Evaluation (GRADE) assessments were conducted on outcomes of meta-analyses and non-pooled trials. No trials were graded as providing strong evidence, primarily because small sample sizes were used (even after meta-analysis), and because studies were found to have high risk of bias due to lack of adequate randomisation methods, lack of blinding, high attrition, unclear reporting of outcomes and other biases such as industry bias and bias in the presentation of data. Furthermore, we graded evidence as low or very low in quality because of imprecision in clinically relevant outcomes.

See Summary of findings 1, Summary of findings 2, Summary of findings 3, Summary of findings 4, Summary of findings 5, Summary of findings 6, Summary of findings 7 and Summary of findings 8 for complete assessments and the rationale for ratings.

We suspected 10 trials to be at potential risk of industry bias (Bennett 1970; Bergdahl 1978; Chopra 1971; Depaepe 1974; Keefe 1986; Lie 1974; Pitt 1971; Rademaker 1986; Rossi 1976; Sbarbaro 1979). This review conducted a subgroup analysis of trials at risk of industry bias versus trials without risk of industry bias that examined lidocaine versus placebo or no intervention. Review authors were not able to detect significant differences between subgroups in risk of all-cause mortality (Analysis 1.9).

Trials with high risk of bias generate SPIN randomised controlled trials, which distort results presented by using specific reporting strategies, whatever their motive, to highlight that the experimental treatment is beneficial, despite a statistically non-significant difference for the primary outcome, or to distract the reader from statistically non-significant results when published reports of randomised controlled trials present such results for primary outcomes (Boutron 2010).

This Cochrane review has identified the following issues, which may be particularly relevant to consider as future trials are planned. Overall, information on all-cause mortality and cardiac mortality has been found to be inconsistent because included trials did not appropriately discriminate between participants with proven and non-proven myocardial infarction, and because investigators used different outcome definitions for 'ventricular arrhythmias' and reported outcomes inconsistently. Researchers should adopt an agreed upon set of core outcomes for each medical condition (Clarke 2007) with the goal of reducing the impact of outcome reporting bias (Kirkham 2010).

The impact of outcome reporting bias may be reduced if investigators adopt the recommendations of the Patient-Centered Outcomes Research Institute (PCORI) (PCORI 2012), an independent, non-profit organisation established by the US Congress to conduct research with the goal of providing information about the best available evidence required to make informed decisions. Research conducted by PCORI is intended to help patients better understand available prevention, treatment and care options, and the science that supports those options (Basch 2012; Gabriel 2012; Selby 2012).

Potential biases in the review process

A systematic review process involves a group of biases called 'significance-chasing biases', such as publication bias and selective outcome reporting bias (Ioannidis 2010). Publication bias represents a major threat to the validity of a systematic review, particularly a review that includes small trials. However,

this Cochrane review is at low risk of publication bias because a meticulous trial search was conducted by research authors, which ensured identification of randomised controlled trials reported in English and non-English languages. Also, review authors found no evidence of asymmetry in the funnel plot prepared for all-cause mortality among participants with proven or non-proven myocardial infarction (Figure 4; Figure 6) and ventricular fibrillation (Figure 9).

Selective outcome reporting bias is seen in suppression of information on specific outcomes and is similar to publication bias in whole studies or trials, in that 'negative' results remain unpublished (Ioannidis 2010). We were surprised to find that many trials did not provide data on all-cause mortality, ventricular fibrillation or safety. The authors of this Cochrane review observed that 38% of included randomised controlled trials are at high risk of selective outcome reporting. For example, adverse events were reported in nine trials comparing lidocaine versus placebo or no intervention, and all-cause mortality was reported in 18 trials assessing this comparison. This indicates that safety data for 50% (11,727/2) of randomly assigned participants in trials comparing lidocaine versus placebo or no intervention remain unknown.

Agreements and disagreements with other studies or reviews

Overall, our results are similar to those of other, non-Cochrane reviews (De Silva 1981; Hine 1989; MacMahon 1988; Sadowski 1999; Teo 1993). These five reviews differ from one another in their eligibility criteria, and from this Cochrane review in the following ways: (1) inclusion of non-randomised clinical trials by MacMahon 1988 (one; Singh 1976); Hine 1989 (two; Bleifeld 1973; Mogensen 1971 and Sadowski 1999 (three; Bleifeld 1973; Mogensen 1971; Singh 1976); (2) inclusion by MacMahon 1988 and Sadowski 1999 of one trial with bias in the presentation of data (Wyse 1988; this trial randomly assigned participants to lidocaine and placebo, but published results compared two approaches: prophylactic vs selective); (3) inability of Cochrane review authors to extract data from Kostuk 1969 and Sandler 1976 (because these trials were at high risk of selective outcome reporting, i.e. investigators did not report all-cause mortality or ventricular fibrillation data; however, both trials were included by Sadowski 1999); (4) inclusion by MacMahon 1988 and Sadowski 1999 of data from a trial with bias in the presentation of data (Wyse 1988; we considered this trial to have high risk of bias in selective outcome reporting for the above mentioned reason); (5) assessment by MacMahon 1988 of data from Dunn 1985 on lidocaine use through intramuscular and intravenous bolus; (6) publication bias of one meta-analysis due to exclusion of non-English language trials (Hine 1989); (7) inclusion by Cochrane review authors of head-to-head comparisons of lidocaine versus other antiarrhythmic drugs such as disopyramide, tocainide, mexiletine, propafenone, amiodarone, dimethylammonium chloride, aprindine and pirmenol; and, finally, (8) inclusion in this Cochrane systematic review of additional trials (not included in the non-Cochrane reviews) comparing lidocaine versus placebo or no intervention (Poprawski 1987; Rossi 1976; Solimene 1983; inclusion of these additional studies allowed us to obtain more accurate estimates for our outcomes of interest). Despite these differences, all systematic reviews have reached similar results for the most relevant outcomes, showing no significant effects derived from prophylactic lidocaine use on all-cause mortality, cardiac mortality and ventricular fibrillation. However, a limitation of this Cochrane review was introduced by trials that included participants both with and without myocardial infarction. Trial authors must report data on the entire study population and on those with proven myocardial infarction to reduce uncertainty.

AUTHORS' CONCLUSIONS

Implications for practice

This Cochrane review provides low-quality evidence to suggest that prophylactic lidocaine leads to very little or no effect on all-cause mortality and ventricular fibrillation following myocardial infarction. These results are based on 37 trials (11,948 participants) comparing lidocaine at any dosage and route of administration versus placebo or no intervention or antiarrhythmic drugs. Included trials showed no benefit for preventing death among individuals with acute myocardial infarction at low or high risk of death. Results are based on the findings of randomised controlled trials at high risk of bias, and safety data remain unclear. Therefore, we conclude that based on this systematic review and meta-analyses comparing lidocaine versus placebo, no intervention or other antiarrhythmic drugs, prescription of lidocaine prophylactically is not justified in acute myocardial infarction.

Implications for research

Trial sequential analysis suggests that no additional trials may be needed to disprove an intervention effect of 20% relative risk reduction for assessing benefits of prophylactic lidocaine in myocardial infarction. Smaller risk reductions might require higher trials. Potential trials should include clinical outcomes such as all-cause mortality, ventricular fibrillation and adverse events. Trials should be designed according to the SPIRIT statement (Chan 2013) and reported according to the CONSORT statement to improve the quality of reporting of efficacy and harms in clinical research (Ioannidis 2004 Moher 2010). Future trials should be planned in accordance with the recommendations of the Patient-Centered Outcomes Research Initiative (Basch 2012; Gabriel 2012; McKinney 2012).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

ALIT 1985

Study characteristics	
Methods	Parallel design (2 arms) Duration of the study: 33 months Country: The Netherlands Follow-up: unclear
Participants	Enrolled: 7026 Randomly assigned, N = 6024 • Lidocaine group: 2987 • Control group (not stated): 3037 Age, mean, years (standard deviation) • Lidocaine group: 66.0 (12.6) • Control group (not stated): 66.0 (12.32) Gender, male, % (n/N) • Lidocaine group: 57.7 (1724/2987) • Control group (not stated): 58.6 (1782/3037) Inclusion criteria: suspected to have acute myocardial infarction Exclusion criteria • Severe congestive failure • Pre-treatment with lidocaine • Heart rate < 45 bpm • Technical failure (refusal, equipment failure, misunderstanding of study procedure and so forth)
Interventions	Lidocaine: 400 mg, intramuscular route Control group: not stated
Outcomes	Mortality Incidence of ventricular fibrillation Frequent termination of ventricular tachycardia
Notes	Sample size calculation a priori: not reported Sponsor: The Netherlands Heart Fundation Role of sponsor: not reported Trial conduction dates: 16 September 1986 and 17 June 1983

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"...was thus randomized... " (page 1106)

ALIT 1985 *(Continued)*

		Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the allocation concealment process to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of ´'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...observers who were blinded to randomization" (page 1106)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Design bias (Porta 2008)

Baker 1971

Study characteristics	
Methods	Parallel design (2 arms) Country: England Follow-up period: 48 hours
Participants	Enrolled: 91 Randomly assigned: N = 44 (acute myocardial infarction within 48 hours before admission) • Lidocaine group: 47.72% (21/44) • Placebo (5% dextrose solution) group: 52.27% (23/44) Age, % (n/N) • Lidocaine group (≥ 50 years): 61.9 (13/21) • Placebo (5% dextrose solution) group (≥ 50 years): 65.21 (15/23) Gender, male, % (n/N) • Lidocaine group: 76.19 (16/21) • Placebo (5% dextrose solution) group: 86.95 (20/23) Inclusion criterion: patients with acute myocardial infarction Exclusion criteria • Heart rate < 60/min • Hepatic disease
Interventions	Lidocaine: continuous infusion of 1.5 mg of lidocaine per minute in 5% dextrose solution

Baker 1971 *(Continued)*

	Placebo: 5% dextrose solution: continuous infusion alone at same speed as intervention Co-intervention: "additional lidocaine, either as bolus injection or as increased infusion doses, was given to four patients" (page 53)
Outcomes	Mortality Incidence and types of dysrhythmias
Notes	Sample size calculation a priori: not reported Sponsor: not reported Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...numbered according to a randomized sequence" (page 2) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	"... cards in sealed envelopes number ..." (page 2) Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	" a double-blind trial" (page 1) Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified
Other bias	High risk	Design bias (Porta 2008)

Bennett 1970

Study characteristics

Methods	Parallel design (3 arms) Country: USA Follow-up period: 48 hours
Participants	Randomly assigned: N = 374 • Lidocaine: 249/374 • Group A (lidocaine infusion at 0.5 mg/min): 118/249 • Group B (lidocaine infusion at 1 mg/min): 131/249

Bennett 1970 *(Continued)*

- Control (not reported): 125/374

Age ≥ 50 years, %

- Lidocaine: 73.9
- Control: 95.2

Age < 50 years, %

- Lidocaine: 26.1
- Control: 4.8

Gender, male, %: 70

Inclusion criteria

- Age, years: 31 to 90
- Suspicion of recent infarction on clinical grounds

Exclusion criteria

- Severe left ventricular failure
- Shock (systolic pressure < 80 mmHg; clinical evidence of poor peripheral perfusion)
- Second- or third-degree heart block
- Sinus or nodal bradycardia < 50/min
- Any patient who already had ventricular fibrillation or tachycardia before the trial could start

Interventions	Lidocaine (2 arms) • Lidocaine 60 mg intravenously on admission to the trial, followed by lidocaine 0.5 mg/min by constant infusion • Lidocaine 60 mg intravenously on admission to the trial, followed by lidocaine 1 mg/min Placebo: quote "no lidocaine" (page 910). Nature of control not reported Co-intervention: not described
Outcomes	Mortality Incidence of ventricular arrhythmias
Notes	Sample size calculation a priori: not reported Sponsor: Astra Chemicals Ltd Role of sponsor: not reported Trial conduction data: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Prearranged code held by a member of nursing staff" (page 910) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information about the blinding process to permit judgement of 'low risk' or 'high risk'

Bennett 1970 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about the blinding process to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal from study, % (n/N) • Overall: 17 (63/374) • Group A: 19.4 (23/118) • Group B: 16 (21/131) • Control group: 15.2 (19/125) Reasons • Sinus or functional bradycardia: group A (N = 4), group B (N = 3), group C (N = 4); total = 11 • Second-degree atrioventricular block: group A (N = 4), group B (N = 6), group C (N = 5); total = 15 • Complete atrioventricular block: group A (N = 4), group B (N = 3), group C (N = 2); total = 9 • Pulmonary oedema:group A (N = 6), group B (N = 7), group C (N = 6); total = 19 • Shock: group A (N = 5), group B (N = 2), group C (N = 2); total = 9
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Design bias (Porta 2008) Industry bias

Bergdahl 1978

Study characteristics	
Methods	Parallel design (2 arms) Country: Sweden Follow-up period: unclear
Participants	Randomly assigned: N = 31 • Lidocaine group: 48.8% (15/31) • Dimethylammonium chloride group: 51.6% (16/31) Age ≥ 50 years, % (n/N) • Lidocaine: 93.3 (14/15) • Dimethylammonium chloride group: 93.8 (15/16) Age < 50 years, % (n/N) • Lidocaine: 6.6 (1/15) • Dimethylammonium chloride group: 6.2 (1/16) Gender, male, % (n/N) • Total group: 90.3 (28/31) • Lidocaine: 86.6 (13/15)

Bergdahl 1978 *(Continued)*

	• Dimethylammonium chloride group: 93.7 (15/16) Inclusion criterion: ventricular arrhythmias had not been controlled or recurred 0.5 to 24 hours after initiation of lidocaine treatment Exclusion criteria (1 of the following) • Heart rate < 60 beats/min • Manifest left ventricular failure • Shock • Systolic blood pressure < 90 mmHg • Atrial flutter or fibrillation • Second- or third-degree heart block
Interventions	Lidocaine group: 50 mg (bolus) and infusion at 3 mg/min Dimethylammonium chloride: infusion (600 mg in 200 mL saline solution). Infusion time: 30 minutes; first 3 participants; and 60 minutes; next 13 participants Co-interventions: oxygen 4 Lts/min (nasal catheter), hydromorphone or pentazocine (endovenous) for relief pain
Outcomes	Type and frequency of side effects
Notes	A priori sample size estimation: not reported Sponsor: Hässle AB, Gothenburg Sweden Role of sponsor: supplied the drugs studied and performed the analysis of plasma drug concentrations Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were allocated randomly" (page 311) Insufficient information to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal from study • Overall: 23% (7/31) • Reason: blood pressure fall • Lidocaine group: 25% (4/15) • Dimethylammonium chloride group: 19% (3/16)
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome that would be expected to have been reported for such a study

Bergdahl 1978 *(Continued)*

		Comments: This study did not include important outcomes (mortality and ventricular fibrillation)
Other bias	High risk	Design bias (Porta 2008) Industry bias

Capucci 1985

Study characteristics	
Methods	Parallel design (2 arms) Country: Italy Follow-up period: not reported
Participants	Randomly assigned: N = 25 • Lidocaine: 60% (15/25) • Amiodarone: 40% (10/25) Age, years, mean (standard deviation not reported) • Lidocaine group: 57.8 • Amiodarone group: 58.9 Gender, male, % (n/N) • Lidocaine group: 66.6 (10/15) • Amiodarone group: 80 (8/10) Inclusion criteria • Age < 70 years old • Acute myocardial infarction • Chest pain < 12 hours • Ventricular arrhythmia class 2 (Lown's classification): complex ventricular extrasystole, ventricular tachycardia and persistent ventricular tachycardia Exclusion criteria • Heart rate < 50/min • Atrioventricular block II and III grade • Hypokalemia • Ventricular failure • Blood pressure ≤ 95 mmHg • Torsade de pointes
Interventions	Lidocaine group: initial bolus of 1 mg/kg, in a pump infusion at a dose of 10 mg/min for 20 minutes. Maintenance dose of 1.5 mg/min Amiodarone group: initial bolus of 5 mg/kg in 2 minutes followed by a second bolus of 150 mg after 3 minutes (if previous dose was insufficient). Maintenance dose: 1.8 g/24 hours in continuous infusion pump Co-intervention: defibrillation
Outcomes	Number and type of ventricular premature beats Number and duration of episodes of ventricular tachycardia

Capucci 1985 *(Continued)*

	Appearance of ventricular fibrillation Blood pressure at baseline, every 2 minutes to 10 minutes from beginning of infusion, every 5 minutes from 11 to 60 minutes, every 2 hours in the remaining 23 hours Symptoms and/or clinical signs of congestive heart failure Electrocardiographic parameters at baseline, at 60 minutes and 24 hours after infusion of the drug
Notes	A priori sample size estimation: not reported Sponsor: not reported Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome that would be expected to have been reported in such a study Comments: This study did not report mortality
Other bias	High risk	Design bias (Porta 2008)

Chopra 1971

Study characteristics

Methods	Parallel design (2 arms) Country: Canada Follow-up period: unclear
Participants	Enrolled: 805 Randomly assigned: N = 82 • Lidocaine group: 47.56% (39/82) • Control (normal saline solution) group: 52.43% (43/82)

Chopra 1971 *(Continued)*

	Age, years • Total group: 52.5 (33 to 72) • By comparison groups: not reported Gender, male, % (n/N) • Total group: 76.82 (63/82) • By comparison groups: not reported Inclusion criteria (≥ 1 of the following types of ventricular ectopic activity within 72 hours of infarction) • Unifocal ectopics at a rate > 5/min • ≥ 2 but < 5 consecutive ectopics • Multi-focal ectopics • Ectopic occurring during "vulnerable period" of preceding beat Exclusion criteria • Circulatory shock • Cardiac failure • Cardiac arrest • Any other arrhythmias
Interventions	Lidocaine group Single rapid intravenous injection of 50 mg of lidocaine (first bolus) • If ectopic activity was still present 5 minutes after, 100 mg of lidocaine (second bolus) injected • If ectopic activity was suppressed by first or second bolus, continuous intravenous infusion of 1000 mg of lidocaine added to 480 mL of 5% dextrose solution was administered at a rate of 1 mg/min • If ectopic activity recurred after start of the infusion, drip rate was increased to 2 mg/min Infusion was continued for 24 hours and then tapered off by a reduction of the infusion rate to half the previous rate for 2 hours. In participants whose ectopic activity was not suppressed by first or second bolus, no further treatment was given Placebo: normal saline solution under the same parameters as for the intervention group Co-interventions: not reported
Outcomes	Mortality Incidence of major ventricular arrhythmias Effectiveness of intravenous lidocaine in suppressing ventricular ectopic activity after acute myocardial infarction
Notes	Sample size calculation a priori: not reported Sponsor: Pharmaceutical Manufacturing Co. Ltd. Role of sponsor: supplied lidocaine, saline ampoules and randomisation code Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	" ... according to a randomised numerical code, ... " (page 668) Insufficient information to permit judgement of 'low risk' or 'high risk'

Chopra 1971 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "the present double-blind trial" (page 668) Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome that would be expected to have been reported for such a study Comment: This study did not discuss safety
Other bias	High risk	Design bias (Porta 2008) Industry bias

Cuendet 1988

Study characteristics	
Methods	Parallel design (2 arms) Country: Switzerland Follow-up period: 24 hours
Participants	Randomly assigned: N = 19 • Lidocaine group: 47.3% (9/19) • Pirmenol group: 52.6% (10/19) Age, years, mean (SE or SD) • Total group: 57.4 (9.1) • By comparison group: not reported Gender, male, % (n/N) • Total group: 95 (18/19) • By comparison group: not reported Inclusion criteria • Presence of ≥ 2 premature ventricular contractions/min • R/T premature ventricular contractions • ≥ 2 polymorphic premature ventricular contractions/5 min Exclusion criteria: not reported
Interventions	Lidocaine, infusion at mean dose of 42 (8.8) µg/min/kg Pirmenol, infusion at mean dose of 6.1 (1.6) µg/min/kg

Cuendet 1988 *(Continued)*

	Co-interventions: not reported
Outcomes	Prevalence of ventricular arrhythmias (non-ventricular fibrillation). Safety
Notes	A priori sample size estimation: no Sponsor: not reported Data were taken from "Resumés du XVIII. Congres de l Union Therapeutique Internationale" (date: unclear)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	" ...have been randomised..." (page 158) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the allocation concealment process to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double blind randomized study" (page 158) Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome that would be expected to have been reported in such a study Comment: This study did not report mortality and ventricular fibrillation ≥ 1 outcomes of interest in the review are reported incompletely, so they cannot be entered into a meta-analysis Quote: "...side effects have been observed in 10 pts, 5 in each group, but interruption of treatment was not necessary" (page 158)
Other bias	High risk	Design bias (Porta 2008) Bias in presentation of data (Porta 2008)

Darby 1972

Study characteristics

Methods	Parallel design (2 arms) Country: United Kigndom Follow-up period: 48 hours

Darby 1972 *(Continued)*

Participants	Enrolled: 322 Randomly assigned: N = 203 • Lidocaine group: 50.73% (103/203) • Control group: 49.26% (100/203) Age, years: not reported Gender, male, %: 79.3 (both groups) Inclusion criterion: myocardial infarction in preceding 48 hours Exclusion criteria • Blood pressure < 90 mmHg • Bradycardia < 50/min • Atrioventricular block of second or third degree • Pulmonary oedema
Interventions	Lidocaine: 200 mg, intramuscular Injection in emergency department, and infusion of 2 mg lidocaine/min for 48 hours on arrival at the coronary care unit Control: no routine antiarrhythmic treatment; no details supplied Co-intervention: not stated
Outcomes	Mortality Incidence of ventricular arrhythmias (ventricular extrasystole, ventricular fibrillation, ventricular tachycardia)
Notes	Sample size estimation a priori: not reported Sponsor: not reported Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...randomly consigned..." (page 818) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal from study Lidocaine group: 11% (11/103) Reasons • Cardiogenic shock: N = 4

Darby 1972 *(Continued)*

		• Profound sinus bradycardia: N = 3 • Pressure on beds: N = 4 Control group: no reported withdrawal
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Design bias (Porta 2008)

Depaepe 1974

Study characteristics	
Methods	Parallel design (2 arms) Country: Belgium Follow-up period: 3 days
Participants	Randomly assigned patients: N = 24 • Lidocaine group: 50% (12/24) • Aprindine: 50% (12/24) Age, years, mean (standard error) • Lidocaine group: 58.92 (2.90) • Aprindine group: 58.42 (3.81) Gender, male, % (n/N) • Lidocaine group: 83.3 (10/12) • Aprindine: 75 (9/12) Inclusion criterion: Participants with acute myocardial infarction confirmed by cardiac enzyme dosage (creatinine phosphokinase, serum glutamic oxaloacetic transaminase, lactate dehydrogenase but not troponin) and for which symptoms occurred within 36 hours Exclusion criteria (≥ 1 of the following were present) • Patients with cardiogenic shock or requiring advanced resuscitation techniques before admission to the coronary care unit
Interventions	Lidocaine, hours 0 to 0.5: 2 mg/min = 60 mg 0.5 to 24: 2 mg/min = 2800 mg 24 to 48: 2 mg/min = 2800 mg 48 to 72: 2 mg/min = 2800 mg Aprinidine, intravenously, hours 0 to 0.5: 2 mg/min = 200 mg 0.5 to 24: 2 mg/min = 200 mg 24 to 48: 2 mg/min = 200 mg 48 to 72: 2 mg/min = 200 mg

Depaepe 1974 *(Continued)*

	Co-intervention: not reported
Outcomes	Mortality Safety
Notes	Sample size estimation a priori: not reported Sponsor: A. Christiaens, S.A. Role of sponsor: aprindine provided freely by Christiaens Pharmaceutical Company Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...were randomly divided in two groups" (page 412) Comment: They used a random number table
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals from study Lidocaine group: 10% (1/10) Reasons Neurological coma
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon) Comment: This trial did not report ventricular fibrillation
Other bias	High risk	Design bias (Porta 2008) Industry bias

Dunn 1985

Study characteristics

Methods	Parallel design (2 arms) Country: Northern Ireland Follow-up period: not reported
Participants	Randomly assigned: N = 425

Dunn 1985 *(Continued)*

Withdrawal from study: 7.3% (31/425)

Eight participants who had a proved myocardial infarction did not enter the study (page 354). Twenty-three patients did not fulfil entry criteria

Analysed, % (n/N)

- Lidocaine group: 51.49 (207/402)
- Placebo (normal saline) group: 48.50 (195/402)

Age: 56 years (both groups); not reported by comparison groups

Gender, male, % (n/N)

- Total group: 71.14 (286/402)
- By comparison group: not reported

Inclusion criteria

- Suspected acute myocardial infarction
- Age < 70 years
- Assessed within 6 hours of onset of symptoms

