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[Intervention Review]

Oxygen therapy for acute myocardial infarction

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ABSTRACT

Background

Oxygen (O_2) is widely used in people with acute myocardial infarction (AMI) although it has been suggested it may do more harm than good. Previous systematic reviews have concluded that there was insufficient evidence to know whether oxygen reduced, increased or had no effect on heart ischaemia or infarct size, as did our original Cochrane review on this topic in 2010. The wide dissemination of the lack of evidence to support this widely-used intervention since 2010 may stimulate the needed trials of oxygen therapy, and it is therefore important that this review is updated regularly.

Objectives

To review the evidence from randomised controlled trials to establish whether routine use of inhaled oxygen in acute myocardial infarction (AMI) improves patient-centred outcomes, in particular pain and death.

Search methods

The following bibliographic databases were searched last in July 2012: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE (OVID), EMBASE (OVID), CINAHL (EBSCO) and Web of Science (ISI). LILACS (Latin American and Caribbean Health Sciences Literature) and PASCAL were last searched in May 2013. We also contacted experts to identify any studies. We applied no language restrictions.

Selection criteria

Randomised controlled trials of people with suspected or proven AMI (ST-segment elevation myocardial infarction (STEMI) or non-STEMI), less than 24 hours after onset, in which the intervention was inhaled oxygen (at normal pressure) compared to air and regardless of cotherapies provided these were the same in both arms of the trial.

Data collection and analysis

Two authors independently reviewed the titles and abstracts of identified studies to see if they met the inclusion criteria, and independently undertook the data extraction. The quality of studies and the risk of bias were assessed according to guidance in the *Cochrane Handbook*. The primary outcomes were death, pain and complications. The measure of effect used was the risk ratio (RR) with a 95% confidence interval (CI).

Main results

The updated search identified one new trial. In total, four trials involving 430 participants were included and 17 deaths occurred. The pooled RR of death was 2.05 (95% CI 0.75 to 5.58) in an intention-to-treat analysis and 2.11 (95% CI 0.78 to 5.68) in participants with confirmed AMI. While suggestive of harm, the small number of deaths recorded means that this could be a chance occurrence. Pain was measured by analgesic use. The pooled RR for the use of analgesics was 0.97 (95% CI 0.78 to 1.20).

Authors' conclusions

There is no conclusive evidence from randomised controlled trials to support the routine use of inhaled oxygen in people with AMI. A definitive randomised controlled trial is urgently required, given the mismatch between trial evidence suggestive of possible harm from routine oxygen use and recommendations for its use in clinical practice guidelines.

PLAIN LANGUAGE SUMMARY

Routine use of oxygen in people who have had a heart attack

Many people who are having a heart attack are routinely given oxygen to breathe. We looked for the evidence to support this practice by searching for randomised controlled trials that compared the outcomes for people given oxygen to the outcomes for those given normal air to breathe. We were primarily interested in seeing whether there was a difference in the number of people who died, but we also looked at whether administering oxygen reduced pain.

We found four randomised controlled trials that compared one group given oxygen to another group given air. These trials involved a total of 430 participants of whom 17 died. In that group, more than twice as many people known to have been given oxygen died compared to those known to have been given air. However, because the trials had few participants and few deaths, this result does not necessarily mean that giving oxygen increases the risk of death. The difference in numbers may have occurred simply by chance. Nonetheless, since the evidence suggests that oxygen may in fact be harmful, we think it is important to evaluate this widely-used treatment in a large trial as soon as possible, to make sure that current practice is not causing harm to people who have had a heart attack.

BACKGROUND

Description of