Exclusion criteria (≥ 1 of the following was present)

- Heart rate ≤ 50 bpm
- Heart rate ≥ 100 bpm after pain relief
- Systolic blood pressure ≤ 80 mmHg after pain relief
- Acute pulmonary oedema
- Second-degree or complete atrioventricular block
- Sustained ventricular tachycardia
- Ventricular fibrillation
- Prior therapy with antiarrhythmic agents but excluding beta-blockers or digoxin

Interventions	Lidocaine, 300 mg, intramuscular route, followed by lidocaine, 100 mg, by intravenous bolus over 3 minutes Placebo: normal saline (equivalent volume of normal saline)
Outcomes	Incidence of ventricular fibrillation, sustained ventricular tachycardia, warning arrhythmias Incidence of central nervous system side effects, hypotension, tachycardia, bradycardia, asystole
Notes	Sample size calculation a priori: not reported Sponsor: not reported Trial conduction dates: November 1981 to February 1983

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	" ...we undertook a double-blind randomised trial..." (page 354) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'

Dunn 1985 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals from study: 7.3% (31/425) Eight patients who had a proved myocardial infarction did not enter the study (page 354) Twenty-three patients did not fulfil entry criteria • Heart rate > 110 bpm before receipt of trial drug: 9 • Taking oral antiarrhythmic (mexiletine, amiodarone) before the study: 7 • Age > 70 years: 3 • Delay in time > 6 hours: 1 • Other reasons: 2 Comment: Trial authors did not report lost participants by comparison group
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Bias of presentation data, design bias (Porta 2008)

Hargarten 1990

Study characteristics	
Methods	Parallel-design (2 arms) Country: USA Follow-up: unclear
Participants	Randomly assigned: N = 1427 • Lidocaine group: 49.33% (704/1427) • Control group: 50.66% (723/1427) Age, years, mean (standard error or standard deviation unclear) (total group) • Male: 62.1 (13.7) • Female: 67.5 (14.2) Gender, male, % (n/N) Total group: 50.17 (716/1427) Inclusion criteria • ≥ 18 years of age • Chest pain of suspected cardiac origin Exclusion criteria

Hargarten 1990 *(Continued)*

	• Warning arrhythmias • Second- or third-degree heart block • Bradycardia < 50 • Hypotension < 90 mmHg • Known allergy to lidocaine
Interventions	Lidocaine, intravenous (IV), initial bolus of 1 mg/kg; simultaneous 2 mg/min IV drip to maintain therapeutic blood levels. Ten minutes after first dose of lidocaine, second bolus of 0.5 mg/kg to prevent decrease to below therapeutic range Control group: not detailed Co-intervention: not reported
Outcomes	Incidence of sudden death Incidence of warning arrhythmia
Notes	Sample size calculation a priori: not reported Sponsor: not reported Trial conduction dates: January 1984 to January 1988

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"... was generated from a table of numbers from the Minitab software package of Perkin-Elmer 3230 Supermini Computer" (page 82)
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Bias in presentation data (Porta 2008)

Horowitz 1981

Study characteristics

Methods	Parallel design (2 arms)

Horowitz 1981 *(Continued)*

	Country: Australia Follow-up period: 48 hours
Participants	Randomly assigned: N = 24 • Lidocaine group: 50% (12/24) • Mexiletine group: 50% (12/24) Age, years, mean (standard error) • Lidocaine group: 60 (4) • Mexiletine group: 59 (3) Gender, male, % (n/N) • Lidocaine group: 75 (9/12) • Mexiletine group: 75 (9/12) Inclusion criteria • Suspected or proven acute myocardial infarction • Ventricular tachycardia • Ventricular fibrillation developing within 48 hours of onset of chest pain Exclusion criteria • Evidence of atrioventricular conduction delay • Supraventricular tachycardia • Left ventricular failure • Administration af any antiarrhythmic agent or β-adrenoceptor antagonist in the preceding for 48 hours
Interventions	Lidocaine: 100 mg/bolus, infusion of 3 mg/min for 1 hour; thereafter, reduced to 2 mg/min after 1 hour Mexiletine: 200 mg/bolus, infusion of 1 mg/min for 1 hour; thereafter, reduced to 0.5 mg/min after 1 hour Co-interventions: electroversion, bolus of mexiletine (200 mg) or lidocaine (100 mg) (page 410)
Outcomes	Ocurrence of complex ventricular tachyarrhythmia Comment: Trial did not assess the outcome explicitly
Notes	Sample size calculation a priori: not reported Sponsor: Austin Hospital Research Foundation Role of sponsor: support of the study Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"... were randomised and allocated to receive..." (page 410) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the allocation concealment process to permit judgement of 'low risk' or 'high risk'

Horowitz 1981 *(Continued)*

		"Patients who had persisted multifocal ventricular extrasystoles or ventricular tachycardia or ventricular fibrillation... were given additional bolus of 200 mg of mexiletine or 100 mg of lignocaine" (page 410) This trial did not report whether the co-intervention (additional bolus) was allocated concealment or not
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal from study, % (n/N) • Overall: 29.1 (7/24) • Lidocaine: 25 (3/12) • Mexiletine: 33 (4/12) Reasons 1. Cardiogenic shock (mexiletine: 1) 2. Pulmonary oedema (mexiletine: 2/lidocaine group: 2) 3. 2:1 atrioventricular block (mexiletine: 1) 4. Severe vomiting, nausea and confusion (lidocaine: 1)
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon) Comment: This trial did report safety Quote: "the greater efficacy of mexiletine was not associated with increased drug toxicity" (page 409)
Other bias	High risk	Design bias and bias in presentation of data (Porta 2008)

Keefe 1986

Study characteristics	
Methods	Parallel design (2 arms) Follow-up: 48 hours Country: USA
Participants	Randomly assigned: N = 29 • Lidocaine group: 44.8% (13/29) • Tocainide group: 55.17% (16/29) Age, years, mean (SD) • Total group: 58 (39 to 73) • Lidocaine group: 52 (9) • Tocainide group: 62 (9)

Keefe 1986 *(Continued)*

	Gender, male, % (n/N) • Total group: 68.96 (20/29) • Lidocaine group: 76.92 (10/13) • Tocainide group: 62.5 (10/16) Inclusion criterion: acute myocardial infarction Exclusion criteria • Ventricular arrhythmias • Clinically significant abnormal laboratory values other than cardiac enzymes • Second- or third-degree atrioventricular block • Sick sinus syndrome • Atrial flutter • Fibrillation or atrial tachycardia • Patients with permanent or temporary pacemakers
Interventions	Lidocaine, 100 mg over 2 minutes, was given, followed by 60 mg over 15 minutes, then 1000 mg every 6 hours for 48 hours; additional bolus of 100 mg could be given for breakthrough arrhythmias and the maintenance dose of lidocaine reduced to 1000 mg over 8 hours for signs of toxicity, for 3 to 7 days Tocainide, 250 mg over 2 minutes, 500 mg over 15 minutes, then 500 mg every 6 hours for 48 hours; bolus of 250 mg of tocainide could be given for breakthrough arrhythmias and the infusion lengthened to 500 mg over 8 hours for signs of toxicity, for 3 to 7 days Co-interventions: oxygen by nasal cannula, subcutaneous heparin, nitroglycerin, morphine sulphate and furosemide
Outcomes	Prophylaxis of ventricular arrhythmias
Notes	Sample size calculation a priori: not reported Sponsor: Merck Sharp and Dohme, West Point, Pennsylvania Role of sponsor: not reported Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"... with a randomized block sign design with two treatment groups" (page 528) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'

Keefe 1986 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal from study Overall: 24.13% (7/29): "Of the 29 patients who entered the study, 22 completed the infusion portion of the study and 18 entered the oral phase..." (page 528) On page 530, table III, this was reported: "withdrawn because of adverse effects" 1. Tocainide:13% (2/16) 2. Lidocaine: 8% (1/13) Inconsistency is evident between information published on page 528 and page 530 regarding withdrawal
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Design bias (Porta 2008) Bias in the presentation of data (Porta 2008) Industry bias

Kostuk 1969

Study characteristics	
Methods	Parallel design (2 arms) Country: Canada Follow-up: 48 hours
Participants	Enrolled: 95 Randomly assigned: N = 65 • Lidocaine group: 52.3% (34/65) • Placebo (5% glucose in water) group: 48% (31/65) Age: not stated Gender: not stated Inclusion criteria: acute myocardial infarction Exclusion criteria • Acute pulmonary oedema • Cardiogenic shock • Arrhythmia
Interventions	Lidocaine 1 mg/min (infusion rate) Placebo: 5% glucose in water (at similar infusion rate) Co-intervention: not reported
Outcomes	Prophylactic benefit in prevention of ventricular arrhythmias

Kostuk 1969 *(Continued)*

Notes	Source of data: abstract of scientific sessions Sample size calculation a priori: not reported Sponsor: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"in random fashion..." (page III-125) Insufficient information to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Pts received, unknown to the nurses, either..." (page III-125) 'pts' means patients
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome that would be expected to have been reported for such a study Comments: This trial does not report mortality, ventricular fibrillation
Other bias	High risk	Design bias (Porta 2008)

Kuck 1985

Study characteristics

Methods	Parallel design (2 arms) Country: Germany Follow-up period: unclear
Participants	Randomly assigned: N = 49 • Lidocaine group: 46.9% (23/49) • Control group: 53.06% (26/49) Age, years, mean (standard error or deviation not reported explicitly) • Lidocaine group: 56 (11) • Control group: 58 (11) Gender, male, % (n/N) • Total group: 85.7 (42/49)

Kuck 1985 *(Continued)*

	• Lidocaine group: 91.3 (21/23) • Control group: 80.7 (21/26) Inclusion criterion: patients with acute myocardial infarction Exclusion criterion: not stated
Interventions	Lidocaine, initial bolus of 200 mg following intravenous infusion of 2 mg/min Control: no lidocaine; no details were stated Co-intervention: intracoronary thrombolysis
Outcomes	Prophylactic of ventricular tachyarrhythmias following recanalisation of an occluded coronary artery
Notes	Sample size calculation a priori: not reported Sponsor: not reported Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...were randomized into two groups..." (page 807) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome that would be expected to have been reported for such a study Comments: This trial reported neither mortality nor ventricular fibrillation
Other bias	High risk	Design bias (Porta 2008)

Lie 1974

Study characteristics

Methods	Parallel design (2 arms) Country: The Netherlands Follow-up period: 48 hours

Lie 1974 *(Continued)*

Participants	Enrolled: 225 Randomly assigned: N = 212 • Lidocaine group: 50.4% (107/212) • Control (5% glucose and water) group: 49.5% (105/212) Age, years, mean • Lidocaine group: 58.1 • Control (5% glucose and water) group: 59 Gender, male, % (n/N) • Lidocaine group: 78.5 (84/107) • Control (5% glucose and water) group: 79.04 (83/105) Inclusion criteria • Patients < 70 years • Within 6 hours of onset of symptoms • Typical Q waves and evolutionary ST-T changes in electrocardiogram • Creatine phosphokinase, glutamic oxalacetic transaminase and lactic dehydrogenase increased levels Exclusion criteria • Congestive heart failure • Cardiogenic shock • Complete atrioventricular block • Persistent ventricular tachycardia or ventricular fibrillation
Interventions	Lidocaine, initial bolus of 100 mg, followed by infusion of 3 mg/min Placebo: 5% glucose and water Co-interventions: defibrillation
Outcomes	Preventing primary ventricular fibrillation
Notes	Sample size calculation a priori: not reported Sponsor: Ottenvanger (Astra) Pharmaceutical Role of sponsor: not reported Trial conduction dates: June 1973 to September 1974

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"... on the basis of randomization" (page 1324) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the allocation concealment process to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias)	Low risk	"The patients were not informed whether they might or might not receive lidocaine..." (page 1324)

Lie 1974 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about the blinding assessors to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals from the study Post randomisation Overall: 6% (13/212) Reasons • Congestive heart failure: N = 4 • Cardiac rupture: N = 2 • Complete AV block: N = 4 • Bradycardia: N = 3
Selective reporting (reporting bias)	High risk	One clinically relevant and reasonably expected outcome (mortality) was not reported, and data on that outcome were likely to have been recorded Comment: Side effects in control group were not reported
Other bias	High risk	Design bias (Porta 2008) Industry bias

Lie 1978

Study characteristics	
Methods	Parallel design (2 arms) Country: The Netherlands Follow -up: 1 hour
Participants	Enrolled: 321 Randomly assigned: N = 300 • Lidocaine group: 147 • Control (sodium chloride 0.65% and water in deltoid muscle) group: 153 Age, years • Lidocaine group: 58.8 • Control (sodium chloride 0.65% and water in deltoid muscle) group: 57.1 Gender, male, % (n/N) • Lidocaine group: 80.27 (118/147) • Control (sodium chloride 0.65% and water in deltoid muscle) group: 74.4 (117/153) Inclusion criteria • Patients < 70 years old within 6 hours of onset of symptoms of acute myocardial infarction • History of chest pain correlated with typical electrocardiographic changes (new Q waves and loss of R wave voltage) • Serial rise in serum enzyme values, creatine phosphokinase, glutamic oxalacetic transaminase and lactic dehydrogenase

Lie 1978 *(Continued)*

	Exclusion criteria • Patients with bradycardia with a ventricular rate < 50 beats/min • Pulmonary congestion • Complete atrioventricular block • Persistent ventricular tachycardia or fibrillation
Interventions	Lidocaine group: lidocaine 300 mg intramuscular in a 10% solution Placebo: "sodium chloride 0.65 percent and water in the deltoid muscle..." (page 487)
Outcomes	Incidence of major ventricular arrhythmias Mortality
Notes	Sample size calculation a priori: not reported Sponsor: not reported Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...randomized patients received..." (page 487) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the allocation concealment process to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The nature of the injected solution was unknown to the medical and nursing staff" (page 487)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawls from the study • Post randomisation: The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Design bias (Porta 2008)

NNLIT 1992

Study characteristics

Methods	Parallel design (2 arms) Country: Norwegian countries

NNLIT 1992 *(Continued)*

	Follow-up period: 3 hours
Participants	Enrolled: 204 Randomly assigned: N = 197 • Lidocaine group: 48.7% (96/197) • Placebo (physiological saline solution) group: 51.2% (101/197) Proved diagnosis of acute myocardial infarction: 63% (125/197) • Lidocaine group: 68% (65/96) • Placebo (physiological saline solution) group: 59.1% (60/101) Age ≥ 50 years, % (n/N) • Lidocaine group: 22.9 (22/96) • Placebo (physiological saline solution) group: 18.8 (19/101) Age < 50 years, % (n/N(• Lidocaine group: 76.04 (73/96) • Placebo (physiological saline solution) group: 81.1 (82/101) Gender, male, % (n/N) • Lidocaine group: 76 (73/96) • Placebo (physiological saline solution) group: 74 (71/101) Inclusion criteria: suspected of myocardial infarction Exclusion criteria • Symptoms lasting > 6 hours • Pulse rate < 45 bpm • Systolic blood pressure < 85 mmHg • Pulmonary oedema • Preexisting antiarrhythmic treatment with drug other than β-blockers, calcium antagonist, or digitalis • Indication for treatment of manifest arrhythmias with lidocaine • Patient refusal to participate
Interventions	Lidocaine, 100 mg, intravenous bolus, followed by 300 mg intramuscular injection Placebo group: physiological saline solution Co-interventions: defibrillation, thrombolytic and streptokinase therapy
Outcomes	Prevention of ventricular fibrillation
Notes	Sample size calculation a priori: yes (Berntsen 1991) This trial was stopped early ("the study had to be terminated at this time") (page 1479) Sponsor: Norwegian Council on Cardiovascular Disease and the Laerdal Fundation. Role of sponsor: not reported Trial conduction dates: 19 March 1988 to 12 July 1991

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	" randomly allocated... " (page 1479)

NNLIT 1992 *(Continued)*

		Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The nature of the trial material contained in each packet was unknown to all involved parties" (page 1479)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals from the study, % (n/N) • Overall: 3.6 (7/197) • Lidocaine group: 5.2 (5/96) • Placebo (physiological saline solution) group: 1.98 (2/101)
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Design bias (Porta 2008)

O'Brien 1973

Study characteristics	
Methods	Parallel design (2 arms) Country: New Zealand Follow-up period: 48 hours
Participants	Randomly assigned: N = 300 • Lidocaine group: 51.3% (154/300) • Control (5% dextrose solution) group: 48.7% (146/300) Age: not reported Gender (male): not reported Inclusion criterion: proven myocardial infarction Exclusion criteria • Known ventricular fibrillation • Known ventricular tachycardia • Cardiac arrest before admission
Interventions	Lidocaine, 75 mg, first bolus. Infusion 2.5 mg/min in 5% dextrose at 1 mL/min Placebo: 5% dextrose solution Co-intervention: not reported
Outcomes	Reducing the frequent of ventricular fibrillation and ventricular tachycardia

O'Brien 1973 *(Continued)*

Notes	Sample size calculation a priori: not reported Sponsor: not reported Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"allocation.... by means of random selection" (page 36) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk' Comments: This was described as double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Design bias (Porta 2008)

Pedersen 1986

Study characteristics

Methods	Parallel design (2 arms) Country: Denmark Study phase: III Follow-up: 12 hours
Participants	Randomly assigned: N = 76 • Lidocaine group: 38 • Disopyramide group: 38 Age, years • Lidocaine group: not described • Disopyramide: not described • Total group (mean): 65 Gender: not stated Inclusion criteria

Pedersen 1986 *(Continued)*

- Patients admitted to Bispebjerg Coronary unit under suspicion of myocardial infarction. Presumably if the referring doctor (e.g. the GP) suspected this, or if patients had chest pain, called 911 and admitted by ambulance
- Ventricular arrhythmia (defined as 1 of the criteria below)
- > 10% ventricular extra-systoles for > 5 minutes
- Mulifocal ventricular extra-systoles ≥ 1 minute
- Ventricular extra-systoles with R-on-T phenomenon
- Ventricular tachycardia
- Ventricular fibrillation

Exclusion criteria

- Pulmonary oedema
- Heart failure class IV
- Systolic blood pressure < 80 mmHg
- Heart frequency < 50/min after atropine
- Atrioventricular blockage grade II or III
- Internal pacemaker
- Glaucoma
- Uremia (not defined)
- Current antiarrhythmic treatment

Interventions	Disopyramide (Norpace): bolus injection 150 mg + infusion 24 mg/h. Infusion regulated depending on effect and side effects to between 30 to 90 mL/h Lidocaine: bolus injection 100 mg + infusion 100 mg/h. Infusion regulated depending on effects and side effects to between 30 to 90 mL/h Co-interventions: not stated
Outcomes	Not defined in Methods Ventricular extrasystoles Death
Notes	A priori sample size estimation: no Sponsor: not stated Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"...double blind study plan" (page 1) Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'

Pedersen 1986 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss after lidocaine: 7.89% (3/38) Loss after disopyramide: 5.26% (2/38)
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified
Other bias	High risk	Design bias (Porta 2008)

Pharand 1995

Study characteristics	
Methods	Parallel design (2 arms) Country: USA Follow-up: 40 hours
Participants	Randomly assigned: N = 200 • Lidocaine: 100 • Placebo (5% dextrose in water): 100 Age, years, mean (standard deviation) • Lidocaine: 61 (12) • Placebo (5% dextrose in water): 61 (12) Gender, male, % (n/N) • Total: 78 (155/200) • Lidocaine: 80 (80/100) • Placebo (5% dextrose in water): 75 (75/100) Inclusion criteria • < 6 hours of onset of symptoms • Chest pain accompanied by ST-segment elevation ≥ 2 mm in 2 contiguous leads • Killip class I or II Exclusion criteria • > 6 hours after onset of symptoms • Killip class III or IV • Refusal to participate • Use of antiarrythmic agents, except for β-blockers and calcium channel blockers • Liver disease • Lidocaine allergy
Interventions	Lidocaine 2 gr in 500 mL of 5% dextrose in water: infusion for a period of 40 hours Placebo: 5% dextrose in water Co-intervention group: Quote: "As a part of the standard practice in the Emergency Department of our hospital, patients received an intravenous lidocaine bolus" (page 472)

Pharand 1995 *(Continued)*

Outcomes	Efficacy and safety for prophylaxis of ventricular arrhythmias in patients with uncomplicated acute myocardial infarction
Notes	Sample size calculation a priori: no Sponsor: not reported Trial conduction dates: March 1990 to November 1992

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients were randomized..." (page 472) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "This was a double-blind, randomised placebo-controlled trial" (page 471) Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk' (e.g. number randomly assigned not stated, no reasons for missing data provided)
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Bias of presentation data, design bias (Porta 2008)

Pitt 1971

Study characteristics

Methods	Parallel design (2 arms) Country: Australia. Follow-up: 48 hours
Participants	Randomly assigned: N = 222 Class 1 (participants without haemodynamic disturbances): 113 • Lidocaine group: 54 • Placebo (dextrose 5% by intravenous infusion) group: 59 Class 2 (hypotension blood pressure < 90 mmHg after relief of pain, or left ventricular failure): 109

Pitt 1971 *(Continued)*

- Lidocaine group: 54
- Placebo (dextrose 5% by intravenous infusion) group: 55

Age, years (range)

Class 1

- Lidocaine group: 52 (27 to 69)
- Placebo (dextrose 5% by intravenous infusion) group: 56 (30 to 80)

Class 2

- Lidocaine group: 58 (43 to 74)
- Placebo (dextrose 5% by intravenous infusion) group: 58 (33 to 77)

Gender, male, % (n/N)

Class 1

- Lidocaine group: 92.59 (50/54)
- Placebo (dextrose 5% by intravenous infusion) group: 94.9 (56/59)

Class 2

- Lidocaine group: 87 (47/54)
- Placebo (dextrose 5% by intravenous infusion) group: 89 (49/55)

Inclusion criteria: not reported

Exclusion criteria

- 24 hours elapsed since onset of symptoms
- Ventricular tachyarrhythmia
- Third-degree heart block

Interventions	Lidocaine: 2.5 mg/min for 48 hours in 5% dextrose For the first half of the trial, all participants receiving lidocaine were given an intravenous bolus injection of 75 to 100 mg, but this was not routinely administered in the second half of the trial Placebo: dextrose 5% by intravenous infusion Co-interventions: pacemaker and lidocaine in control group because of the development of ventricular tachyarrhythmia
Outcomes	Mortality Fequency of ventricular tachyarrhythmia
Notes	Sample size calculation a priori: no Sponsor: Astra Chemicals Pty. Ltd. Rol of the sponsor: not reported Trial conduction dates: 5 January 1968 to 30 June 1970

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly allotted..." (page 613) Insufficient information about the sequence generation process to permit judgement of ‘low risk’ or ‘high risk’

Pitt 1971 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"165 patients were excluded..." (page 613) It is unclear whether these exclusions occurred before or after randomisation
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Bias of presentation data, design bias (Porta 2008) Industry bias

Poprawski 1987

Study characteristics	
Methods	Parallel design (2 arms) Country: Poland Follow-up (hours): not stated
Participants	Randomly assigned: N = 172 • Lidocaine group: 86 • Placebo (5% glucose solution) group: 86 Age, years, mean (range) • Lidocaine: 62 (30 to 91) • Placebo (5% glucose solution) group: 65 (25 to 81) Gender, male, % (n/N) • Lidocaine group: 67.4 (58/86) • Placebo (5% glucose solution) group: 66 (57/86) Inclusion criterion: patients with acute myocardial infarction by World Health Organization and International Cardiology Society Criteria, 1979 Exclusion criteria • Pulmonary oedema • Cardiogenic shock • III° atrio-ventricular block • Advanced intraventricular conduction abnormalities (alternating right and left atrioventricular bundle block, incomplete tri-bundle block)

Poprawski 1987 *(Continued)*

	• Sinus node insufficiency
Interventions	Lidocaine intravenous. 75 mg over 1 minute immediately on admission – no later than within 8 hours of onset of pain, then 3 doses intravenous 50 mg each over 1 minute, followed by 2 mg/min intravenous infusion pump Placebo: 5% glucose solution Co-interventions: routine administration of nitroglycerin and heparin intravenously
Outcomes	Endpoints reported for the 2 arms • Primary atrial fibrillation • Significant ventricular arrhythmia preceding atrial fibrillation • Significant ventricular arrhythmia without atrial fibrillation • Significant ventricular arrhythmia for the whole group/arm • QT interval in patients with atrial fibrillation • QT interval in patients without atrial fibrillation • Hospital mortality in patients with atrial fibrillation • Hospital mortality in patients without atrial fibrillation • Hospital mortality for the whole group/arm • Adverse effects from lidocaine: convulsion, psychomotor excitability, speech disturbance
Notes	Comment: This trial was written in Polish. Therefore, we describe some details here • Intention-to-treat: All 172 participants received the intervention – no indication that any of them did not receive the full multi-dosage of lidocaine/placebo • Adverse events: not reported for the control group. Probable typographical error - 3% adverse events quoted for lidocaine in Results section and table, but 30% in Discussion section • Sponsor: Study is from 1987 - it is unlikely that a commercial sponsor was available before the political and economic changes of 1989, but this cannot be ruled out • Sample size calculation a priori: no information provided • Trial conduction dates: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients were randomly divided in two groups" (page 667) Insufficient information to permit judgement of ‘low risk’ or ‘high risk’
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of ‘low risk’ or ‘high risk’
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of ‘low risk’ or ‘high risk’
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of ‘low risk’ or ‘high risk’
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement of ‘low risk’ or ‘high risk’

Poprawski 1987 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Design bias (Porta 2008)

Rademaker 1986

Study characteristics	
Methods	Parallel design (2 arms) Country: Canada Follow-up period: 48 hours
Participants	Randomly assigned: 285 • Lidocaine group: 50.87% (145/285) • Placebo (not stated) group: 49.1% (140/285) Proven acute myocardial infarction: 75 participants Comparison group not given Age, years, mean (standard error or standard deviation), not stated • Lidocaine group: 56 (10) • Placebo (not stated) group: 57 (10) Gender, male, % (n/N) • Lidocaine group: 53.1 (77/145) • Placebo (not stated) group: 53 (74/140) Inclusion criteria • Onset of chest pain no longer than 6 hours before arrival • Typical Q waves and evolutionary ST-T changes in electrocardiogram • Serial rise in creatine phosphokinase, serum glutamic pyruvic transaminase or lactic dehydrogenase levels • Positive pyrophosphate scan Exclusion criteria • Older than 75 years of age • Antiarrhythmic drugs received immediately before hospital arrival • Complex arrhythmias on arrival • Advance heart failure or shock • Contraindication to lidocaine such as liver disease or allergy
Interventions	Lidocaine, initial 100 mg intravenous bolus given over 3 to 5 minutes, followed by 3 mg/min intravenous by infusion pump and a second 100 mg intravenous bolus 30 minutes after the first bolus Placebo: no stated details Co-intervention: not reported
Outcomes	Safety

Rademaker 1986 *(Continued)*

Notes	Sample size calculation a priori: not reported Sponsor: Astra Pharmaceuticals supplied lidocaine Trial conduction dates: July 1980 to December 1984

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...were randomized in a double-blind manner..." (page 72) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome that would be expected to have been reported for such a study. Investigators did not assess mortality and ventricular fibrillation. Furthemore, safety data were reported incompletely, so they cannot be entered into a meta-analysis
Other bias	High risk	Bias of presentation data, design bias (Porta 2008) Industry bias

Rehnqvist 1983

Study characteristics

Methods	Parallel design (2 arms) Country: Sweden Follow-up period: 24 hours
Participants	Randomly assigned: N = 40 • Lidocaine: 50% (20/40) • Tocainide: 50% (20/40) Age, years, mean (range) • Lidocaine: 62.7 (36 to 78) • Tocainide: 63.1 (39 to 78)

Rehnqvist 1983 *(Continued)*

	Gender, male, % (n/N) • Lidocaine: 75 (15/20) • Tocainide: 80 (16/20) Inclusion criteria (≥ 1 of the following high-grade ventricular arrhythmias had to be present for inclusion) • ≥ 5 premature ventricular complexes/min • Multi-form premature ventricular complexes during 1 hour of registration • Paired premature ventricular complexes • R-on-T premature ventricular complexes • Ventricular tachycardia Exclusion criteria • Hypersensitivity to procaine or amide types of drugs or local anaesthetic drugs • Pulmonary oedema • Hypotension • Cardiogenic shock • Atrioventricular block II and III • Complete bundle branch block • Bradycardia < 50 beats/min • Hepatic or renal insufficiency • Treatment with other antiarrhythmic drugs (including β-blockers), except digitalis
Interventions	Tocainide: bolus injection of 750 mg over 15 minutes, immediately followed by 800 mg orally and thereafter 400 mg TID Lidocaine: bolus injection of 75 mg followed by continuous infusion at a rate of 2 mg/min Co-interventions: not reported
Outcomes	Suppressing premature ventricular contractions
Notes	Sample size calculation a priori: not reported Sponsor: not reported Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"were randomized to treatment" (page 22) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	High risk	"... in an open fashion" (page 22)
Blinding of outcome assessment (detection bias)	High risk	"... in an open fashion" (page 22)

Rehnqvist 1983 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome that would be expected to have been reported for such a study Comment: Trial does not assess mortality and ventricular fibrillation
Other bias	High risk	Bias of presentation data and design bias (Porta 2008)

Rehnqvist 1984

Study characteristics	
Methods	Parallel design (2 arms) Country: Sweden Follow-up period: 24 hours
Participants	Randomly assigned: N = 20 • Lidocaine group: 50% (10/20) • Propofenone group: 50% (10/20) Age, years: 61 (both groups) Gender, male, % (n/N) • Propafenone: 60 (6/10) • Lidocaine: not reported Inclusion criteria • High-grade premature ventricular complexes when monitored routinely within 24 hours of admission • < 75 years of age • Chest pain suggesting an acute myocardial infarction Exclusion criteria • Hypersensitivity to procaine or amide types of drugs or local anaesthetic drugs • Severe congestive heart failure • Atriovenricular block II and III • Complete bundle branch blocks • Bradycardia (< 50 beats/min) • Treatment with other antiarrhythmic drugs, except β-blocking agents or digitalis, long QT interval
Interventions	Lidocaine • Bolus injection of 75 mg • Followed by continuous infusion at a rate of 2 mg/min, which could be increased to 3 mg/min Propafenone • Bolus injection of 1 mg/kg up to 70 mg • Followed by 150 mg orally after 1 hour

Rehnqvist 1984 *(Continued)*

	Co-interventions: not reported
Outcomes	Reduction in premature ventricular complexes
Notes	A priori sample size estimation: not reported Sponsor: not reported. Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomly allocated..." (page 527) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	High risk	"... in an open fashion" (page 22)
Blinding of outcome assessment (detection bias) All outcomes	High risk	"... in an open fashion" (page 22)
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawal from study Propafenone group: 30% (3/10) Lidocaine group: not reported Reason Increasing numbers of premature ventricular complexes
Selective reporting (reporting bias)	High risk	"The study report fails to include results for a key outcome that would be expected to have been reported such a study" This study did not report mortality
Other bias	High risk	Bias of presentation data, design bias (Porta 2008)

Rolli 1981

Study characteristics

Methods	Parallel design (2 arms) Country: Italia Follow-up period: 3 hours
Participants	Randomly assigned: N = 50 • Mexiletine group: 50% (25/50) • Lidocaine group: 50% (25/50)

Rolli 1981 *(Continued)*

	Age, years (standard error or standard deviation), not stated • Mexiletine group: 66 (2) • Lidocaine group: 60 (4) Gender, male, % (n/N) • Total group: 90 (45/50) • Mexiletine group: 92 (23/25) • Lidocaine group: 88 (22/25) Inclusion criteria: not stated Exclusion criteria: not stated
Interventions	Mexiletine: bolus endovenous 2 mg/kg in 5 minutes, followed by a continuous infusion of 500 mg in the next 3 hours (250 mg the first hour, and the other 250 mg the next 2 hours) Maintenance intravenous infusion (0.5 to 1 mg/min) depending on therapeutic response Lidocaine group: bolus intravenous 2 mg/kg, continued to an infusion of 2 mg/min. Continuous infusion of 5% dextrose solution alone at same speed as intervention Co-intervention: not reported
Outcomes	Ventricular arrhythmia
Notes	A priori sample size estimation: not reported Sponsor: not reported Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...randomly allocated into two groups" (page 468) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	Low risk	The study reported information about mortality and safety Comment: Trial did not assess ventricular fibrillation
Other bias	High risk	Bias in presentation of data, design bias (Porta 2008)

Ronnevik 1987

Study characteristics	
Methods	Parallel design (2 arms) Country: Norway Follow-up period: 24 hours
Participants	Randomly assigned: N = 68 • Disopyramide group: 49% (33/68) • Lidocaine group: 51.4% (35/68) Age, years • Disopyramide group: 61.5 • Lidocaine group: 63.2 Gender, male, % (n/N) • Total group: 76.4 (52/68) • Disopyramide group: 76 (25/33) • Lidocaine group: 77.1 (27/35) Inclusion criteria • < 75 years of age, both genders • Pairs or R-on-T premature ventricular contractions Exclusion criteria • Congestive heart failure with basal pulmonary rales > 10 cm • High-degree atrioventricular block (second-degree Mobitz type II or third-degree) • Hypotension (systolic blood pressure < 100 mmHg) • Renal or hepatic insufficiency • Known sensitivity to lidocaine or disopyramide • Treatment with other antiarrhythmic drugs, except beta-blockers or digitalis
Interventions	Disopyramide: intravenous bolus of 150 mg (100 mg to persons < 60 kg), followed by a constant infusion of 30 mg/h for 24 hours Lidocaine: intravenous bolus injection of 100 mg (75 mg to persons < 60 kg), followed by a constant infusion of 3 mg/h for 24 hours Co-interventions • Digitalis (dose not stated) • Diuretics (furosemide dose/24 h)
Outcomes	Death Ventricular arrhythmias
Notes	A priori sample size estimation: not reported Sponsor: not reported Trial conduction dates: not stated

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Ronnevik 1987 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"...were randomised to disopyramide and..." (page 30) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals from study Overall: 15% (10/68) Disopyramide: 15.1% (5/33) Reasons • Hypotension • Pulmonary congestion • Sinoatrial block • Sustained ventricular tachycardia Lidocaine: 14.2% (5/35) Reasons • Confusion • Hypotension • High-degree atrioventricular block • Sustained ventricular tachycardia
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Design bias (Porta 2008)

Rossi 1976

Study characteristics	
Methods	Parallel design (2 arms) Country: Italy Follow-up period: 3 weeks
Participants	Randomly assigned: N = 246 • Lidocaine group: 40.24% (99/246) • Control (physiological solution and intervention in equal volumes) group: 59.7% (147/246)

Rossi 1976 *(Continued)*

	Age, years: not reported Gender, male: not reported Inclusion criteria • Age < 70 years • Sudden chest pain, started no more than 8 hours earlier, lasted longer than 10 minutes, nitroglycerin-resistant and not affected by respiratory movements Exclusion criteria • Hypotension • Bradycardia • Arrhythmia that requires immediate treatment
Interventions	Lidocaine by an intramuscular injection of 250 mg Placebo: physiological solution and intervention in equal volumes Co-intervention: not reported
Outcomes	Mortality Incidence of severe arrhythmias
Notes	Sample size calculation a priori: not reported Sponsor: Astra Company Role of sponsor: Lidocaine and saline solutions have been packaged for the double-blind by Astra Company Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"and was randomised... " (page 221) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The contents of the syringe [are] kept secret until after the search. The distribution of the drug or placebo was randomised at the time of the package" (page 221)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	Low risk	All clinically relevant and reasonably expected outcomes were reported
Other bias	High risk	Design bias (Porta 2008)

Rossi 1976 *(Continued)*

	Industry bias

Sadowski 1999

Study characteristics	
Methods	Parallel design (2 arms) Follow-up period: 48 hours Country: Poland
Participants	Randomly assigned: N = 903 • Lidocaine group: 49.2% (445/903) • Control group (no lidocaine): 50.71% (458/903) 703 randomly assigned to streptokinase plus heparin or heparin alone Age, years, mean • Lidocaine group: 55.16 • Control group (no lidocaine): 53.9 Gender total group, male, %: 79.84 Inclusion criteria • Chest pain lasting < 30 minutes • ST elevation ≥ 0.15 mV in ≥ 2 contiguous precordial leads or ≥ 0.1 mV in ≥ 2 limb leads • No contraindication to intravenous lidocaine or nitroglycerin • Examined at the hospital within 6 hours of symptom onset Exclusion criteria • Sinus bradycardia • Shock • Heart failure • Hypotension • Second- or third-degree atrioventricular block • > 70 years of age • Recent bleeding • Haemostatic disorders • Recent cerebrovascular event • Recent surgery • Non-controlled hypertension • Gastric ulcer • Recent cardiopulmonary reanimation • Pregnancy • Life-threatening condition
Interventions	Lidocaine, intravenously as four 50-mg boluses at 2-minute intervals, followed by continuous infusion of 3 mg/min for 12 hours, then 2 mg/min for 36 hours Control group: no lidocaine Co-interventions: streptokinase, 1.5 million unit intravenous infusion titrated to maintain an activated partial thromboplastin time 2 to 2.5 times normal for 48 hours. All patients received intravenous nitroglycerin, 20 to 150 µg/min, titrated to control blood pressure and heart rate
Outcomes	Mortality

Sadowski 1999 *(Continued)*

	Ventricular fibrillation Asystole Atrioventricular block
Notes	Sample size calculation a priori: not reported Sponsor: not reported Trial conduction dates: "...between 1986 and 1987"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"... were randomly assigned in a 2×2 factory design..." (page 793) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the allocation concealment process to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon) However, safety data were reported incompletely, so they cannot be entered into a meta-analysis
Other bias	High risk	Design bias and bias in data presentation (Porta 2008)

Sandler 1976

Study characteristics

Methods	Parallel design (2 arms) Country: United Kingdom Follow-up period: unclear
Participants	Randomly assigned: N = 181 • Lidocaine group: 50.27% (91/181) • Control (physiological solution) group: 49.73% (90/181) Age, years: not reported Gender: not reported

Sandler 1976 *(Continued)*

	Inclusion criteria: patients with suspected myocardial infarction Exclusion criteria • Cardiac arrhythmias • Left ventricular failure • Heart block (any degree) • Cardiogenic shock • Evidence of renal or hepatic impairment • Patients subsequently found not to have had an infarction according to World Health Organization criteria
Interventions	Lidocaine was given by an intramuscular injection of 200 mg or 300 mg Placebo: physiological solution and intervention in equal volumes Co-intervention: atropine 0.6 mg by intravenous injection
Outcomes	Incidence of arrhythmias
Notes	A priori sample size estimation: not reported Sponsor: not reported Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"... according to a randomised allocation..." (page 564) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the allocation process to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information about the blinding level process to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	High risk	Quote: "The study report fails to include results for a key outcome that would be expected to have been reported for such a study" Comments: Mortality and ventricular fibrillation were not reported in this study
Other bias	High risk	Design bias and bias in data presentation (Porta 2008).

Sbarbaro 1979

Study characteristics	
Methods	Parallel design (2 arms) Country: USA Follow-up period: 2 hours
Participants	Randomly assigned: N = 26 • Lidocaine group:12 • Dysopyramide group: 14 Patients with acute myocardial infarction • Overall: 15.3% (4/26) • Lidocaine: 25% (1/4) • Dysopiramyde: 75% (3/4) Age, years: not reported for patients with acute myocardial infarction Gender, male: not reported for patients with acute myocardial infarction Inclusion criteria • ≥ 4 premature ventricular complexes per minute • ≥ 3 successive premature ventricular complexes Exclusion criteria • Cardiac arrhythmias • Left ventricular failure • Heart block (any degree) • Cardiogenic shock • Evidence of renal or hepatic impairment • Patients subsequently found not to have had an infarction according to World Health Organization criteria
Interventions	Dysopyramide 2 mg/kg over 15 minutes, then 2 mg/kg over 45 minutes, then 0.4 mg/kg per hour maintenance Lidocaine 75 mg or 100 mg bolus injection, then 3 or 4/min maintenance infusion, with additional bolus injection as indicated clinically Co-intervention: not given
Outcomes	Incidence of arrhythmias
Notes	A priori sample size estimation: not reported Sponsor: Searle Labboratories Role of the sponsor: supplied the drug and provided determination of drug blood levels Trial conduction dates: not stated

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"... to a modification of a computer-based randomization scheme" (page 514).

Sbarbaro 1979 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The investigators and the patient´s physician were aware of which agent [was] being administered" (page 514)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated Comment: This trial included only 4 participants with acute myocardial infarction
Selective reporting (reporting bias)	High risk	One or more outcomes of interest in the review are reported incompletely, so they cannot be entered into a meta-analysis Comment: This trial included only 4 participants with acute myocardial infarction. However, researchers did not provide information on these individuals
Other bias	High risk	Design bias and bias in data presentation (Porta 2008) Industry bias

Solimene 1983

Study characteristics	
Methods	Parallel design (2 arms) Country: Brazil Follow-up period: 12 hours
Participants	Randomly assigned: N = 43 • Lidocaine group: 48.82% (21/43) • No lidocaine group: 51.1% (22/43) Age, years, mean (standard error or standard deviation: not stated) • Lidocaine group: 57 (10) • No lidocaine group: 55 (11) Gender, male, % (n/N) • Total group: 86.04 (37/43) • Lidocaine group: 85.7 (18/21) • No lidocaine group: 86.36 (19/22) Inclusion criteria: based on clinic criteria and electrocardiogram (no additional details) Exclusion criteria: not stated
Interventions	Lidocaine • 2 doses of 100 mg intravenous bolus,15 minutes apart

Solimene 1983 *(Continued)*

	• Continuous infusion 2 to 4 mg/min, in 5% glucose and water for 24 hours, initiated at the time of the first 100 mg Control group: no lidocaine Co-intervention: cardioversion
Outcomes	Ventricular extrasystoles Ventricular tachycardia Ventricular fibrillation
Notes	Sample size calculation a priori: not reported Sponsor: not reported Trial conduction dates: not stated E-mail was sent to the main trial author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"... os pacientes foram seleccionados, ao acaso,..." (page 377) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	High risk	The study report fails to include results for a key outcome that would be expected to have been reported for such a study This study did not report mortality data
Other bias	High risk	Design bias and bias in data presentation (Porta 2008).

Touboul 1988

Study characteristics

Methods	Parallel design (3 arms) Country: France Follow-up period: 24 hours
Participants	112 enrolled

Touboul 1988 *(Continued)*

	Randomly assigned: N = 89 • Propafenone: 36 • Lidocaine: 28 • Placebo: 25 Age, years • Lidocaine: 57 • Propafenone: 51 • Placebo: 56 Gender, male, % (n/N) • Overall: 90.62 (90/112) • Lidocaine: 82.2 (25/28) • Propafenone: 92 (33/36) • Placebo: 92 (23/25) Inclusion criteria • Chest pain < 24 hours before hospitalisation • Electrocardiographic changes (modifications of ST-T segment whether or not associated with abnormal Q waves) • Serum enzyme criteria (elevation of creatine phosphokinase and transaminase serum glutamic oxaloacetic transaminase) Exclusion criteria • Patients > 75 years of age • Various severe diseases (neurological, renal, hepatic, bronchopulmonary) • Valvular or myocardial cardiopathy, current antiarrhythmic treatment • Complications on entry, including heart failure (Killip's classes 3 and 4) • Hypotension (< 90 mmHg) • Bradycardia (< 50 beats/min), second- or third-degree atrioventricular block • Complete bundle branch block • Sustained ventricular tachycardia • Ventricular fibrillation • Hypokalemia
Interventions	Lidocaine: intravenous as a bolus injection of 100 mg, followed by an infusion of 2 mg/min Propafenone: bolus of 105 mg, followed by 300 mg orally every 8 hours Placebo: no details of its nature given Co-intervention group: not reported
Outcomes	Suppression of complex arrhythmias, couples and ventricular tachycardia
Notes	Sample size calculation a priori: not reported Sponsor: not reported Trial conduction dates: April 1985 to March 1986

Risk of bias

Bias	Authors' judgement	Support for judgement

Touboul 1988 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"... were randomly assigned to treatments" (page 1189) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"A double blind, placebo-controlled trial" (page 1188) Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals from study Excluded from analysis: 20% (23/112) Comment: It is unknown whether these exclusions were treated Reasons No myocardial infarction; defective Holter recording By comparison groups: not reported Withdrawals among remaining participants: 8% (7/89) • Gastrointestinal Intolerance (placebo; n = 1) • Marked bradycardia (placebo; n = 1) • Right bundle branch block (placebo; n = 1) • Severe heart failure (lidocaine; n = 2) • Neuropsychiatric disturbance (lidocaine; n = 1) • Bilateral bundle branch block (propafenone; n = 1)
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Design bias and bias in data presentation (Porta 2008)

Valentine 1974

Study characteristics	
Methods	Parallel design (2 arms) Trial duration: 15 months Follow-up: 30 days Country: Australia
Participants	Randomly assigned (class 1 or 2): N = 269 • Lidocaine group: 156 • Placebo (physiological saline) group: 113 Age, years

Valentine 1974 *(Continued)*

- Lidocaine group: 57
- Placebo (physiological saline) group: 57

Gender, male, %

- Lidocaine group: 73
- Placebo group: 76.99

Inclusion criteria: chest pain with a provisional diagnosis of acute cardiac infarction

Exclusion criteria

- Individuals > 70 years of age
- ≤ 55 beats per minute
- Systolic blood pressure ≤ 90 mmHg
- Symptoms > 12 hours in duration
- Patients who received lidocaine before or within 2 hours of injection of trial material

Interventions	Lidocaine 300 mg intramuscular (10% solution) Placebo: physiological saline Co-intervention: defibrillation
Outcomes	Mortality
Notes	Sample size calculation a priori: not reported Sponsor: not reported Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...trial randomly..." (page 1327) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Low risk	"... a reply-paid envelope and another sealed envelope containing the code..." (page 1327)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"participating doctors remained ignorant of the nature of the trial material injected..." (page 1327)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)

Valentine 1974 *(Continued)*

Other bias	High risk	Design bias (Porta 2008)

Wennerblom 1982

Study characteristics	
Methods	Parallel design (2 arms) Country: Sweden Follow-up period: 3 hours
Participants	Enrolled: 407 Randomly assigned: N = 150 • Lidocaine group: 47.33% (71/150) • Placebo (physiological solution) group: 52.66% (79/150) Age, years • Lidocaine group: 64 • Placebo (physiological solution) group: 60 Gender, male, %: 60 Inclusion criteria • Patients with suspected myocardial infarction • Age < 75 years Exclusion criteria • Bradycardia • Second- and third-degree atrioventricular block • Complete atrioventricular block • Atrial fibrillation
Interventions	Lidocaine: intramuscular injection of 300 mg Placebo: physiological solution and intervention in equal volumes Co-intervention: atropine
Outcomes	Mortality Incidence of ventricular arrhythmias
Notes	Sample size calculation a priori: not reported Sponsor: not reported Trial conduction dates: not stated

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"patients were allocated at random..." (page 516) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'

Wennerblom 1982 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information about the allocation concealment process to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"...double blind" (page 516) "Each dose was prepared in advance by person not involved in the study..." (page 517)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The arrhythmia analysis... was done by one of the authors 'blindly'..." (page 517)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated
Selective reporting (reporting bias)	Low risk	The study protocol is not available, but it is clear that published reports describe all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
Other bias	High risk	Design bias (Porta 2008)

Wyse 1988

Study characteristics	
Methods	Parallel design (2 arms) Country: Canada Follow-up period: 24 hours

Participants	Randomly assigned: N = 333
	• Lidocaine group: 49% (165/333)
	• Control group: 50.4% (168/333)
	Age, years, mean (standard error)
	• Participants with myocardial infarction
	  • Selective lidocaine strategy: 57 (1)
	  • Prophylactic lidocaine strategy: 56 (1)
	Gender, male, %
	• Selective group: 75
	• Prophylactic group: 77
	Inclusion criteria
	• Proven myocardial infarction defined as
	  • 6 hours of chest pain
	  • Typical Q waves and evolutionary ST-T changes on electrocardiogram
	  • Serial increase in serum creatine kinase (total or MB fraction or both)
	Excluded criteria
	• > 75 years old
	• Complex ventricular arrhythmia requiring treatment on arrival

Wyse 1988 *(Continued)*

	• Advance heart failure or shock • Contraindication to lidocaine such as persistent sinus bradycardia (< 45 beats/min) • Liver disease • Allergy • Had received antiarrhythmic drugs in the previous 24 hours • Refused consent
Interventions	Lidocaine: 100 mg intravenous loading infusion given over 3 to 5 minutes, followed by 3 mg/min continuous intravenous maintenance. An identical 100 mg intravenous infusion was administered 30 minutes after the first loading infusion. Dosage was adjusted on a milligram-per-kilogram basis for participants < 50 kg or > 90 kg Control: no information given about this issue
Outcomes	Safety of lidocaine therapy in participants with acute myocardial infarction
Notes	Sample size calculation a priori: not reported Sponsor: not reported Trial conduction dates: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"On randomization, drug (placebo or lidocaine) was administered..." (page 508) Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information about the allocation concealment process to permit judgement of 'low risk' or 'high risk'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"...(placebo or lidocaine) was administered in a double blind manner" (page 508) Insufficient information to permit judgement of 'low risk' or 'high risk'
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout from the study • Lidocaine group: 4% (1/26) • Placebo group: 4% (1/28) Reasons • Atrial fibrillation
Selective reporting (reporting bias)	High risk	One or more outcomes of interest in the review are reported incompletely, so they cannot be entered into a meta-analysis "in mortality rate (selective=3%, prophylactic=5%, p=NS)" (page 507) This trial reported results by approach (prophylaxis vs selective) rather than by lidocaine vs placebo
Other bias	High risk	Design bias and bias in data presentation (Porta 2008)

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

Study	Reason for exclusion
Antman 1992	Narrative review
Beloev 1983	Observational study
Bernard 1970	Narrative review
Bernard 1972	Controlled clinical trial
Bertini 1993	It was reported as a "randomised controlled trial" (page 668). However, the sequence generation was conducted by an inappropriate method (born in odd years)
Bleifeld 1973	It was reported as a "randomised controlled trial" (page 119). However, the sequence generation was conducted by an inappropriate method (dates of birth)
Campbell 1978	Observational study
Campbell 1980	Narrative review
Campbell 1983	Narrative review
Church 1972	It was reported as a "randomised controlled trial" (page 139). However, the sequence generation was conducted by an inappropriate method (birthday)
De Silva 1981	Systematic review of randomised clinical trials
Destuelles 1969	Observational study
Diederich 1979	It was reported as a "randomised controlled trial" (page 1007). However, the sequence generation was conducted by an inappropriate method (sequence generated by participant admission to the hospital)
Egre 1981	Observational study
Fehmers 1972	Controlled clinical trial
Formichev 1995	Narrative review
Garratt 1998	Non-randomised clinical trial
Gianelly 1967	Observational study
Gonzalez 1977	Controlled clinical trial
Goodman 1979	Narrative review
Hine 1989	Systematic review of randomised clinical trials
Iosava 1982	Narrative review
Jaffe 1992	Narrative review
Kudenchuk 2013	Observational study

Study	Reason for exclusion
Lechleitner 1987	Narrative review
Leone 1991	Non-randomised clinical trials
MacMahon 1988	Systematic review on randomised clinical trials
Mazur 1982	Observational study
Miller 1973	Controlled clinical trial
Mogensen 1971	It was reported as a "randomised controlled trial" (page 41). However, the sequence generation was conducted by an inappropriate method (date of birth)
Noneman 1978	Narrative review
Oltmanns 1979	Narrative review
Pentecost 1981	Observational study
Riabokon' 1980	Controlled clinical trial
Ribner 1979	Narrative review
Ruano 1989	Observational study
Ryden 1973	It was reported as a "randomised controlled trial" (page 1125). However, the sequence generation was conducted by an inappropriate method (date of birth)
Shih 1995	Observational study
Singh 1976	Controlled clinical trial
Szeplaki 1973	Controlled clinical trial
Szeplaki 1976	Controlled clinical trial
Teo 1993	Systematic review of randomised clinical trials
Wojtala 1982	Non-randomised clinical trial
Wyman 2004	Observational study

Characteristics of studies awaiting classification *[ordered by study ID]*

Bolinska 1971

Methods	Unknown
Participants	Acute myocardial infarct
Interventions	Lidocaine
Outcomes	Unknown

Bolinska 1971 *(Continued)*

Notes	

Hopperstead 1980

Methods	Unknown
Participants	Patients with acute myocardial infarction
Interventions	Prophylactic lidocaine
Outcomes	Unknown
Notes	

Knight 1973

Methods	Unknown
Participants	Myocardial infarction
Interventions	Prophylactic lidocaine
Outcomes	Unknown
Notes	

DATA AND ANALYSES

Comparison 1. Lidocaine vs placebo or no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality (participants with proven or non-proven acute myocardial infarction)	18	11727	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.27]
1.2 All-cause mortality (subgroup analysis by acute myocardial infarction-only participants)	16	5253	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.79, 1.30]
1.3 All-cause mortality in acute myocardial infarction-only participants (subgroup analysis by administration route for lidocaine)	16	5253	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.79, 1.30]
1.3.1 Intravenous route	9	2042	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.82, 1.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.2 Intramuscular route	5	2804	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.50, 1.17]
1.3.3 Both routes	2	407	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.56, 2.42]
1.4 All-cause mortality (subgroup analysis according to intravenous administration)	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.4.1 Trials with infusion only	3	466	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.33, 2.17]
1.4.2 Trials with bolus followed by infusion	6	1576	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.92, 1.83]
1.5 All-cause mortality (subgroup analysis according to bolus-lidocaine dose)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.5.1 Up to 50 mg	1	82	Risk Ratio (M-H, Random, 95% CI)	1.93 [0.61, 6.09]
1.5.2 60 mg	1	374	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.73, 3.38]
1.5.3 75 mg	2	472	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.70, 3.16]
1.5.4 100 mg	1	212	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.32, 1.91]
1.5.5 1 mg/kg-p	1	436	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.12, 5.96]
1.6 All-cause mortality (subgroup analysis according to number of lidocaine boluses)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.6.1 One bolus	4	968	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.90, 2.38]
1.6.2 Two bolus	2	608	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.72, 1.95]
1.7 All-cause mortality (subgroup analysis according to intravenous infusion dose)	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.7.1 1 mg/min to 1.5 mg/min	3	618	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.71, 2.95]
1.7.2 2 mg/min to 3 mg/min	6	1424	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.72, 1.62]

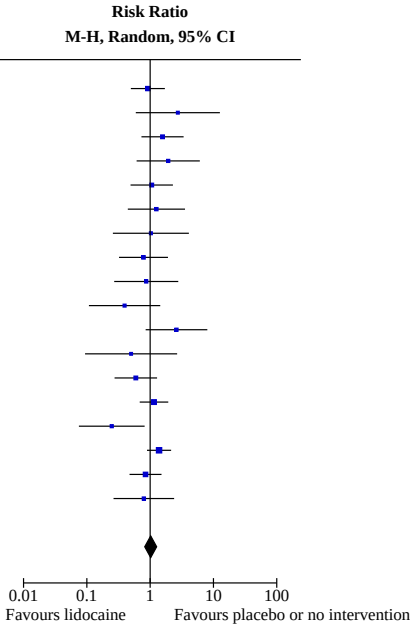
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.8 All-cause mortality (subgroup analysis by clinical setting)	16	5253	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.79, 1.30]
1.8.1 Pre-hospital setting lidocaine use	2	1989	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.46, 2.19]
1.8.2 Hospital setting lidocaine use	11	2250	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.69, 1.32]
1.8.3 Lidocaine use in both pre-hospital and hospital settings	3	1014	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.77, 3.02]
1.9 All-cause mortality (subgroup analysis according to non-suspected trials with industry bias compared with suspected trials with industry bias)	16	5253	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.79, 1.30]
1.9.1 Trials non-sponsored by industry	11	4117	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.82, 1.44]
1.9.2 Trials sponsored by industry	5	1136	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.44, 1.58]
1.10 All-cause mortality (sensitivity analysis by attrition bias)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.10.1 Best-worst case scenario	3	774	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.30, 1.08]
1.10.2 Worst-best case scenario	3	774	Risk Ratio (M-H, Random, 95% CI)	2.20 [1.02, 4.73]
1.11 Cardiac mortality	12	8277	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.70, 1.50]
1.12 Cardiac mortality (sensitivity analysis according to non-suspected trials of industry bias versus suspected trials of industry bias)	12	8277	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.70, 1.50]
1.12.1 Trials non-sponsored by drug company	8	7387	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.52, 1.39]
1.12.2 Trials sponsored by drug company	4	890	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.77, 2.39]
1.13 Ventricular fibrillation	16	10115	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.55, 1.12]
1.14 Cardiovascular adverse events	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.14.1 Asystole	4	6826	Risk Ratio (M-H, Random, 95% CI)	2.32 [1.26, 4.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.14.2 Sinus bradycardia	8	2549	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.66, 1.80]
1.14.3 Bundle branch block	5	1586	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.80, 1.44]
1.14.4 Non-complete atrioventricular block	4	1661	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.75, 1.37]
1.14.5 Complete atrioventricular block	3	758	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.66, 4.78]
1.14.6 Unknown grade atrioventricular block	4	1727	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.75, 1.67]
1.14.7 Pulmonary oedema	4	1630	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.80, 1.46]
1.14.8 Cardiogenic shock	4	1630	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.77, 1.41]
1.14.9 Hypotension	5	1699	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.81, 1.41]
1.14.10 Cardiac arrest	2	2330	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.77, 1.39]
1.14.11 Heart failure	4	1751	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.63, 1.33]
1.15 Neurological adverse events	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.15.1 Seizures	3	6481	Risk Ratio (M-H, Random, 95% CI)	3.58 [0.59, 21.85]
1.15.2 Drowsiness/Dizziness	5	2533	Risk Ratio (M-H, Random, 95% CI)	3.85 [2.29, 6.47]
1.15.3 Nausea/Vomiting	2	485	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.45, 5.89]
1.15.4 Speech disturbances	4	869	Risk Ratio (M-H, Random, 95% CI)	4.34 [1.00, 18.81]
1.15.5 Confusion	4	6809	Risk Ratio (M-H, Random, 95% CI)	2.44 [0.76, 7.81]
1.15.6 Agitation	2	372	Risk Ratio (M-H, Random, 95% CI)	1.35 [0.26, 7.06]
1.15.7 Global adverse events in central nervous system	2	602	Risk Ratio (M-H, Random, 95% CI)	2.24 [0.44, 11.31]

Analysis 1.1. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 1: All-cause mortality (participants with proven or non-proven acute myocardial infarction)

Study or Subgroup	Lidocaine Events	Lidocaine Total	Placebo or no intervention Events	Placebo or no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
ALIT 1985	19	2987	21	3037	9.3%	0.92 [0.50 , 1.71]
Baker 1971	5	21	2	23	1.9%	2.74 [0.59 , 12.64]
Bennett 1970	25	249	8	125	6.6%	1.57 [0.73 , 3.38]
Chopra 1971	7	39	4	43	3.3%	1.93 [0.61 , 6.09]
Darby 1972	12	103	11	100	6.6%	1.06 [0.49 , 2.29]
Dunn 1985	8	207	6	195	3.9%	1.26 [0.44 , 3.55]
Hargarten 1990	4	704	4	723	2.3%	1.03 [0.26 , 4.09]
Lie 1974	8	107	10	105	5.1%	0.79 [0.32 , 1.91]
Lie 1978	5	147	6	153	3.2%	0.87 [0.27 , 2.78]
NNLIT 1992	3	96	8	101	2.6%	0.39 [0.11 , 1.44]
O'Brien 1973	11	154	4	146	3.4%	2.61 [0.85 , 8.00]
Pharand 1995	2	100	4	100	1.6%	0.50 [0.09 , 2.67]
Pitt 1971	9	108	16	114	6.5%	0.59 [0.27 , 1.29]
Poprawski 1987	23	86	20	86	12.0%	1.15 [0.68 , 1.93]
Rossi 1976	3	99	18	147	3.0%	0.25 [0.07 , 0.82]
Sadowski 1999	43	445	32	458	14.9%	1.38 [0.89 , 2.14]
Valentine 1974	21	156	18	113	10.2%	0.85 [0.47 , 1.51]
Wennerblom 1982	5	71	7	79	3.5%	0.79 [0.26 , 2.39]
Total (95% CI)		**5879**		**5848**	**100.0%**	**1.02 [0.82 , 1.27]**
Total events:	213		199			

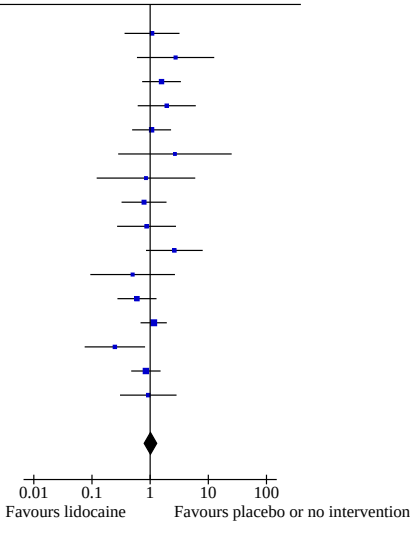
Heterogeneity: Tau² = 0.03; Chi² = 20.05, df = 17 (P = 0.27); I² = 15%
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 2: All-cause mortality (subgroup analysis by acute myocardial infarction-only participants)

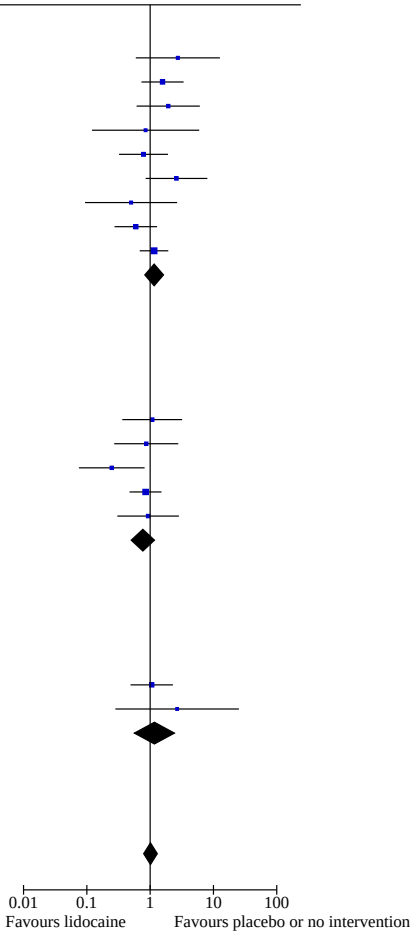
Study or Subgroup	Lidocaine Events	Lidocaine Total	Placebo or no intervention Events	Placebo or no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
ALIT 1985	7	1006	6	929	4.8%	1.08 [0.36 , 3.19]
Baker 1971	5	21	2	23	2.5%	2.74 [0.59 , 12.64]
Bennett 1970	25	249	8	125	9.1%	1.57 [0.73 , 3.38]
Chopra 1971	7	39	4	43	4.4%	1.93 [0.61 , 6.09]
Darby 1972	12	103	11	100	9.0%	1.06 [0.49 , 2.29]
Dunn 1985	3	108	1	96	1.2%	2.67 [0.28 , 25.21]
Hargarten 1990	2	236	2	200	1.6%	0.85 [0.12 , 5.96]
Lie 1974	8	107	10	105	7.0%	0.79 [0.32 , 1.91]
Lie 1978	5	147	6	153	4.3%	0.87 [0.27 , 2.78]
O'Brien 1973	11	154	4	146	4.6%	2.61 [0.85 , 8.00]
Pharand 1995	2	100	4	100	2.1%	0.50 [0.09 , 2.67]
Pitt 1971	9	108	16	114	9.0%	0.59 [0.27 , 1.29]
Poprawski 1987	23	86	20	86	17.2%	1.15 [0.68 , 1.93]
Rossi 1976	3	99	18	147	4.1%	0.25 [0.07 , 0.82]
Valentine 1974	21	156	18	113	14.5%	0.85 [0.47 , 1.51]
Wennerblom 1982	5	28	5	26	4.6%	0.93 [0.30 , 2.84]
Total (95% CI)		**2747**		**2506**	**100.0%**	**1.01 [0.79 , 1.30]**
Total events:	148		135			

Heterogeneity: Tau² = 0.02; Chi² = 16.47, df = 15 (P = 0.35); I² = 9%
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable



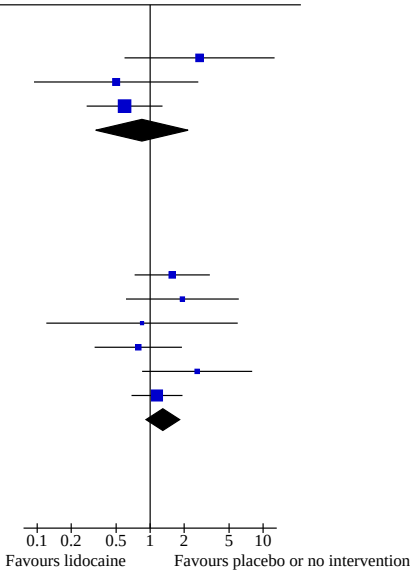
Analysis 1.3. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 3: All-cause mortality in acute myocardial infarction-only participants (subgroup analysis by administration route for lidocaine)

Study or Subgroup	Lidocaine Events	Lidocaine Total	Placebo or no intervention Events	Placebo or no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Intravenous route						
Baker 1971	5	21	2	23	2.5%	2.74 [0.59 , 12.64]
Bennett 1970	25	249	8	125	9.1%	1.57 [0.73 , 3.38]
Chopra 1971	7	39	4	43	4.4%	1.93 [0.61 , 6.09]
Hargarten 1990	2	236	2	200	1.6%	0.85 [0.12 , 5.96]
Lie 1974	8	107	10	105	7.0%	0.79 [0.32 , 1.91]
O'Brien 1973	11	154	4	146	4.6%	2.61 [0.85 , 8.00]
Pharand 1995	2	100	4	100	2.1%	0.50 [0.09 , 2.67]
Pitt 1971	9	108	16	114	9.0%	0.59 [0.27 , 1.29]
Poprawski 1987	23	86	20	86	17.2%	1.15 [0.68 , 1.93]
Subtotal (95% CI)		**1100**		**942**	**57.5%**	**1.16 [0.82 , 1.63]**
Total events:	92		70			
Heterogeneity: Tau² = 0.04; Chi² = 9.26, df = 8 (P = 0.32); I² = 14%						
Test for overall effect: Z = 0.84 (P = 0.40)						
1.3.2 Intramuscular route						
ALIT 1985	7	1006	6	929	4.8%	1.08 [0.36 , 3.19]
Lie 1978	5	147	6	153	4.3%	0.87 [0.27 , 2.78]
Rossi 1976	3	99	18	147	4.1%	0.25 [0.07 , 0.82]
Valentine 1974	21	156	18	113	14.5%	0.85 [0.47 , 1.51]
Wennerblom 1982	5	28	5	26	4.6%	0.93 [0.30 , 2.84]
Subtotal (95% CI)		**1436**		**1368**	**32.2%**	**0.77 [0.50 , 1.17]**
Total events:	41		53			
Heterogeneity: Tau² = 0.01; Chi² = 4.19, df = 4 (P = 0.38); I² = 4%						
Test for overall effect: Z = 1.23 (P = 0.22)						
1.3.3 Both routes						
Darby 1972	12	103	11	100	9.0%	1.06 [0.49 , 2.29]
Dunn 1985	3	108	1	96	1.2%	2.67 [0.28 , 25.21]
Subtotal (95% CI)		**211**		**196**	**10.2%**	**1.17 [0.56 , 2.42]**
Total events:	15		12			
Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.68)						
Total (95% CI)		**2747**		**2506**	**100.0%**	**1.01 [0.79 , 1.30]**
Total events:	148		135			
Heterogeneity: Tau² = 0.02; Chi² = 16.47, df = 15 (P = 0.35); I² = 9%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Test for subgroup differences: Chi² = 2.39, df = 2 (P = 0.30), I² = 16.3%						



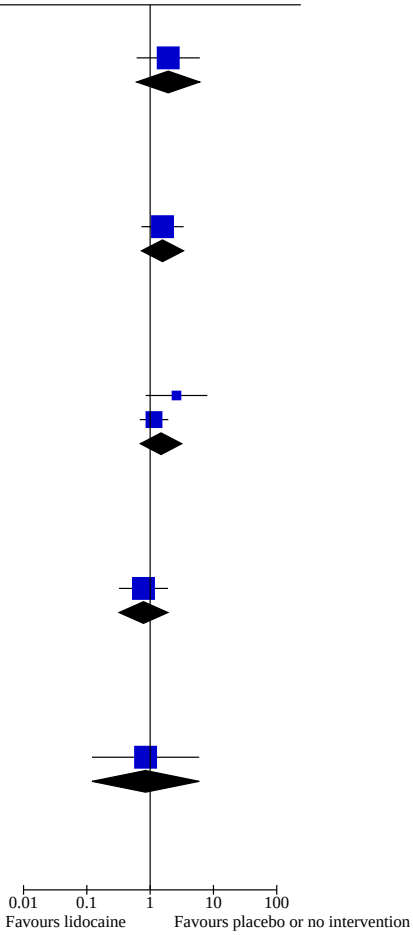
Analysis 1.4. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 4: All-cause mortality (subgroup analysis according to intravenous administration)

Study or Subgroup	Lidocaine Events	Lidocaine Total	Placebo or no intervention Events	Placebo or no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Trials with infusion only						
Baker 1971	5	21	2	23	25.7%	2.74 [0.59 , 12.64]
Pharand 1995	2	100	4	100	22.6%	0.50 [0.09 , 2.67]
Pitt 1971	9	108	16	114	51.7%	0.59 [0.27 , 1.29]
Subtotal (95% CI)		**229**		**237**	**100.0%**	**0.85 [0.33 , 2.17]**
Total events:	16		22			
Heterogeneity: Tau² = 0.29; Chi² = 3.33, df = 2 (P = 0.19); I² = 40%						
Test for overall effect: Z = 0.35 (P = 0.73)						
1.4.2 Trials with bolus followed by infusion						
Bennett 1970	25	249	8	125	20.1%	1.57 [0.73 , 3.38]
Chopra 1971	7	39	4	43	8.9%	1.93 [0.61 , 6.09]
Hargarten 1990	2	236	2	200	3.1%	0.85 [0.12 , 5.96]
Lie 1974	8	107	10	105	14.9%	0.79 [0.32 , 1.91]
O'Brien 1973	11	154	4	146	9.4%	2.61 [0.85 , 8.00]
Poprawski 1987	23	86	20	86	43.7%	1.15 [0.68 , 1.93]
Subtotal (95% CI)		**871**		**705**	**100.0%**	**1.30 [0.92 , 1.83]**
Total events:	76		48			
Heterogeneity: Tau² = 0.00; Chi² = 3.82, df = 5 (P = 0.58); I² = 0%						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Chi² = 0.70, df = 1 (P = 0.40), I² = 0%						



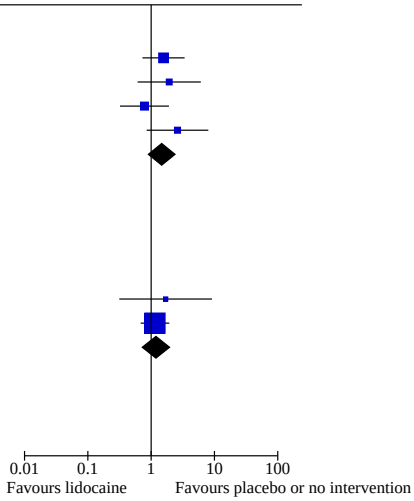
Analysis 1.5. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 5: All-cause mortality (subgroup analysis according to bolus-lidocaine dose)

Study or Subgroup	Lidocaine Events	Lidocaine Total	Placebo or no intervention Events	Placebo or no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Up to 50 mg						
Chopra 1971	7	39	4	43	100.0%	1.93 [0.61 , 6.09]
Subtotal (95% CI)		**39**		**43**	**100.0%**	**1.93 [0.61 , 6.09]**
Total events:	7		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
1.5.2 60 mg						
Bennett 1970	25	249	8	125	100.0%	1.57 [0.73 , 3.38]
Subtotal (95% CI)		**249**		**125**	**100.0%**	**1.57 [0.73 , 3.38]**
Total events:	25		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.15 (P = 0.25)						
1.5.3 75 mg						
O'Brien 1973	11	154	4	146	31.3%	2.61 [0.85 , 8.00]
Poprawski 1987	23	86	20	86	68.7%	1.15 [0.68 , 1.93]
Subtotal (95% CI)		**240**		**232**	**100.0%**	**1.49 [0.70 , 3.16]**
Total events:	34		24			
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 1.73$, df = 1 (P = 0.19); $I^2 = 42\%$						
Test for overall effect: Z = 1.03 (P = 0.30)						
1.5.4 100 mg						
Lie 1974	8	107	10	105	100.0%	0.79 [0.32 , 1.91]
Subtotal (95% CI)		**107**		**105**	**100.0%**	**0.79 [0.32 , 1.91]**
Total events:	8		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.59)						
1.5.5 1 mg/kg-p						
Hargarten 1990	2	236	2	200	100.0%	0.85 [0.12 , 5.96]
Subtotal (95% CI)		**236**		**200**	**100.0%**	**0.85 [0.12 , 5.96]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.87)						
Test for subgroup differences: $Chi^2 = 2.22$, df = 4 (P = 0.70), $I^2 = 0\%$						



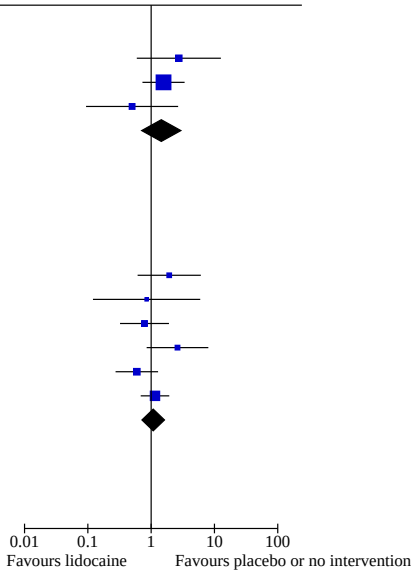
Analysis 1.6. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 6: All-cause mortality (subgroup analysis according to number of lidocaine boluses)

Study or Subgroup	Lidocaine Events	Lidocaine Total	Placebo or no intervention Events	Placebo or no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 One bolus						
Bennett 1970	25	249	8	125	36.9%	1.57 [0.73 , 3.38]
Chopra 1971	7	39	4	43	17.2%	1.93 [0.61 , 6.09]
Lie 1974	8	107	10	105	28.0%	0.79 [0.32 , 1.91]
O'Brien 1973	11	154	4	146	18.0%	2.61 [0.85 , 8.00]
Subtotal (95% CI)		**549**		**419**	**100.0%**	**1.47 [0.90 , 2.38]**
Total events:	51		26			
Heterogeneity: Tau² = 0.01; Chi² = 3.16, df = 3 (P = 0.37); I² = 5%						
Test for overall effect: Z = 1.55 (P = 0.12)						
1.6.2 Two bolus						
Hargarten 1990	4	236	2	200	8.7%	1.69 [0.31 , 9.16]
Poprawski 1987	23	86	20	86	91.3%	1.15 [0.68 , 1.93]
Subtotal (95% CI)		**322**		**286**	**100.0%**	**1.19 [0.72 , 1.95]**
Total events:	27		22			
Heterogeneity: Tau² = 0.00; Chi² = 0.19, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.49)						
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.55), I² = 0%						

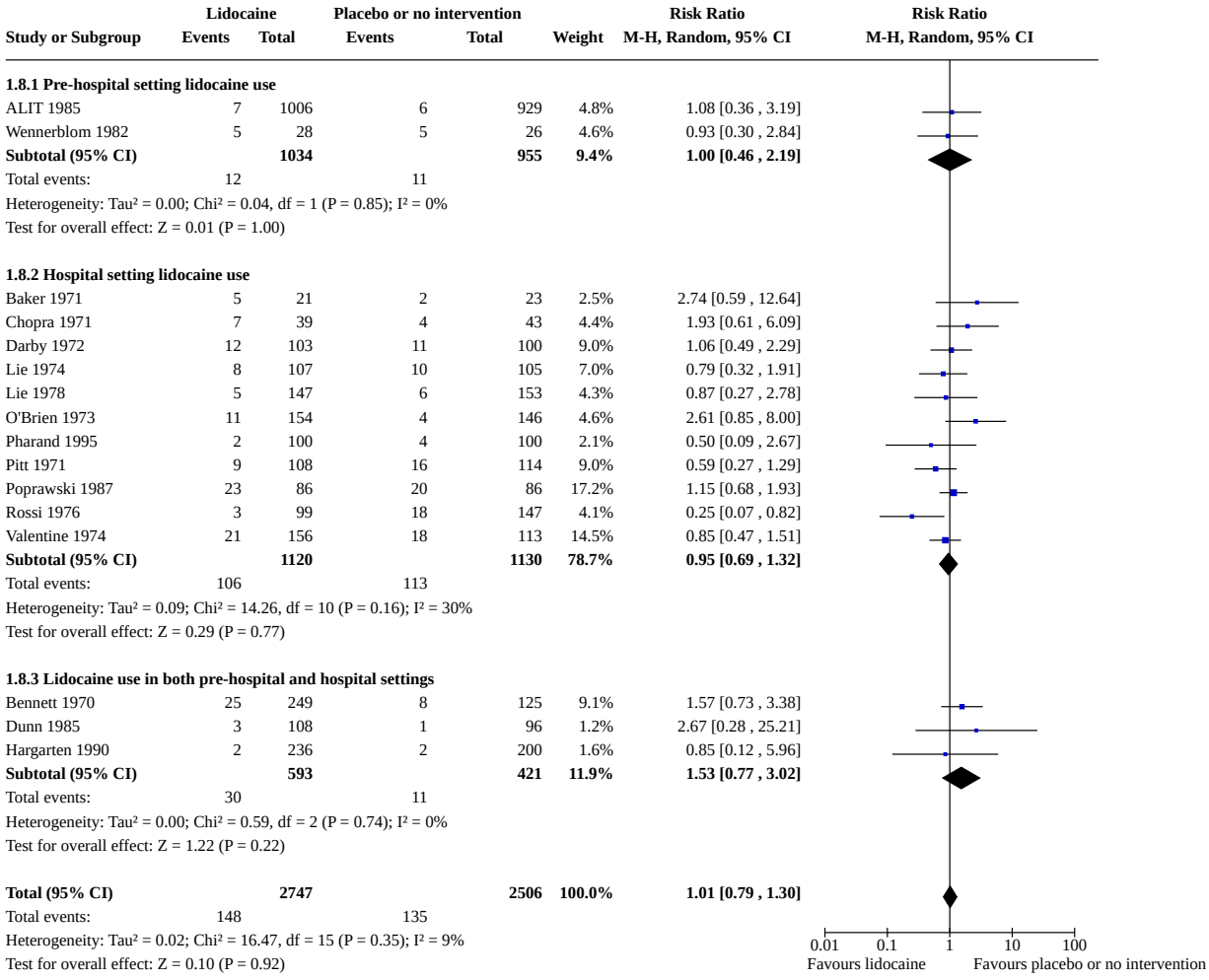


Analysis 1.7. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 7: All-cause mortality (subgroup analysis according to intravenous infusion dose)

Study or Subgroup	Lidocaine Events	Lidocaine Total	Placebo or no intervention Events	Placebo or no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 1 mg/min to 1.5 mg/min						
Baker 1971	5	21	2	23	19.9%	2.74 [0.59 , 12.64]
Bennett 1970	25	249	8	125	63.3%	1.57 [0.73 , 3.38]
Pharand 1995	2	100	4	100	16.8%	0.50 [0.09 , 2.67]
Subtotal (95% CI)		**370**		**248**	**100.0%**	**1.45 [0.71 , 2.95]**
Total events:	32		14			
Heterogeneity: Tau² = 0.06; Chi² = 2.26, df = 2 (P = 0.32); I² = 11%						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.7.2 2 mg/min to 3 mg/min						
Chopra 1971	7	39	4	43	11.0%	1.93 [0.61 , 6.09]
Hargarten 1990	2	236	2	200	4.2%	0.85 [0.12 , 5.96]
Lie 1974	8	107	10	105	16.9%	0.79 [0.32 , 1.91]
O'Brien 1973	11	154	4	146	11.5%	2.61 [0.85 , 8.00]
Pitt 1971	9	108	16	114	21.0%	0.59 [0.27 , 1.29]
Poprawski 1987	23	86	20	86	35.5%	1.15 [0.68 , 1.93]
Subtotal (95% CI)		**730**		**694**	**100.0%**	**1.08 [0.72 , 1.62]**
Total events:	60		56			
Heterogeneity: Tau² = 0.05; Chi² = 6.26, df = 5 (P = 0.28); I² = 20%						
Test for overall effect: Z = 0.36 (P = 0.72)						
Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.48), I² = 0%						

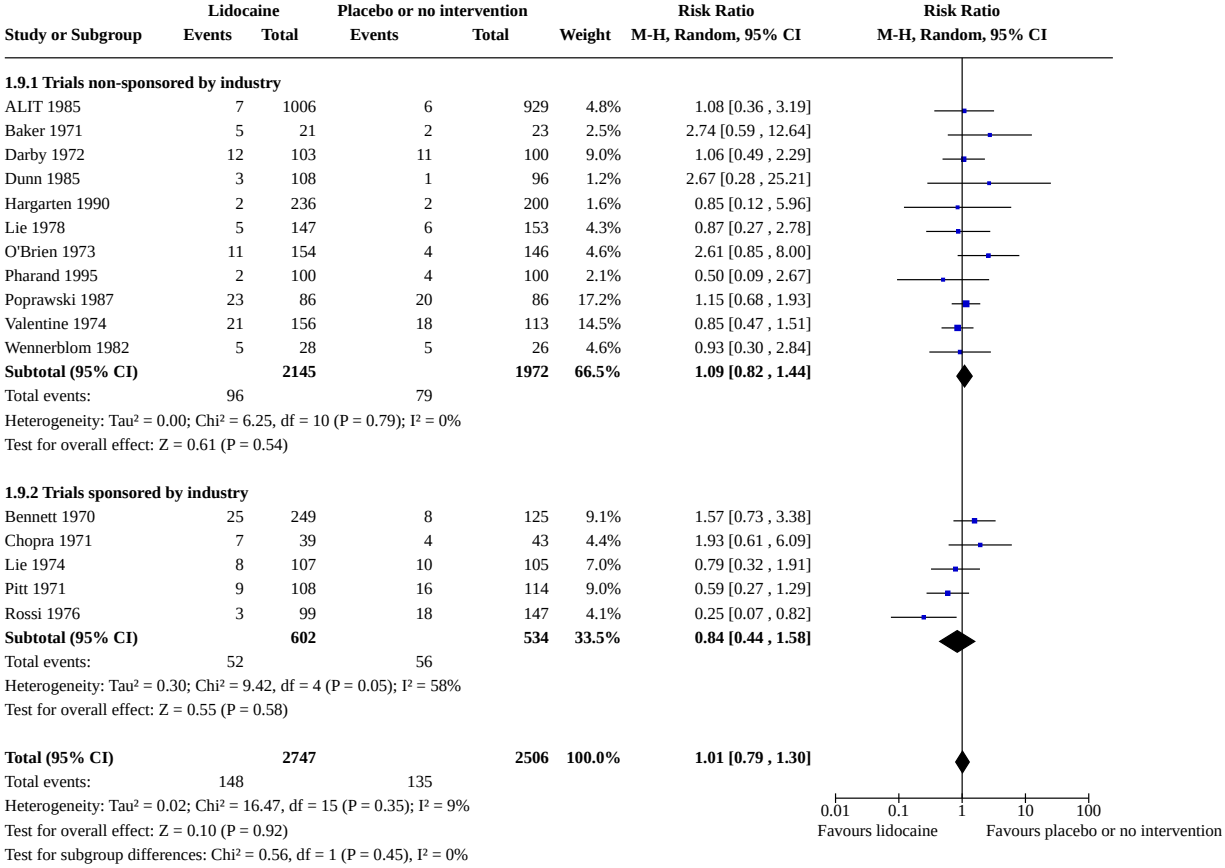


Analysis 1.8. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 8: All-cause mortality (subgroup analysis by clinical setting)

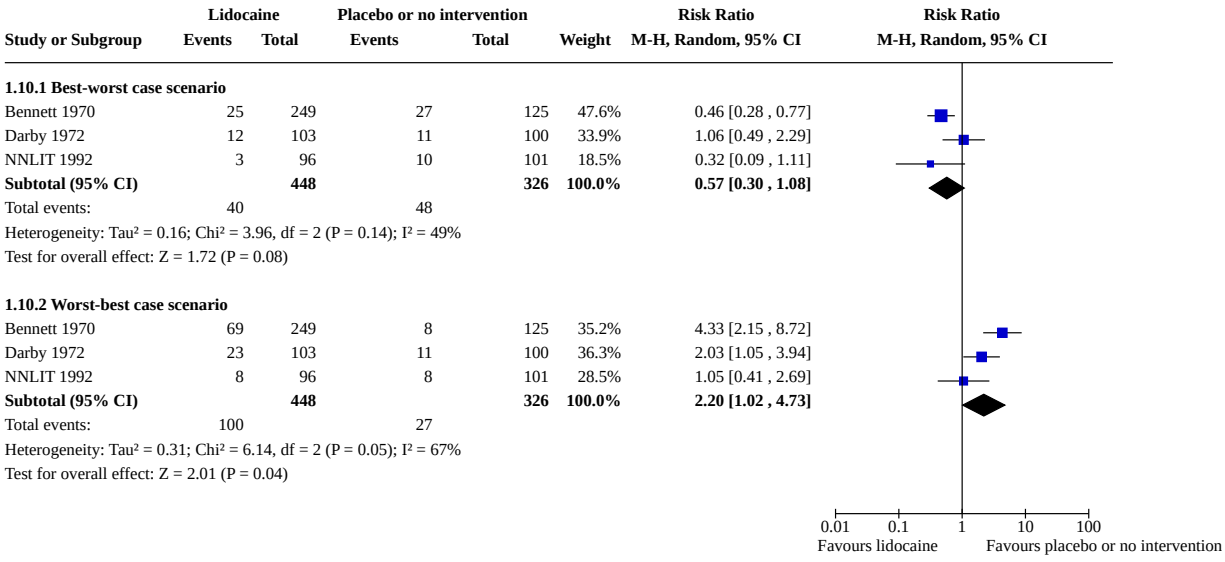


Study or Subgroup	Lidocaine Events	Lidocaine Total	Placebo or no intervention Events	Placebo or no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Pre-hospital setting lidocaine use						
ALIT 1985	7	1006	6	929	4.8%	1.08 [0.36 , 3.19]
Wennerblom 1982	5	28	5	26	4.6%	0.93 [0.30 , 2.84]
Subtotal (95% CI)		**1034**		**955**	**9.4%**	**1.00 [0.46 , 2.19]**
Total events:	12		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.01 (P = 1.00)						
1.8.2 Hospital setting lidocaine use						
Baker 1971	5	21	2	23	2.5%	2.74 [0.59 , 12.64]
Chopra 1971	7	39	4	43	4.4%	1.93 [0.61 , 6.09]
Darby 1972	12	103	11	100	9.0%	1.06 [0.49 , 2.29]
Lie 1974	8	107	10	105	7.0%	0.79 [0.32 , 1.91]
Lie 1978	5	147	6	153	4.3%	0.87 [0.27 , 2.78]
O'Brien 1973	11	154	4	146	4.6%	2.61 [0.85 , 8.00]
Pharand 1995	2	100	4	100	2.1%	0.50 [0.09 , 2.67]
Pitt 1971	9	108	16	114	9.0%	0.59 [0.27 , 1.29]
Poprawski 1987	23	86	20	86	17.2%	1.15 [0.68 , 1.93]
Rossi 1976	3	99	18	147	4.1%	0.25 [0.07 , 0.82]
Valentine 1974	21	156	18	113	14.5%	0.85 [0.47 , 1.51]
Subtotal (95% CI)		**1120**		**1130**	**78.7%**	**0.95 [0.69 , 1.32]**
Total events:	106		113			
Heterogeneity: Tau² = 0.09; Chi² = 14.26, df = 10 (P = 0.16); I² = 30%						
Test for overall effect: Z = 0.29 (P = 0.77)						
1.8.3 Lidocaine use in both pre-hospital and hospital settings						
Bennett 1970	25	249	8	125	9.1%	1.57 [0.73 , 3.38]
Dunn 1985	3	108	1	96	1.2%	2.67 [0.28 , 25.21]
Hargarten 1990	2	236	2	200	1.6%	0.85 [0.12 , 5.96]
Subtotal (95% CI)		**593**		**421**	**11.9%**	**1.53 [0.77 , 3.02]**
Total events:	30		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.22 (P = 0.22)						
Total (95% CI)		**2747**		**2506**	**100.0%**	**1.01 [0.79 , 1.30]**
Total events:	148		135			
Heterogeneity: Tau² = 0.02; Chi² = 16.47, df = 15 (P = 0.35); I² = 9%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Test for subgroup differences: Chi² = 1.52, df = 2 (P = 0.47), I² = 0%						

Analysis 1.9. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 9: All-cause mortality (subgroup analysis according to non-suspected trials with industry bias compared with suspected trials with industry bias)



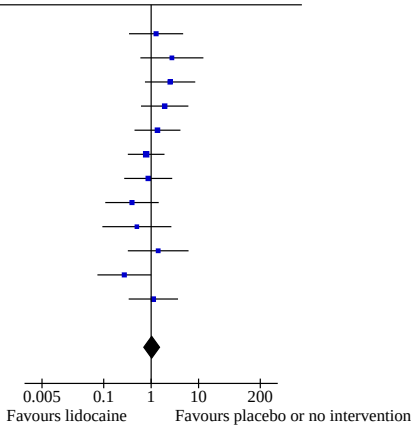
Analysis 1.10. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 10: All-cause mortality (sensitivity analysis by attrition bias)



Analysis 1.11. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 11: Cardiac mortality

Study or Subgroup	Lidocaine Events	Lidocaine Total	Placebo or no intervention Events	Placebo or no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
ALIT 1985	5	2987	4	3037	7.5%	1.27 [0.34 , 4.73]
Baker 1971	5	21	2	23	5.7%	2.74 [0.59 , 12.64]
Bennett 1970	15	249	3	125	8.5%	2.51 [0.74 , 8.51]
Chopra 1971	7	39	4	43	9.5%	1.93 [0.61 , 6.09]
Darby 1972	7	103	5	100	10.0%	1.36 [0.45 , 4.14]
Lie 1974	8	107	10	105	14.5%	0.79 [0.32 , 1.91]
Lie 1978	5	147	6	153	9.3%	0.87 [0.27 , 2.78]
NNLIT 1992	3	96	8	101	7.7%	0.39 [0.11 , 1.44]
Pharand 1995	2	100	4	100	4.8%	0.50 [0.09 , 2.67]
Pitt 1971	4	108	3	114	6.1%	1.41 [0.32 , 6.14]
Valentine 1974	3	156	8	113	7.6%	0.27 [0.07 , 1.00]
Wennerblom 1982	5	71	5	79	8.8%	1.11 [0.34 , 3.68]
Total (95% CI)		**4184**		**4093**	**100.0%**	**1.03 [0.70 , 1.50]**
Total events:	69		62			

Heterogeneity: Tau² = 0.06; Chi² = 12.55, df = 11 (P = 0.32); I² = 12%
Test for overall effect: Z = 0.13 (P = 0.90)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 12: Cardiac mortality (sensitivity analysis according to non-suspected trials of industry bias versus suspected trials of industry bias)

Study or Subgroup	Lidocaine Events	Lidocaine Total	Placebo or no intervention Events	Placebo or no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Trials non-sponsored by drug company						
ALIT 1985	5	2987	4	3037	7.5%	1.27 [0.34 , 4.73]
Baker 1971	5	21	2	23	5.7%	2.74 [0.59 , 12.64]
Darby 1972	7	103	5	100	10.0%	1.36 [0.45 , 4.14]
Lie 1978	5	147	6	153	9.3%	0.87 [0.27 , 2.78]
NNLIT 1992	3	96	8	101	7.7%	0.39 [0.11 , 1.44]
Pharand 1995	2	100	4	100	4.8%	0.50 [0.09 , 2.67]
Valentine 1974	3	156	8	113	7.6%	0.27 [0.07 , 1.00]
Wennerblom 1982	5	71	5	79	8.8%	1.11 [0.34 , 3.68]
Subtotal (95% CI)		**3681**		**3706**	**61.4%**	**0.85 [0.52 , 1.39]**
Total events:	35		42			

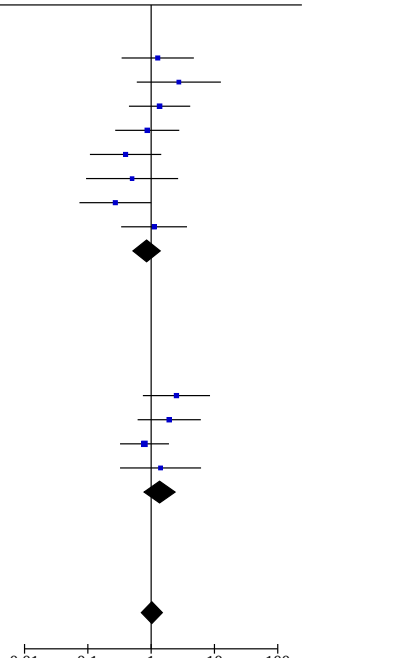
Heterogeneity: Tau² = 0.07; Chi² = 8.17, df = 7 (P = 0.32); I² = 14%
Test for overall effect: Z = 0.66 (P = 0.51)

1.12.2 Trials sponsored by drug company						
Bennett 1970	15	249	3	125	8.5%	2.51 [0.74 , 8.51]
Chopra 1971	7	39	4	43	9.5%	1.93 [0.61 , 6.09]
Lie 1974	8	107	10	105	14.5%	0.79 [0.32 , 1.91]
Pitt 1971	4	108	3	114	6.1%	1.41 [0.32 , 6.14]
Subtotal (95% CI)		**503**		**387**	**38.6%**	**1.36 [0.77 , 2.39]**
Total events:	34		20			

Heterogeneity: Tau² = 0.00; Chi² = 2.81, df = 3 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.07 (P = 0.29)

Total (95% CI)		**4184**		**4093**	**100.0%**	**1.03 [0.70 , 1.50]**
Total events:	69		62			

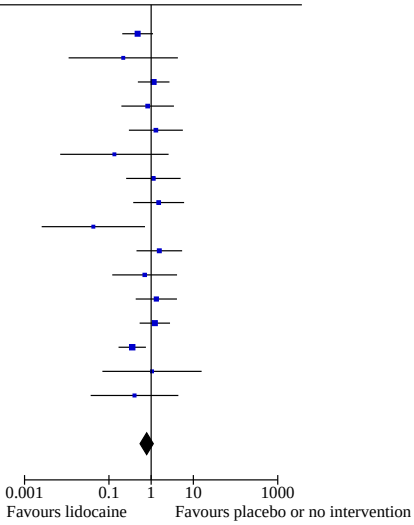
Heterogeneity: Tau² = 0.06; Chi² = 12.55, df = 11 (P = 0.32); I² = 12%
Test for overall effect: Z = 0.13 (P = 0.90)
Test for subgroup differences: Chi² = 1.52, df = 1 (P = 0.22), I² = 34.4%



Analysis 1.13. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 13: Ventricular fibrillation

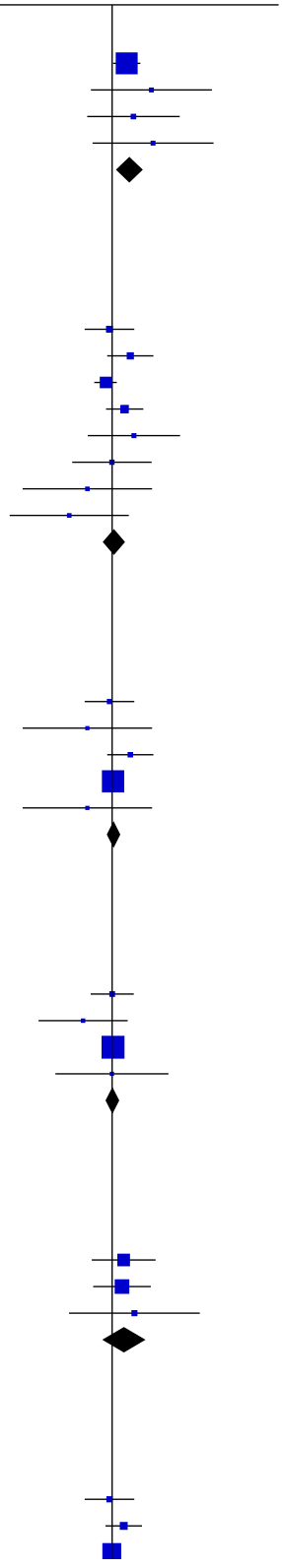
Study or Subgroup	Lidocaine Events	Lidocaine Total	Placebo or no intervention Events	Placebo or no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
ALIT 1985	8	2987	17	3037	12.4%	0.48 [0.21 , 1.11]
Baker 1971	0	21	2	23	1.4%	0.22 [0.01 , 4.30]
Bennett 1970	16	249	7	125	12.0%	1.15 [0.48 , 2.72]
Chopra 1971	3	39	4	43	5.4%	0.83 [0.20 , 3.47]
Darby 1972	4	103	3	100	5.2%	1.29 [0.30 , 5.64]
Dunn 1985	0	207	3	195	1.4%	0.13 [0.01 , 2.59]
Hargarten 1990	4	236	3	200	5.1%	1.13 [0.26 , 4.99]
Kuck 1985	4	23	3	26	5.7%	1.51 [0.38 , 6.04]
Lie 1974	0	107	11	105	1.6%	0.04 [0.00 , 0.72]
Lie 1978	6	147	4	153	6.9%	1.56 [0.45 , 5.42]
NNLIT 1992	2	96	3	101	3.8%	0.70 [0.12 , 4.11]
O'Brien 1973	7	154	5	146	8.1%	1.33 [0.43 , 4.09]
Poprawski 1987	11	86	9	86	12.6%	1.22 [0.53 , 2.80]
Sadowski 1999	9	445	26	458	14.4%	0.36 [0.17 , 0.75]
Solimene 1983	1	21	1	22	1.7%	1.05 [0.07 , 15.69]
Valentine 1974	1	207	2	167	2.1%	0.40 [0.04 , 4.41]
Total (95% CI)		**5128**		**4987**	**100.0%**	**0.78 [0.55 , 1.12]**
Total events:	76		103			

Heterogeneity: Tau² = 0.09; Chi² = 18.20, df = 15 (P = 0.25); I² = 18%
Test for overall effect: Z = 1.33 (P = 0.18)
Test for subgroup differences: Not applicable



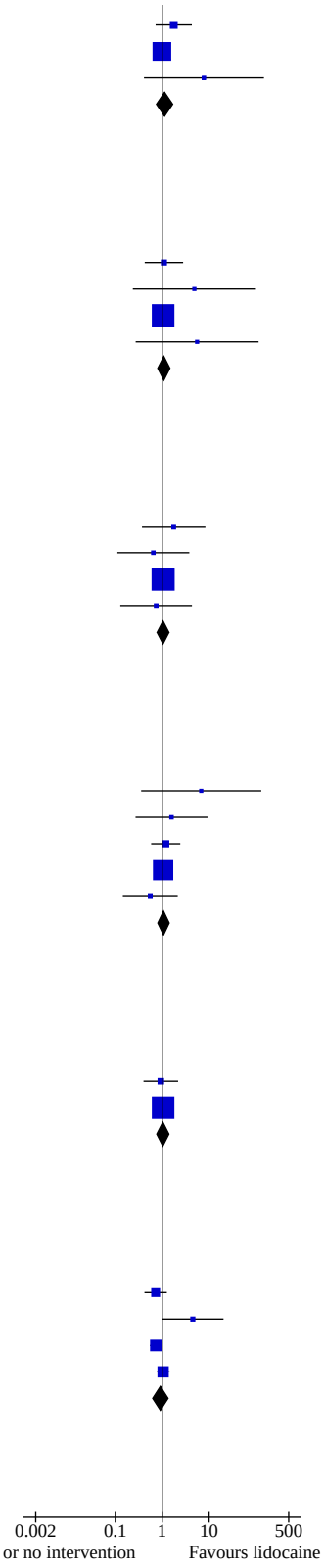
Analysis 1.14. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 14: Cardiovascular adverse events

Study or Subgroup	Lidocaine Events	Lidocaine Total	Placebo or no intervention Events	Placebo or no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
1.14.1 Asystole						
ALIT 1985	26	2987	13	3037	84.2%	2.03 [1.05 , 3.95]
Darby 1972	3	103	0	100	4.3%	6.80 [0.36 , 129.95]
Dunn 1985	3	207	1	195	7.3%	2.83 [0.30 , 26.94]
NNLIT 1992	3	96	0	101	4.3%	7.36 [0.39 , 140.65]
Subtotal (95% CI)		**3393**		**3433**	**100.0%**	**2.32 [1.26 , 4.26]**
Total events:	35		14			
Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 3 (P = 0.73); I² = 0%						
Test for overall effect: Z = 2.70 (P = 0.007)						
1.14.2 Sinus bradycardia						
Bennett 1970	7	249	4	125	13.4%	0.88 [0.26 , 2.94]
Darby 1972	10	103	4	100	15.0%	2.43 [0.79 , 7.49]
Dunn 1985	20	207	26	195	35.4%	0.72 [0.42 , 1.25]
Hargarten 1990	13	452	7	449	20.3%	1.84 [0.74 , 4.58]
Rademaker 1986	3	145	1	140	4.6%	2.90 [0.30 , 27.52]
Sandler 1976	2	91	2	90	6.0%	0.99 [0.14 , 6.87]
Touboul 1988	0	28	1	25	2.4%	0.30 [0.01 , 7.02]
Wennerblom 1982	0	71	4	79	2.8%	0.12 [0.01 , 2.25]
Subtotal (95% CI)		**1346**		**1203**	**100.0%**	**1.09 [0.66 , 1.80]**
Total events:	55		49			
Heterogeneity: Tau² = 0.11; Chi² = 8.89, df = 7 (P = 0.26); I² = 21%						
Test for overall effect: Z = 0.33 (P = 0.74)						
1.14.3 Bundle branch block						
Bennett 1970	7	249	4	125	5.9%	0.88 [0.26 , 2.94]
Capucci 1985	0	28	1	25	0.9%	0.30 [0.01 , 7.02]
Darby 1972	10	103	4	100	6.8%	2.43 [0.79 , 7.49]
Sadowski 1999	66	445	65	458	85.6%	1.05 [0.76 , 1.43]
Touboul 1988	0	28	1	25	0.9%	0.30 [0.01 , 7.02]
Subtotal (95% CI)		**853**		**733**	**100.0%**	**1.07 [0.80 , 1.44]**
Total events:	83		75			
Heterogeneity: Tau² = 0.00; Chi² = 3.41, df = 4 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.64)						
1.14.4 Non-complete atrioventricular block						
Bennett 1970	10	249	5	125	8.1%	1.00 [0.35 , 2.87]
Darby 1972	1	103	4	100	1.9%	0.24 [0.03 , 2.13]
Sadowski 1999	66	445	65	458	88.9%	1.05 [0.76 , 1.43]
Sandler 1976	1	91	1	90	1.2%	0.99 [0.06 , 15.57]
Subtotal (95% CI)		**888**		**773**	**100.0%**	**1.01 [0.75 , 1.37]**
Total events:	78		75			
Heterogeneity: Tau² = 0.00; Chi² = 1.71, df = 3 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.08 (P = 0.93)						
1.14.5 Complete atrioventricular block						
Bennett 1970	7	249	2	125	40.5%	1.76 [0.37 , 8.33]
Darby 1972	5	103	3	100	49.8%	1.62 [0.40 , 6.59]
Sandler 1976	1	91	0	90	9.7%	2.97 [0.12 , 71.89]
Subtotal (95% CI)		**443**		**315**	**100.0%**	**1.77 [0.66 , 4.78]**
Total events:	13		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.13 (P = 0.26)						
1.14.6 Unknown grade atrioventricular block						
Bennett 1970	7	249	4	125	10.3%	0.88 [0.26 , 2.94]
O'Brien 1973	13	154	7	146	18.3%	1.76 [0.72 , 4.29]
Sadowski 1999	43	445	45	458	69.6%	0.98 [0.66 , 1.46]



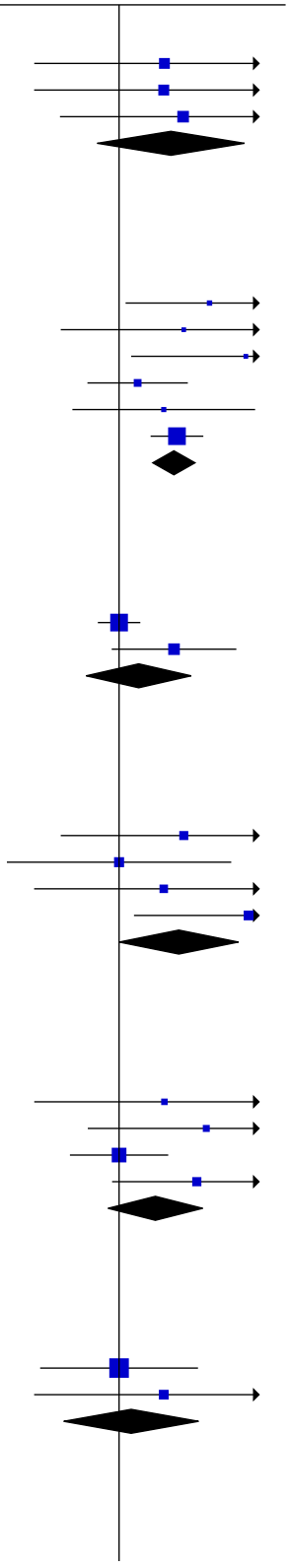
Analysis 1.14. (Continued)

O'Brien 1973	13	154	7	146	18.3%	1.76 [0.72 , 4.29]
Sadowski 1999	43	445	45	458	69.6%	0.98 [0.66 , 1.46]
Wennerblom 1982	3	71	0	79	1.8%	7.78 [0.41 , 148.01]
Subtotal (95% CI)		**919**		**808**	**100.0%**	**1.12 [0.75 , 1.67]**
Total events:	66		56			
Heterogeneity: Tau² = 0.02; Chi² = 3.23, df = 3 (P = 0.36); I² = 7%						
Test for overall effect: Z = 0.57 (P = 0.57)						
1.14.7 Pulmonary oedema						
Bennett 1970	13	249	6	125	9.9%	1.09 [0.42 , 2.79]
Darby 1972	2	103	0	100	1.0%	4.86 [0.24 , 99.90]
Sadowski 1999	66	445	65	458	88.1%	1.05 [0.76 , 1.43]
Wennerblom 1982	2	71	0	79	1.0%	5.56 [0.27 , 113.80]
Subtotal (95% CI)		**868**		**762**	**100.0%**	**1.08 [0.80 , 1.46]**
Total events:	83		71			
Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 3 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.52 (P = 0.60)						
1.14.8 Cardiogenic shock						
Bennett 1970	7	249	2	125	3.7%	1.76 [0.37 , 8.33]
Darby 1972	2	103	3	100	2.9%	0.65 [0.11 , 3.79]
Sadowski 1999	66	445	65	458	90.4%	1.05 [0.76 , 1.43]
Wennerblom 1982	2	71	3	79	2.9%	0.74 [0.13 , 4.31]
Subtotal (95% CI)		**868**		**762**	**100.0%**	**1.04 [0.77 , 1.41]**
Total events:	77		73			
Heterogeneity: Tau² = 0.00; Chi² = 0.86, df = 3 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.80)						
1.14.9 Hypotension						
Darby 1972	3	103	0	100	0.9%	6.80 [0.36 , 129.95]
NNLIT 1992	3	96	2	101	2.5%	1.58 [0.27 , 9.24]
Rossi 1976	12	99	15	147	15.1%	1.19 [0.58 , 2.43]
Sadowski 1999	66	445	65	458	77.2%	1.05 [0.76 , 1.43]
Wennerblom 1982	3	71	6	79	4.3%	0.56 [0.14 , 2.14]
Subtotal (95% CI)		**814**		**885**	**100.0%**	**1.07 [0.81 , 1.41]**
Total events:	87		88			
Heterogeneity: Tau² = 0.00; Chi² = 2.71, df = 4 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
1.14.10 Cardiac arrest						
Hargarten 1990	10	704	11	723	12.2%	0.93 [0.40 , 2.18]
Sadowski 1999	66	445	65	458	87.8%	1.05 [0.76 , 1.43]
Subtotal (95% CI)		**1149**		**1181**	**100.0%**	**1.03 [0.77 , 1.39]**
Total events:	76		76			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
1.14.11 Heart failure						
Dunn 1985	20	207	26	195	23.3%	0.72 [0.42 , 1.25]
Pharand 1995	9	100	2	100	5.5%	4.50 [1.00 , 20.31]
Rossi 1976	39	99	79	147	36.4%	0.73 [0.55 , 0.98]
Sadowski 1999	66	445	65	458	34.8%	1.05 [0.76 , 1.43]
Subtotal (95% CI)		**851**		**900**	**100.0%**	**0.91 [0.63 , 1.33]**
Total events:	134		172			
Heterogeneity: Tau² = 0.08; Chi² = 7.88, df = 3 (P = 0.05); I² = 62%						
Test for overall effect: Z = 0.47 (P = 0.64)						



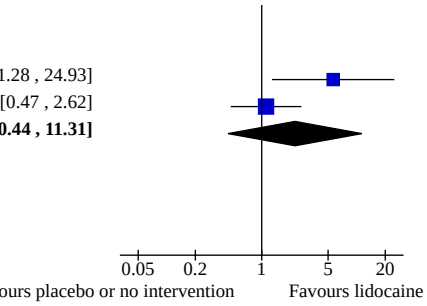
Analysis 1.15. Comparison 1: Lidocaine vs placebo or no intervention, Outcome 15: Neurological adverse events

Study or Subgroup	Lidocaine Events	Lidocaine Total	Placebo or no intervention Events	Placebo or no intervention Total	Weight	Risk Ratio M-H, Random, 95% CI
1.15.1 Seizures						
ALIT 1985	1	2987	0	3037	32.0%	3.05 [0.12 , 74.84]
Poprawski 1987	1	86	0	86	32.3%	3.00 [0.12 , 72.63]
Rademaker 1986	2	145	0	140	35.7%	4.83 [0.23 , 99.70]
Subtotal (95% CI)		**3218**		**3263**	**100.0%**	**3.58 [0.59 , 21.85]**
Total events:	4		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); I² = 0%						
Test for overall effect: Z = 1.38 (P = 0.17)						
1.15.2 Drowsiness/Dizziness						
Hargarten 1990	9	704	1	723	6.3%	9.24 [1.17 , 72.76]
Lie 1974	2	107	0	105	2.9%	4.91 [0.24 , 101.01]
Lie 1974	11	107	0	105	3.4%	22.57 [1.35 , 378.24]
NNLIT 1992	6	96	4	101	17.7%	1.58 [0.46 , 5.42]
Pharand 1995	3	100	1	100	5.3%	3.00 [0.32 , 28.35]
Rademaker 1986	43	145	10	140	64.3%	4.15 [2.17 , 7.93]
Subtotal (95% CI)		**1259**		**1274**	**100.0%**	**3.85 [2.29 , 6.47]**
Total events:	74		16			
Heterogeneity: Tau² = 0.00; Chi² = 4.55, df = 5 (P = 0.47); I² = 0%						
Test for overall effect: Z = 5.09 (P < 0.00001)						
1.15.3 Nausea/Vomiting						
Pharand 1995	22	100	22	100	64.3%	1.00 [0.59 , 1.69]
Rademaker 1986	8	145	2	140	35.7%	3.86 [0.83 , 17.87]
Subtotal (95% CI)		**245**		**240**	**100.0%**	**1.62 [0.45 , 5.89]**
Total events:	30		24			
Heterogeneity: Tau² = 0.60; Chi² = 2.77, df = 1 (P = 0.10); I² = 64%						
Test for overall effect: Z = 0.73 (P = 0.46)						
1.15.4 Speech disturbances						
Lie 1974	2	107	0	105	23.5%	4.91 [0.24 , 101.01]
Pharand 1995	1	100	1	100	28.3%	1.00 [0.06 , 15.77]
Poprawski 1987	1	86	0	86	21.2%	3.00 [0.12 , 72.63]
Rademaker 1986	12	145	0	140	27.1%	24.14 [1.44 , 403.93]
Subtotal (95% CI)		**438**		**431**	**100.0%**	**4.34 [1.00 , 18.81]**
Total events:	16		1			
Heterogeneity: Tau² = 0.00; Chi² = 2.95, df = 3 (P = 0.40); I² = 0%						
Test for overall effect: Z = 1.96 (P = 0.05)						
1.15.5 Confusion						
ALIT 1985	1	2987	0	3037	11.8%	3.05 [0.12 , 74.84]
O'Brien 1973	4	154	0	146	13.9%	8.54 [0.46 , 157.16]
Pharand 1995	5	100	5	100	50.1%	1.00 [0.30 , 3.35]
Rademaker 1986	7	145	1	140	24.2%	6.76 [0.84 , 54.23]
Subtotal (95% CI)		**3386**		**3423**	**100.0%**	**2.44 [0.76 , 7.81]**
Total events:	17		6			
Heterogeneity: Tau² = 0.32; Chi² = 3.80, df = 3 (P = 0.28); I² = 21%						
Test for overall effect: Z = 1.50 (P = 0.13)						
1.15.6 Agitation						
Pharand 1995	2	100	2	100	73.0%	1.00 [0.14 , 6.96]
Poprawski 1987	1	86	0	86	27.0%	3.00 [0.12 , 72.63]
Subtotal (95% CI)		**186**		**186**	**100.0%**	**1.35 [0.26 , 7.06]**
Total events:	3		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.73)						
1.15.7 Global adverse events in central nervous system						



Analysis 1.15. (Continued)

1.15.7 Global adverse events in central nervous system						
Dunn 1985	12	207	2	195	43.1%	5.65 [1.28 , 24.93]
Pharand 1995	10	100	9	100	56.9%	1.11 [0.47 , 2.62]
Subtotal (95% CI)		**307**		**295**	**100.0%**	**2.24 [0.44 , 11.31]**
Total events:	22		11			
Heterogeneity: Tau² = 1.01; Chi² = 3.64, df = 1 (P = 0.06); I² = 73%						
Test for overall effect: Z = 0.98 (P = 0.33)						



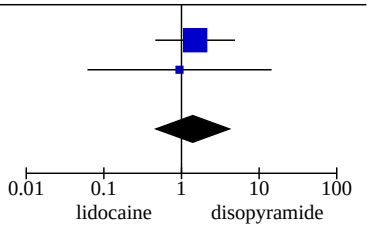
Comparison 2. Lidocaine vs disopyramide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality	2	144	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.47, 4.13]
2.2 All-cause mortality (sensitivity analysis by risk of attrition bias)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.2.1 Best-worst case scenario	2	144	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.08, 3.02]
2.2.2 Worst-best case scenario	2	144	Risk Ratio (M-H, Random, 95% CI)	2.75 [1.05, 7.20]
2.3 Cardiac mortality	2	144	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.21, 4.87]
2.4 Ventricular fibrillation	1	76	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.04, 3.06]
2.5 Cardiovascular adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.5.1 Pulmonary oedema	2	144	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.12, 3.10]
2.5.2 Cardiogenic shock	1	76	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.19, 21.14]
2.5.3 Asystole	1	76	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.93]
2.5.4 Sinoatrial block	1	68	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.06, 14.47]
2.5.5 Cardiac blocks (high-degree atrioventricular block and bundle branch block)	1	68	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.15, 2.18]
2.6 Neurological adverse events	1	68	Risk Ratio (M-H, Random, 95% CI)	6.61 [0.35, 123.30]

Analysis 2.1. Comparison 2: Lidocaine vs disopyramide, Outcome 1: All-cause mortality

Study or Subgroup	Lidocaine Events	Lidocaine Total	Disopyramide Events	Disopyramide Total	Weight	Risk Ratio M-H, Random, 95% CI
Pedersen 1986	6	38	4	38	84.2%	1.50 [0.46 , 4.89]
Ronnevik 1987	1	35	1	33	15.8%	0.94 [0.06 , 14.47]
Total (95% CI)		**73**		**71**	**100.0%**	**1.39 [0.47 , 4.13]**
Total events:	7		5			

Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



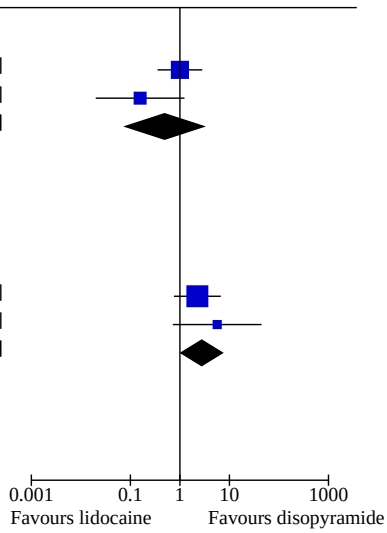
Analysis 2.2. Comparison 2: Lidocaine vs disopyramide, Outcome 2: All-cause mortality (sensitivity analysis by risk of attrition bias)

Study or Subgroup	Lidocaine Events	Lidocaine Total	Disopyramide Events	Disopyramide Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Best-worst case scenario						
Pedersen 1986	6	38	6	38	61.4%	1.00 [0.35 , 2.82]
Ronnevik 1987	1	35	6	33	38.6%	0.16 [0.02 , 1.24]
Subtotal (95% CI)		**73**		**71**	**100.0%**	**0.49 [0.08 , 3.02]**
Total events:	7		12			

Heterogeneity: Tau² = 1.12; Chi² = 2.62, df = 1 (P = 0.11); I² = 62%
Test for overall effect: Z = 0.77 (P = 0.44)

2.2.2 Worst-best case scenario						
Pedersen 1986	9	38	4	38	78.2%	2.25 [0.76 , 6.68]
Ronnevik 1987	6	35	1	33	21.8%	5.66 [0.72 , 44.51]
Subtotal (95% CI)		**73**		**71**	**100.0%**	**2.75 [1.05 , 7.20]**
Total events:	15		5			

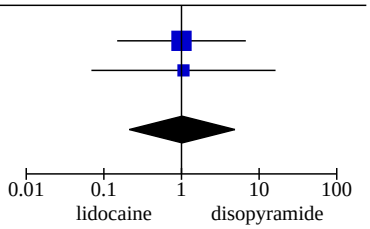
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)



Analysis 2.3. Comparison 2: Lidocaine vs disopyramide, Outcome 3: Cardiac mortality

Study or Subgroup	Lidocaine Events	Lidocaine Total	Disopyramide Events	Disopyramide Total	Weight	Risk Ratio M-H, Random, 95% CI
Pedersen 1986	2	38	2	38	67.2%	1.00 [0.15 , 6.74]
Ronnevik 1987	1	33	1	35	32.8%	1.06 [0.07 , 16.27]
Total (95% CI)		**71**		**73**	**100.0%**	**1.02 [0.21 , 4.87]**
Total events:	3		3			

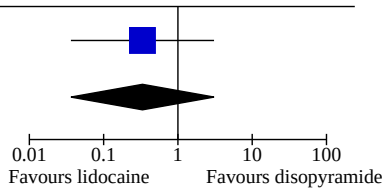
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.98)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Lidocaine vs disopyramide, Outcome 4: Ventricular fibrillation

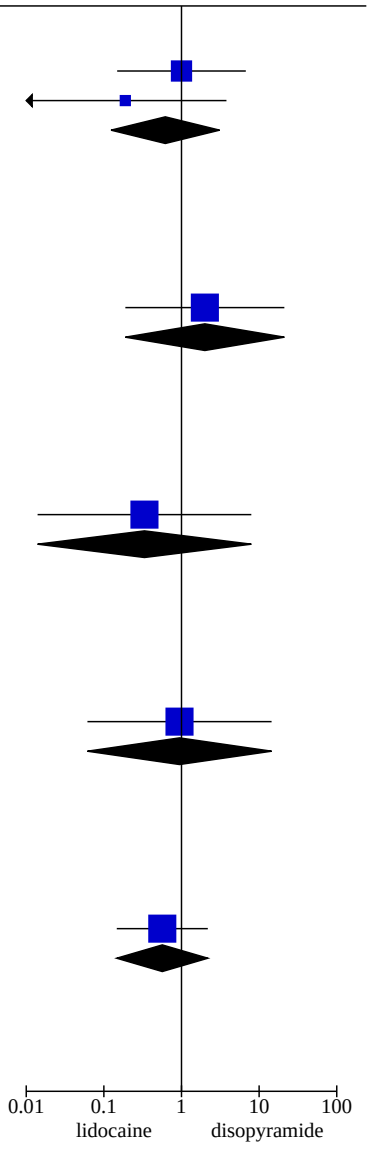
Study or Subgroup	Lidocaine Events	Lidocaine Total	Disopyramide Events	Disopyramide Total	Weight	Risk Ratio M-H, Random, 95% CI
Pedersen 1986	1	38	3	38	100.0%	0.33 [0.04 , 3.06]
Total (95% CI)		**38**		**38**	**100.0%**	**0.33 [0.04 , 3.06]**
Total events:	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Lidocaine vs disopyramide, Outcome 5: Cardiovascular adverse events

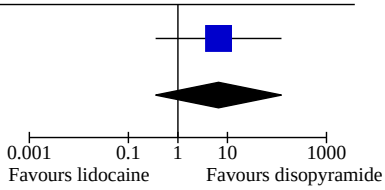
Study or Subgroup	Lidocaine Events	Lidocaine Total	Disopyramide Events	Disopyramide Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Pulmonary oedema						
Pedersen 1986	2	38	2	38	71.2%	1.00 [0.15 , 6.74]
Ronnevik 1987	0	35	2	33	28.8%	0.19 [0.01 , 3.79]
Subtotal (95% CI)		**73**		**71**	**100.0%**	**0.62 [0.12 , 3.10]**
Total events:	2		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						
2.5.2 Cardiogenic shock						
Pedersen 1986	2	38	1	38	100.0%	2.00 [0.19 , 21.14]
Subtotal (95% CI)		**38**		**38**	**100.0%**	**2.00 [0.19 , 21.14]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
2.5.3 Asystole						
Pedersen 1986	0	38	1	38	100.0%	0.33 [0.01 , 7.93]
Subtotal (95% CI)		**38**		**38**	**100.0%**	**0.33 [0.01 , 7.93]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
2.5.4 Sinoatrial block						
Ronnevik 1987	1	35	1	33	100.0%	0.94 [0.06 , 14.47]
Subtotal (95% CI)		**35**		**33**	**100.0%**	**0.94 [0.06 , 14.47]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
2.5.5 Cardiac blocks (high-degree atrioventricular block and bundle branch block)						
Ronnevik 1987	3	35	5	33	100.0%	0.57 [0.15 , 2.18]
Subtotal (95% CI)		**35**		**33**	**100.0%**	**0.57 [0.15 , 2.18]**
Total events:	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						



Analysis 2.6. Comparison 2: Lidocaine vs disopyramide, Outcome 6: Neurological adverse events

Study or Subgroup	Lidocaine Events	Lidocaine Total	Disopyramide Events	Disopyramide Total	Weight	Risk Ratio M-H, Random, 95% CI
Ronnevik 1987	3	35	0	33	100.0%	6.61 [0.35 , 123.30]
Total (95% CI)		**35**		**33**	**100.0%**	**6.61 [0.35 , 123.30]**
Total events:	3		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.27 (P = 0.21)
Test for subgroup differences: Not applicable



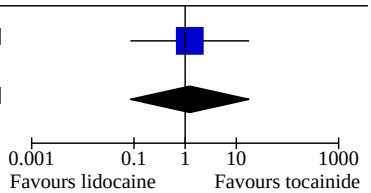
Comparison 3. Lidocaine vs tocainide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality	1	29	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.08, 17.83]
3.2 All-cause mortality (sensitivity analysis by risk of attrition bias)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.2.1 Best-worst case scenario	1	29	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.06, 6.05]
3.2.2 Worst-best case scenario	1	29	Risk Ratio (M-H, Random, 95% CI)	2.46 [0.25, 24.21]
3.3 Cardiac mortality	1	29	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.08, 17.83]
3.4 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.4.1 Any adverse event	2	69	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.07, 2.68]

Analysis 3.1. Comparison 3: Lidocaine vs tocainide, Outcome 1: All-cause mortality

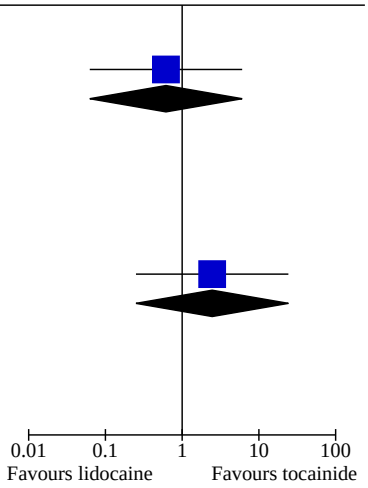
Study or Subgroup	Lidocaine Events	Lidocaine Total	Tocainide Events	Tocainide Total	Weight	Risk Ratio M-H, Random, 95% CI
Keefe 1986	1	13	1	16	100.0%	1.23 [0.08 , 17.83]
Total (95% CI)		**13**		**16**	**100.0%**	**1.23 [0.08 , 17.83]**
Total events:	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable



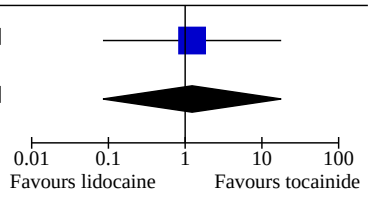
Analysis 3.2. Comparison 3: Lidocaine vs tocainide, Outcome 2: All-cause mortality (sensitivity analysis by risk of attrition bias)

Study or Subgroup	Lidocaine Events	Lidocaine Total	Tocainide Events	Tocainide Total	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Best-worst case scenario						
Keefe 1986	1	13	2	16	100.0%	0.62 [0.06 , 6.05]
Subtotal (95% CI)		**13**		**16**	**100.0%**	**0.62 [0.06 , 6.05]**
Total events:	1		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.42 (P = 0.68)						
3.2.2 Worst-best case scenario						
Keefe 1986	2	13	1	16	100.0%	2.46 [0.25 , 24.21]
Subtotal (95% CI)		**13**		**16**	**100.0%**	**2.46 [0.25 , 24.21]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						



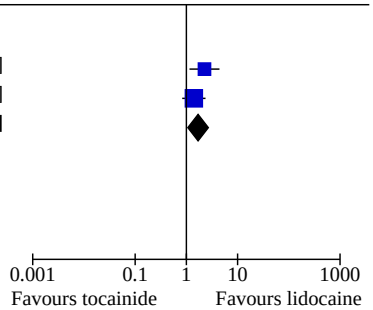
Analysis 3.3. Comparison 3: Lidocaine vs tocainide, Outcome 3: Cardiac mortality

Study or Subgroup	Lidocaine Events	Lidocaine Total	Tocainide Events	Tocainide Total	Weight	Risk Ratio M-H, Random, 95% CI
Keefe 1986	1	13	1	16	100.0%	1.23 [0.08 , 17.83]
Total (95% CI)		**13**		**16**	**100.0%**	**1.23 [0.08 , 17.83]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
Test for subgroup differences: Not applicable						



Analysis 3.4. Comparison 3: Lidocaine vs tocainide, Outcome 4: Adverse events

Study or Subgroup	Lidocaine Events	Lidocaine Total	Tocainide Events	Tocainide Total	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Any adverse event						
Keefe 1986	11	13	6	16	39.8%	2.26 [1.15 , 4.43]
Rehnqvist 1983	14	20	10	20	60.2%	1.40 [0.83 , 2.36]
Subtotal (95% CI)		**33**		**36**	**100.0%**	**1.69 [1.07 , 2.68]**
Total events:	25		16			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 1.21$, df = 1 (P = 0.27); $I^2 = 17\%$						
Test for overall effect: Z = 2.25 (P = 0.02)						



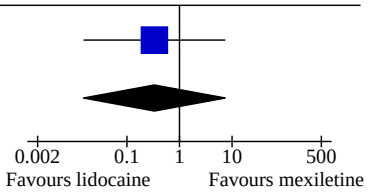
Comparison 4. Lidocaine vs mexiletine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 All-cause mortality	1	24	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.45]
4.2 Cardiac mortality	1	24	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.45]
4.3 Ventricular fibrillation	1	24	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 67.06]
4.4 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.4.1 Cardiogenic shock	1	24	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.45]
4.4.2 Atrioventricular block	1	24	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.45]
4.4.3 Pulmonary oedema	1	24	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.30, 7.43]
4.4.4 Composite neurological adverse event (confusion, vertigo, nystagmus and diplopia)	2	74	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.16, 2.47]

Analysis 4.1. Comparison 4: Lidocaine vs mexiletine, Outcome 1: All-cause mortality

Study or Subgroup	Lidocaine Events	Lidocaine Total	Mexiletine Events	Mexiletine Total	Weight	Risk Ratio M-H, Random, 95% CI
Horowitz 1981	0	12	1	12	100.0%	0.33 [0.01 , 7.45]
Total (95% CI)		**12**		**12**	**100.0%**	**0.33 [0.01 , 7.45]**
Total events:	0		1			

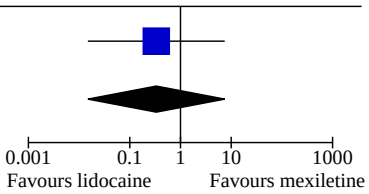
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Lidocaine vs mexiletine, Outcome 2: Cardiac mortality

Study or Subgroup	Lidocaine Events	Lidocaine Total	Mexiletine Events	Mexiletine Total	Weight	Risk Ratio M-H, Random, 95% CI
Horowitz 1981	0	12	1	12	100.0%	0.33 [0.01 , 7.45]
Total (95% CI)		**12**		**12**	**100.0%**	**0.33 [0.01 , 7.45]**
Total events:	0		1			

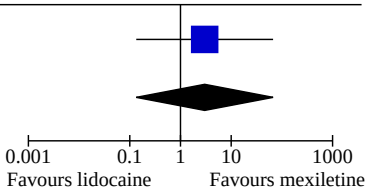
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



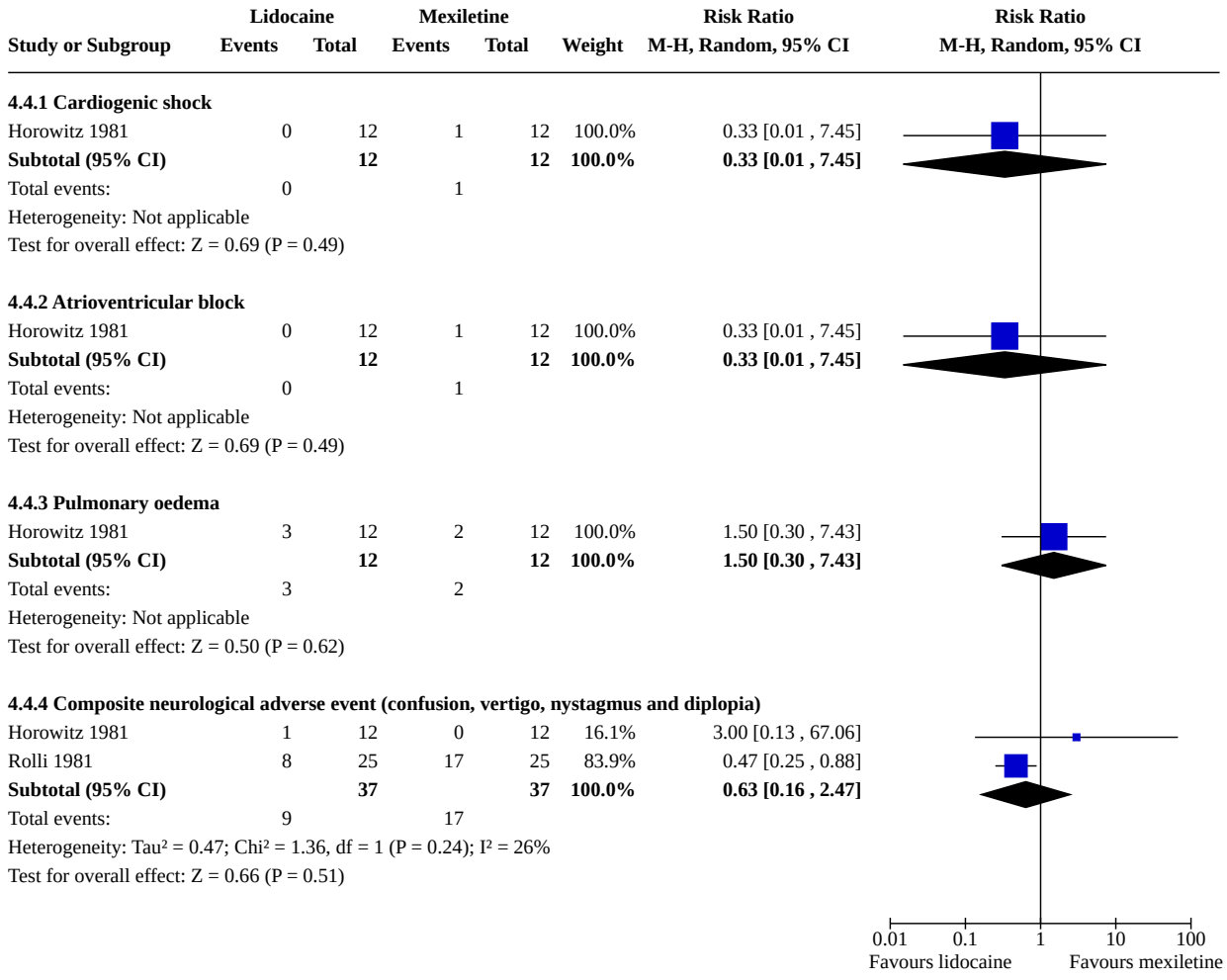
Analysis 4.3. Comparison 4: Lidocaine vs mexiletine, Outcome 3: Ventricular fibrillation

Study or Subgroup	Lidocaine Events	Lidocaine Total	Mexiletine Events	Mexiletine Total	Weight	Risk Ratio M-H, Random, 95% CI
Horowitz 1981	1	12	0	12	100.0%	3.00 [0.13 , 67.06]
Total (95% CI)		**12**		**12**	**100.0%**	**3.00 [0.13 , 67.06]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Analysis 4.4. Comparison 4: Lidocaine vs mexiletine, Outcome 4: Adverse events

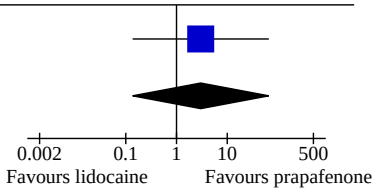


Comparison 5. Lidocaine vs propafenone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Ventricular fibrillation	1	20	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.14, 65.90]
5.2 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.2.1 Heart failure	1	64	Risk Ratio (M-H, Random, 95% CI)	6.38 [0.32, 127.77]
5.2.2 Bilateral bundle branch block	1	64	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.02, 10.06]
5.2.3 Neuropsychiatric disturbances	2	84	Risk Ratio (M-H, Random, 95% CI)	6.95 [0.86, 55.94]

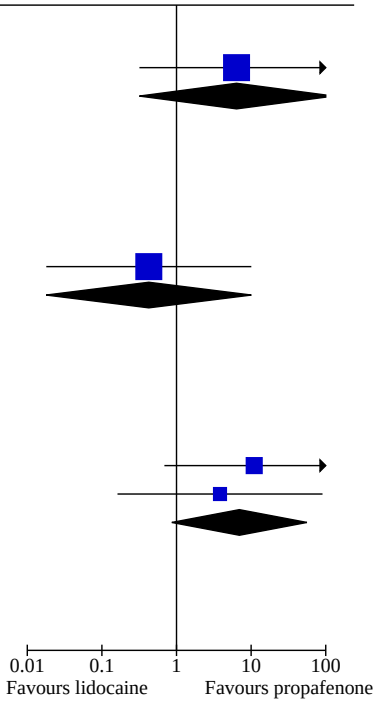
Analysis 5.1. Comparison 5: Lidocaine vs propafenone, Outcome 1: Ventricular fibrillation

Study or Subgroup	Lidocaine Events	Lidocaine Total	Propafenone Events	Propafenone Total	Weight	Risk Ratio M-H, Random, 95% CI
Rehnqvist 1984	1	10	0	10	100.0%	3.00 [0.14 , 65.90]
Total (95% CI)		**10**		**10**	**100.0%**	**3.00 [0.14 , 65.90]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
Test for subgroup differences: Not applicable						



Analysis 5.2. Comparison 5: Lidocaine vs propafenone, Outcome 2: Adverse events

Study or Subgroup	Lidocaine Events	Lidocaine Total	Propafenone Events	Propafenone Total	Weight	Risk Ratio M-H, Random, 95% CI
5.2.1 Heart failure						
Touboul 1988	2	28	0	36	100.0%	6.38 [0.32 , 127.77]
Subtotal (95% CI)		**28**		**36**	**100.0%**	**6.38 [0.32 , 127.77]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
5.2.2 Bilateral bundle branch block						
Touboul 1988	0	28	1	36	100.0%	0.43 [0.02 , 10.06]
Subtotal (95% CI)		**28**		**36**	**100.0%**	**0.43 [0.02 , 10.06]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
5.2.3 Neuropsychiatric disturbances						
Rehnqvist 1984	5	10	0	10	56.6%	11.00 [0.69 , 175.86]
Touboul 1988	1	28	0	36	43.4%	3.83 [0.16 , 90.53]
Subtotal (95% CI)		**38**		**46**	**100.0%**	**6.95 [0.86 , 55.94]**
Total events:	6		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 1.82 (P = 0.07)						



Comparison 6. Lidocaine vs amiodarone

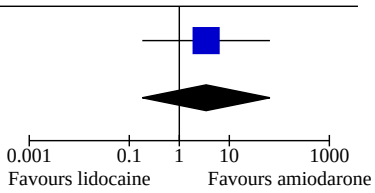
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Ventricular fibrillation	1	25	Risk Ratio (M-H, Random, 95% CI)	3.44 [0.18, 64.88]
6.2 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.2.1 Bradycardia	1	25	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.01, 5.12]
6.2.2 Hypotension	1	25	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2.3 Diplopia plus sleepiness	1	25	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.09, 46.11]

Analysis 6.1. Comparison 6: Lidocaine vs amiodarone, Outcome 1: Ventricular fibrillation

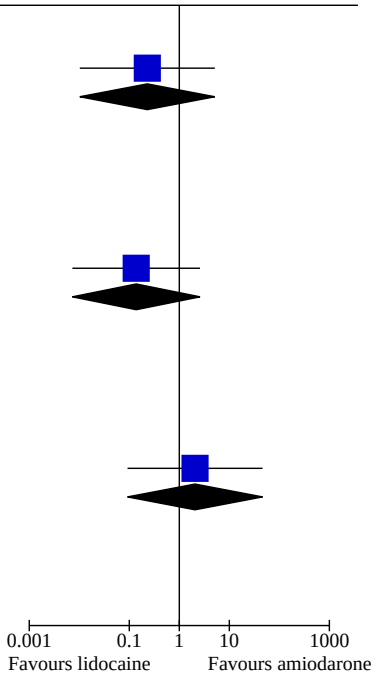
Study or Subgroup	Lidocaine Events	Lidocaine Total	Amiodarone Events	Amiodarone Total	Weight	Risk Ratio M-H, Random, 95% CI
Capucci 1985	2	15	0	10	100.0%	3.44 [0.18 , 64.88]
Total (95% CI)		**15**		**10**	**100.0%**	**3.44 [0.18 , 64.88]**
Total events:	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable



Analysis 6.2. Comparison 6: Lidocaine vs amiodarone, Outcome 2: Adverse events

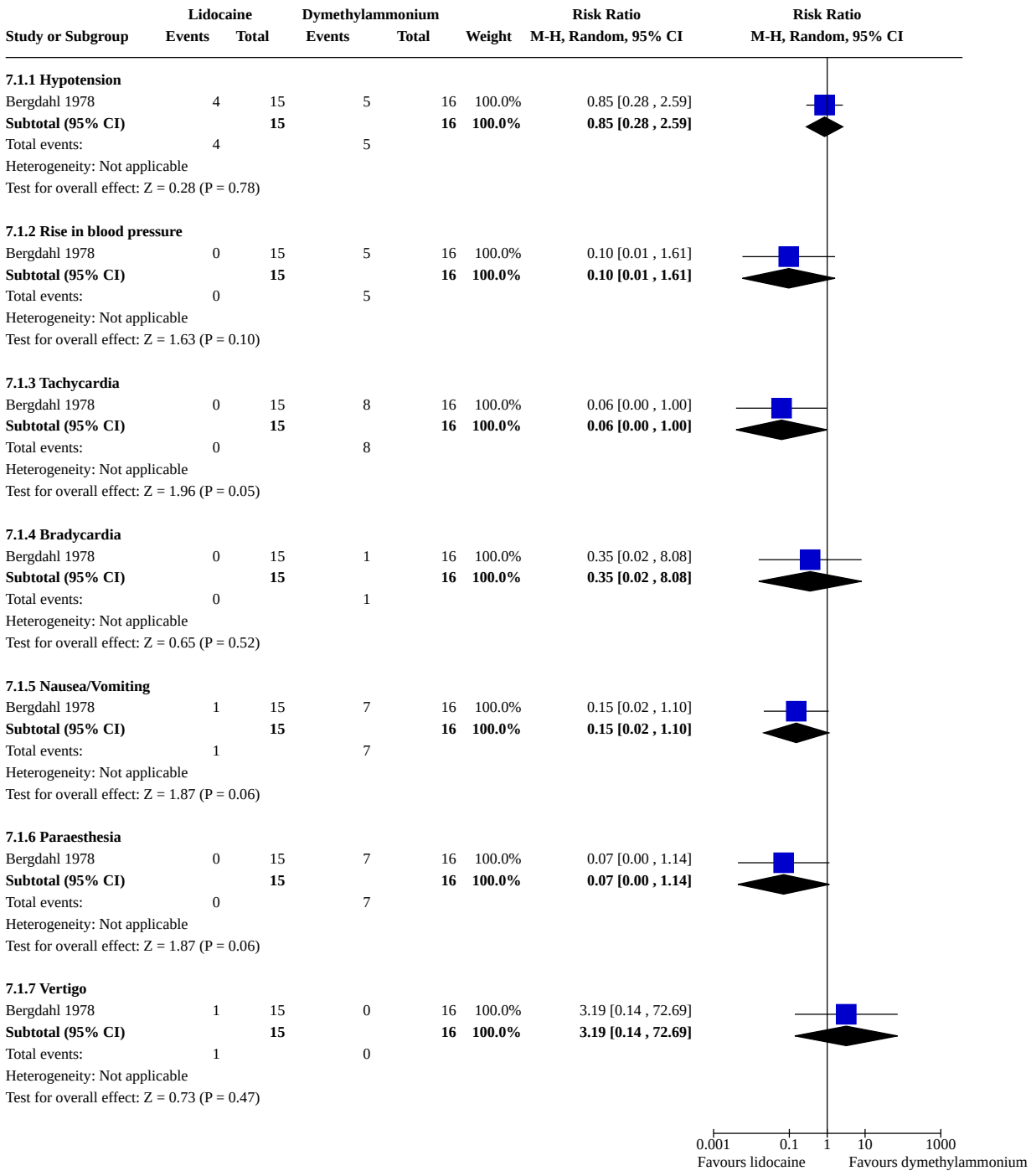
Study or Subgroup	Lidocaine Events	Lidocaine Total	Amiodarone Events	Amiodarone Total	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Bradycardia						
Capucci 1985	0	15	1	10	100.0%	0.23 [0.01 , 5.12]
Subtotal (95% CI)		**15**		**10**	**100.0%**	**0.23 [0.01 , 5.12]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
6.2.2 Hypotension						
Capucci 1985	0	15	2	10	100.0%	0.14 [0.01 , 2.60]
Subtotal (95% CI)		**15**		**10**	**100.0%**	**0.14 [0.01 , 2.60]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.32 (P = 0.19)						
6.2.3 Diplopia plus sleepiness						
Capucci 1985	1	15	0	10	100.0%	2.06 [0.09 , 46.11]
Subtotal (95% CI)		**15**		**10**	**100.0%**	**2.06 [0.09 , 46.11]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						



Comparison 7. Lidocaine vs dimethylammonium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1.1 Hypotension	1	31	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.28, 2.59]
7.1.2 Rise in blood pressure	1	31	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 1.61]
7.1.3 Tachycardia	1	31	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.00, 1.00]
7.1.4 Bradycardia	1	31	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.02, 8.08]
7.1.5 Nausea/Vomiting	1	31	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.02, 1.10]
7.1.6 Paraesthesia	1	31	Risk Ratio (M-H, Random, 95% CI)	0.07 [0.00, 1.14]
7.1.7 Vertigo	1	31	Risk Ratio (M-H, Random, 95% CI)	3.19 [0.14, 72.69]

Analysis 7.1. Comparison 7: Lidocaine vs dimethylammonium, Outcome 1: Adverse events

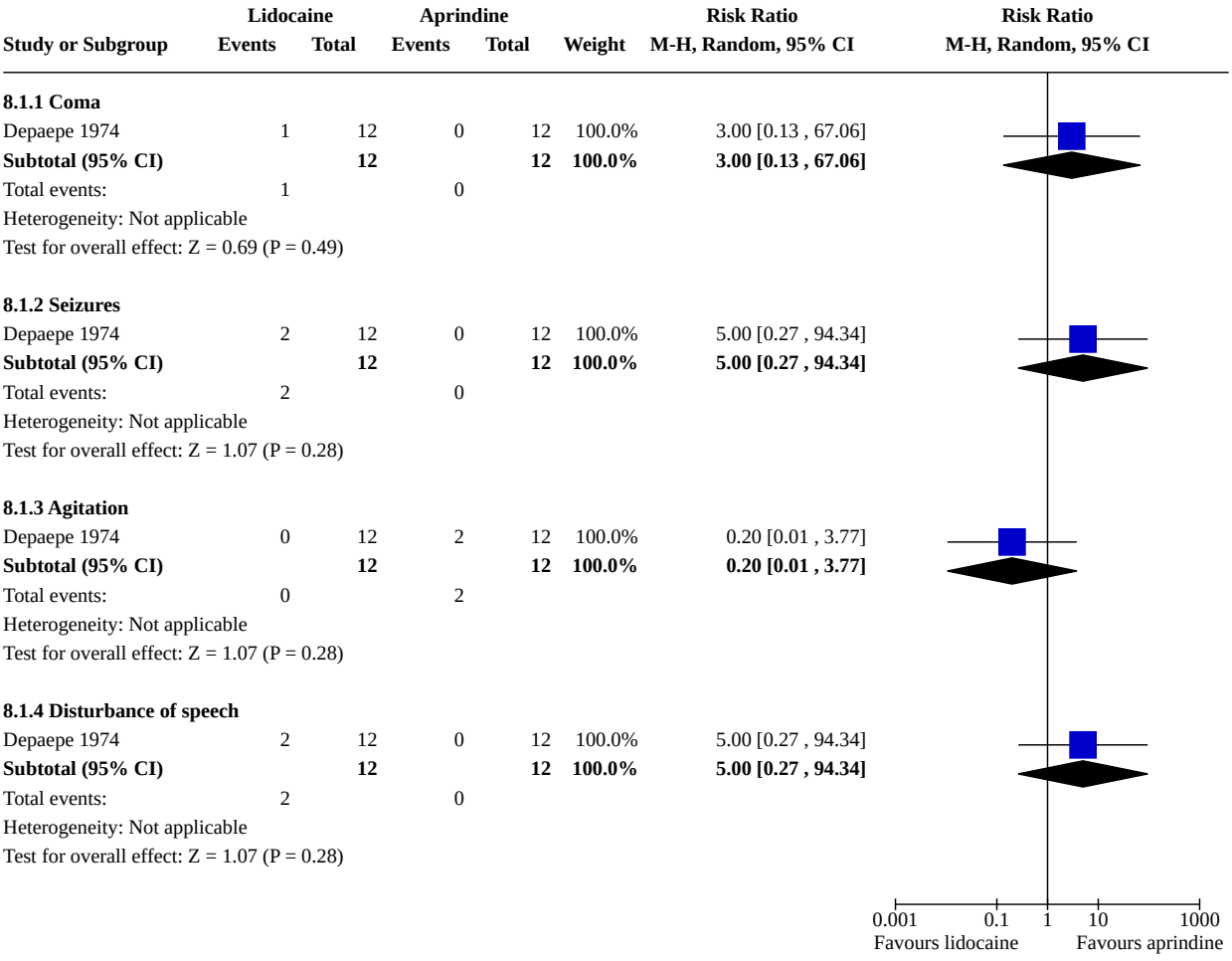


Comparison 8. Lidocaine vs aprindine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1.1 Coma	1	24	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 67.06]
8.1.2 Seizures	1	24	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.27, 94.34]
8.1.3 Agitation	1	24	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 3.77]
8.1.4 Disturbance of speech	1	24	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.27, 94.34]

Analysis 8.1. Comparison 8: Lidocaine vs aprindine, Outcome 1: Adverse events



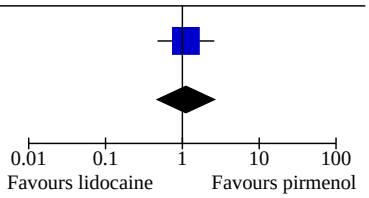
Comparison 9. Lidocaine vs pirmenol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Adverse event	1	19	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.47, 2.60]

Analysis 9.1. Comparison 9: Lidocaine vs pirmenol, Outcome 1: Adverse event

Study or Subgroup	Lidocaine Events	Lidocaine Total	Pirmenol Events	Pirmenol Total	Weight	Risk Ratio M-H, Random, 95% CI
Cuendet 1988	5	9	5	10	100.0%	1.11 [0.47 , 2.60]
Total (95% CI)		**9**		**10**	**100.0%**	**1.11 [0.47 , 2.60]**
Total events:	5		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Glossary of clinical and epidemiological terms

Terms	DEFINITION	REFERENCE
Acute coronary syndrome	An episode of myocardial ischemia that generally lasts longer than a transient anginal episode and ultimately may lead to myocardial infarction.	MeSH Database from PubMed U.S. National Library of Medicine
Amiodarone	An antianginal and antiarrhythmic drug. It increases the duration of ventricular and atrial muscle action by inhibiting Na,K-activated myocardial adenosine triphosphatase. A decrease in heart rate and in vascular resistance results. .	MeSH Database from PubMed U.S. National Library of Medicine
Anterior wall myocardial infarction	Myocardial infarction in which the anterior wall of the heart is involved. Anterior wall myocardial infarction is often caused by occlusion of the left anterior descending coronary artery. It can be categorised as anteroseptal or anterolateral wall myocardial infarction.	MeSH Database from PubMed U.S. National Library of Medicine
Antiarrhythmic treatment	Agents used for the treatment or prevention of cardiac arrhythmias. They may affect the polarisation-repolarisation phase of the action potential, its excitability or refractoriness or impulse conduction or membrane responsiveness within cardiac fibers.	MeSH Database from PubMed U.S. National Library of Medicine
Arrhythmias	Any disturbances of the normal rhythmical beating of the heart or myocardial contraction. Cardiac arrhythmias can be classified by abnormalities in heart rate, disorders of electrical impulse generation or impulse conduction.	MeSH Database from PubMed U.S. National Library of Medicine
Atrioventricular block	Impaired impulse conduction from heart atria to heart ventricles. AV block can mean delayed or completely blocked impulse conduction.	MeSH Database from PubMed U.S. National Library of Medicine
Atropine	An alkaloid, originally from *Atropa belladonna*.	MeSH Database from PubMed U.S. National Library of Medicine

(Continued)

B		
Bradycardia	Cardiac arrhythmias characterised by excessively slow heart rate, usually below 50 beats per minute in human adults. These arrhythmias can be classified broadly into sinoatrial node dysfunction and atrioventricular blocks.	MeSH Database from PubMed U.S. National Library of Medicine
Bundle branch block	Form of heart block in which electrical stimulation of heart ventricles is interrupted at one of the branches of the bundle of His, thus preventing simultaneous depolarisation of the 2 ventricles.	MeSH Database from PubMed U.S. National Library of Medicine
C		
Calcium antagonist drugs	A class of drugs that act by selective inhibition of calcium influx through cell membranes or on release and binding of calcium in intracellular pools. As they are inducers of vascular and other smooth muscle relaxation, these agents are used in drug therapy for hypertension and cerebrovascular spasms, as myocardial protective agents and in relaxation of uterine spasms.	MeSH Database from PubMed U.S. National Library of Medicine
Cardiac complexes, premature	A group of cardiac arrhythmias in which cardiac contractions are not initiated at the sinoatrial node. They include both atrial and ventricular premature beats, and are also known as extra or ectopic heartbeats. Their frequency is increased in individuals with heart disease.	MeSH Database from PubMed U.S. National Library of Medicine
Cardiogenic shock	Shock resulting from diminution of cardiac output in heart disease.	MeSH Database from PubMed U.S. National Library of Medicine
Central nervous system	The main information-processing organs of the nervous system, consisting of brain, spinal cord and meninges.	MeSH Database from PubMed U.S. National Library of Medicine
Congestive heart failure	A heterogeneous condition in which the heart is unable to pump out sufficient blood to meet the metabolic needs of the body. Heart failure can be caused by structural defects, functional abnormalities (ventricular dysfunction) or sudden overload beyond capacity. Chronic heart failure is more common than acute heart failure, which results from sudden insult to cardiac function, such as myocardial infarction.	MeSH Database from PubMed U.S. National Library of Medicine
Consciousness disorders	Organic mental disorders characterised by impairment of the ability to maintain awareness of self and environment, and to respond to environmental stimuli. Dysfunction of the cerebral hemispheres or of the brain stem reticular formation may result in this condition.	MeSH Database from PubMed U.S. National Library of Medicine
Coronary care unit	The hospital unit in which patients with acute cardiac disorders receive intensive care.	MeSH Database from PubMed U.S. National Library of Medicine

(Continued)

Creatine phosphokinase	A transferase that catalyses formation of phosphocreatine from ATP + creatine. The reaction stores ATP energy as phosphocreatine. Three cytoplasmic isoenzymes have been identified in human tissues: the MM type from skeletal muscle, the MB type from myocardial tissue and the BB type from nervous tissue and from a mitochondrial isoenzyme. Macro-creatine kinase refers to creatine kinase complexed with other serum proteins.	MeSH Database from PubMed U.S. National Library of Medicine
Cyanosis	A bluish or purplish discoloration of the skin and mucous membranes due to an increase in the amount of deoxygenated haemoglobin in the blood or a structural defect in the haemoglobin molecule.	MeSH Database from PubMed U.S. National Library of Medicine
D		
Disopyramide	A class I antiarrhythmic agent (one that interferes directly with depolarisation of cardiac membrane and thus serves as a membrane-stabilising agent) with a depressant action on the heart, similar to that of guanidine. It possesses anticholinergic and local anaesthetic properties.	MeSH Database from PubMed U.S. National Library of Medicine
Dysrhythmias	Any disturbances of normal rhythmic beating of the heart or myocardial contraction. Cardiac arrhythmias can be classified by abnormalities in heart rate, disorders of electrical impulse generation or impulse conduction.	MeSH Database from PubMed U.S. National Library of Medicine
E		
Electrocardiography	Recording of the moment-to-moment electromotive forces of the heart as projected onto various sites on the body's surface, delineated as a scalar function of time. The recording is monitored by tracing on slow-moving chart paper or by observing on a cardioscope, which is a cathode ray tube display.	MeSH Database from PubMed U.S. National Library of Medicine
F		
Furosemide	A benzoic-sulfonamide-furan. This diuretic with fast onset and short duration is used for oedema and chronic renal insufficiency.	MeSH Database from PubMed U.S. National Library of Medicine
H		
Heart failure	A heterogeneous condition in which the heart is unable to pump out sufficient blood to meet the metabolic needs of the body. Heart failure can be caused by structural defects, functional abnormalities (ventricular dysfunction) or sudden overload beyond capacity. Chronic heart failure is more common than acute heart failure, which results from sud-	MeSH Database from PubMed U.S. National Library of Medicine

(Continued)

	den insult to cardiac function, such as myocardial infarction.	
Hypokalemia	Abnormally low potassium concentration in the blood. This may result from potassium loss by renal secretion or by the gastrointestinal route, as by vomiting or diarrhoea. It may manifest clinically by neuromuscular disorders ranging from weakness to paralysis, by electrocardiographic abnormalities (depression of the T wave and elevation of the U wave), by renal disease and by gastrointestinal disorders.	MeSH Database from PubMed U.S. National Library of Medicine
Hypotension	Abnormally low blood pressure that can result in inadequate blood flow to the brain and other vital organs. Common symptom is dizziness, but greater negative impacts on the body occur when deprivation of oxygen and nutrients is prolonged.	MeSH Database from PubMed U.S. National Library of Medicine
I		
Inferior wall myocardial infarction	Myocardial infarction involving the inferior wall of the heart. This is often caused by occlusion of the right coronary artery.	MeSH Database from PubMed U.S. National Library of Medicine
Infusion	The administration of liquid medication, nutrient or other fluid through a route other than the alimentary canal, usually over minutes or hours, by gravity flow or often by infusion pumping.	MeSH Database from PubMed U.S. National Library of Medicine
L		
Lidocaine	A local anaesthetic and cardiac depressant used as an antiarrhythmia agent. Its actions are more intense and its effects more prolonged than those of procaine, but its duration of action is shorter than that of bupivacaine or prilocaine.	MeSH Database from PubMed U.S. National Library of Medicine
Loss of consciousness	Loss of the ability to maintain awareness of self and environment combined with markedly reduced responsiveness to environmental stimuli.	MeSH Database from PubMed U.S. National Library of Medicine
M		
Mexiletine	Antiarrhythmic agent pharmacologically similar to lidocaine. It may have some anticonvulsant properties.	MeSH Database from PubMed U.S. National Library of Medicine
Morphine	The principal alkaloid in opium and the prototype opiate analgesic and narcotic. Morphine has widespread effects in the central nervous system and on smooth muscle.	MeSH Database from PubMed U.S. National Library of Medicine
N		

(Continued)

Nausea	An unpleasant sensation in the stomach usually accompanied by the urge to vomit. Common causes are early pregnancy, sea and motion sickness, emotional stress, intense pain, food poisoning and various enteroviruses.	MeSH Database from PubMed U.S. National Library of Medicine
P		
Pacemaker	A device designed to stimulate, by electrical impulses, contraction of the heart muscles. It may be temporary (external) or permanent (internal or internal-external).	MeSH Database from PubMed U.S. National Library of Medicine
Paraesthesia	Subjective cutaneous sensations (e.g. cold, warmth, tingling, pressure) experienced spontaneously in the absence of stimulation.	MeSH Database from PubMed U.S. National Library of Medicine
Prajmalium	A derivative of the rauwolfia alkaloid ajmaline. It is an anti-arrhythmia agent but may cause liver damage.	MeSH Database from PubMed U.S. National Library of Medicine
Premature ventricular complexes	A type of cardiac arrhythmia with premature contractions of the heart ventricles. It is characterised by the premature QRS complex on ECG that is of abnormal shape and great duration (generally >129 msec). It is the most common form of all cardiac arrhythmias. Premature ventricular complexes have no clinical significance, except in concurrence with heart diseases.	MeSH Database from PubMed U.S. National Library of Medicine
Procainamide	A derivative of procaine with less central nervous system action. It acts as a non-nucleoside inhibitor of DNA methylation and has led to systemic lupus erythematosus.	MeSH Database from PubMed U.S. National Library of Medicine
Propafenone	An antiarrhythmia agent that is particularly effective in ventricular arrhythmias. It also has weak beta-blocking activity. The drug is generally well tolerated.	MeSH Database from PubMed U.S. National Library of Medicine
Pulmonary oedema	Excessive accumulation of extravascular fluid in the lung, an indication of a serious underlying disease or disorder. Pulmonary oedema prevents efficient pulmonary gas exchange in the pulmonary alveoli, and can be life-threatening.	MeSH Database from PubMed U.S. National Library of Medicine
Pump failure (heart failure)	A heterogeneous condition in which the heart is unable to pump out sufficient blood to meet the metabolic needs of the body. Heart failure can be caused by structural defects, functional abnormalities (ventricular dysfunction) or sudden overload beyond the capacity of the heart. Chronic heart failure is more common than acute heart failure, which results from sudden insult to cardiac function, such as myocardial infarction.	MeSH Database from PubMed U.S. National Library of Medicine
S		
Saline solution	Hypertonic sodium chloride solution. A solution having an osmotic pressure greater than that of physiological salt solution (0.9 g NaCl in 100 mL purified water).	MeSH Database from PubMed U.S. National Library of Medicine

(Continued)

Seizures	Clinical or subclinical disturbances of cortical function due to a sudden, abnormal, excessive, and disorganised discharge of brain cells. Clinical manifestations include abnormal motor, sensory and psychic phenomena. Recurrent seizures are usually referred to as epilepsy or "seizure disorder".	MeSH Database from PubMed U.S. National Library of Medicine
Shock	A pathological condition manifested by failure to perfuse or oxygenate vital organs.	MeSH Database from PubMed U.S. National Library of Medicine
Streptokinase	Streptococcal fibrinolysin. An enzyme produced by haemolytic streptococci. It hydrolyaes amide linkages and serves as an activator of plasminogen. It is used in thrombolytic therapy and is in mixtures with streptodornase.	MeSH Database from PubMed U.S. National Library of Medicine
Sudden death	The abrupt cessation of all vital bodily functions, manifested by permanent loss of total cerebral, respiratory and cardiovascular functions. Death results from an unexpected circulatory arrest, usually due to a cardiac arrhythmia within an hour of onset of symptoms.	MeSH Database from PubMed U.S. National Library of Medicine Zipes 2006
Sustained ventricular tachycardia	This is a ventricular tachyarrhythmia > 30 seconds in duration and/or requiring termination due to haemodynamic compromise in less than 30 seconds. It can be both, *monomorphic*, with a stable single QRS morphology, or, *polymorphic*, with a changing or multiform QRS morphology at cycle length between 600 and 180 milliseconds.	Zipes 2006
T		
Tachycardia	Abnormally rapid heartbeat, usually with a heart rate above 100 beats per minute for adults. Tachycardia accompanied by disturbance in cardiac depolarisation (cardiac arrhythmia) is called tachyarrhythmia.	MeSH Database from PubMed U.S. National Library of Medicine
Tocainide	An antiarrhythmic agent that exerts potential- and frequency-dependent block of sodium channels.	MeSH Database from PubMed U.S. National Library of Medicine
Torsade de pointes	A malignant form of polymorphic ventricular tachycardia that is characterised by heart rate between 200 and 250 beats per minute, and QRS complexes with changing amplitude and twisting of the points. This term also describes the syndrome of tachycardia with prolonged ventricular repolarisation, long QT intervals exceeding 500 milliseconds or bradycardia. Torsades de pointes may be self limited or may progress to ventricular fibrillation.	MeSH Database from PubMed U.S. National Library of Medicine
V		
Vasodilatation	The physiological widening of blood vessels by relaxing of the underlying vascular smooth muscle.	MeSH Database from PubMed U.S. National Library of Medicine

(Continued)

Venous pressure	The blood pressure in the veins. It is usually measured to assess filling pressure to the heart ventricle.	MeSH Database from PubMed U.S. National Library of Medicine
Ventricular extrasystole	A type of cardiac arrhythmia with premature contractions of the heart ventricles. It is characterised by the premature QRS complex on ECG that is of abnormal shape and great duration (generally > 129 msec). It is the most common form of all cardiac arrhythmias. Premature ventricular complexes have no clinical significance except in concurrence with heart disease.	MeSH Database from PubMed U.S. National Library of Medicine
Ventricular fibrillation	Potentially lethal cardiac arrhythmia that is characterised by unco-ordinated extremely rapid firing of electrical impulses (400-600/min) in heart ventricles. Such asynchronous ventricular quivering or fibrillation prevents any effective cardiac output and results in unconsciousness (syncope). It is one of the major electrocardiographic patterns seen with cardiac arrest.	MeSH Database from PubMed U.S. National Library of Medicine
Ventricular flutter	A potentially lethal cardiac arrhythmia characterised by an extremely rapid, haemodynamically unstable ventricular tachycardia (150-300 beats/min) with a large oscillating sine-wave appearance. If untreated, ventricular flutter typically progresses to ventricular fibrillation.	MeSH Database from PubMed U.S. National Library of Medicine
Ventricular tachycardia	An abnormally rapid ventricular rhythm usually in excess of 150 beats per minute. It is generated within the ventricle below the bundle of HIS, as autonomic impulse formation or reentrant impulse conduction. Depending on the origin, onset of ventricular tachycardia can be paroxysmal (sudden) or non-paroxysmal, its wide QRS complexes can be uniform or polymorphic and ventricular beating may be independent of atrial beating (AV dissociation).	MeSH Database from PubMed U.S. National Library of Medicine

Appendix 2. Search strategies (13 April 2015)

CENTRAL

#1 MeSH descriptor lidocaine this term only
#2 lidocain* in All Text
#3 lignocain* in All Text
#4 xylocain* in All Text
#5 (#1 or #2 or #3 or #4)
#6 MeSH descriptor myocardial infarction explode all trees
#7 myocardial next infarct* in All Text
#8 heart next infarct* in All Text
#9 (coronary in All Text near/3 syndrome* in All Text)
#10 heart next attack in All Text
#11 (#6 or #7 or #8 or #9 or #10)
#12 (#5 and #11)

MEDLINE Ovid

1. Lidocaine/

2. lidocain*.tw.

3. lignocain*.tw.

4. xylocain*.tw.

5. 1 or 2 or 3 or 4

6. exp Myocardial Infarction/

7. (coronary adj3 syndrome*).tw.

8. heart attack.tw.

9. heart infarct*.tw.

10. myocardial infarct*.tw.

11. 6 or 7 or 8 or 9 or 10

12. 5 and 11

13. randomized controlled trial.pt.

14. controlled clinical trial.pt.

15. randomized.ab.

16. placebo.ab.

17. drug therapy.fs.

18. randomly.ab.

19. trial.ab.

20. groups.ab.

21. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. exp animals/ not humans.sh.

23. 21 not 22

24. 12 and 23

EMBASE Ovid

1. lidocaine/

2. lidocain*.tw.

3. lignocain*.tw.

4. xylocain*.tw.

5. 1 or 2 or 3 or 4

6. exp heart infarction/

7. (coronary adj3 syndrome*).tw.

8. heart attack.tw.

9. heart infarct*.tw.

10. myocardial infarct*.tw.

11. 6 or 7 or 8 or 9 or 10

12. 5 and 11

13. random$.tw.

14. factorial$.tw.

15. crossover$.tw.

16. cross over$.tw.

17. cross-over$.tw.

18. placebo$.tw.

19. (doubl$ adj blind$).tw.

20. (singl$ adj blind$).tw.

21. assign$.tw.

22. allocat$.tw.

23. volunteer$.tw.

24. crossover procedure/

25. double blind procedure/

26. randomized controlled trial/

27. single blind procedure/

28. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

29. (animal/ or nonhuman/) not human/

30. 28 not 29

31. 12 and 30

LILACS

lidocain$ or lignocain$ or xylocain$ [Words] and infarct$ or attack$ [Words]

Web of Science – with Conference Proceedings

#13 #12 AND #11

#12 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)

#11 #10 AND #4

#10 #9 OR #8 OR #7 OR #6 OR #5

#9 TS=cardia* infarct*

#8 TS=myocardial infarct*

#7 TS=heart infarct*

#6 TS=heart attack*

#5 TS=(coronary SAME syndrome*)

#4 #3 OR #2 OR #1

#3 TS=xylocain*

#2 TS=lignocain*

#1 TS=lidocain*

WHAT'S NEW

Date	Event	Description
21 September 2021	Review declared as stable	No new studies since the review was published in 2015 (search up to 1 June 2020) and no known ongoing studies.

HISTORY

Protocol first published: Issue 6, 2010
Review first published: Issue 8, 2015

CONTRIBUTIONS OF AUTHORS

Arturo Martí-Carvajal conceived of and drafted the review with comments from Daniel Simancas, Vidhu Anand and Shirikant Bangdiwala. Arturo Martí-Carvajal serves as contact author for this review.

DECLARATIONS OF INTEREST

In 2004, Arturo Martí-Carvajal was employed by Eli Lilly to run a four-hour workshop on 'How to critically appraise clinical trials on osteoporosis and how to teach this'. This activity was not related to his work with The Cochrane Collaboration or to any Cochrane review.

In 2007, Arturo Martí-Carvajal was employed by Merck to run a four-hour workshop on 'How to critically appraise clinical trials and how to teach this'. This activity was not related to his work with The Cochrane Collaboration or to any Cochrane review.

Vidhu Anand: none known.

Shrikant Bangdiwala: The presentation of the results of the sensitivity analysis of the review may be but are in my view unlikely to be informed by results of a grant from the European Commission on "Evaluation and development of measures to uncover and overcome bias due to non-publication of clnical trials".

Daniel Simancas-Racines: none known.

SOURCES OF SUPPORT

Internal sources

- Universidad Tecnológica Equinoccial, Ecuador

  Partially funded.

External sources

- Iberoamerican Cochrane Center, Spain

  Academic.
- Cochrane Heart Group, UK

  Academic.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- Based on the Consolidated Standards of Reporting Trials (CONSORT) statement, we changed the term "Safety" to "Adverse Events". Safety may be considered as substantive evidence of absence of harm. This term is often misused when evidence of harm is simply absent (Ioannidis 2004).
- We did not conduct a cumulative meta-analysis to assess the influence of individual studies (Egger 2001). We prefer to conduct trial sequential analyses to assess risks of random error in our cumulative meta-analyses (CTU 2011).
- We conducted two additional subgroup analyses involving only patients with acute myocardial infarction and trials without suspicion of industry bias versus trials with suspicion of industry bias. We considered both analyses to be of clinical importance.
- As all included trials were rated as having high risk of bias, we were not able to conduct sensitivity analyses to compare trials assigned 'low risk of bias' versus trials assigned 'high risk of bias', as planned.
- A priori, we used a fixed-effect model in combining data. However, we used a random-effects model to minimise sources of variance.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Arrhythmia Agents [*therapeutic use]; Arrhythmias, Cardiac [mortality] [*prevention & control]; Bradycardia [mortality] [prevention & control]; Lidocaine [*therapeutic use]; Myocardial Infarction [*complications] [mortality]; Randomized Controlled Trials as Topic; Ventricular Fibrillation [mortality] [prevention & control]

MeSH check words

Humans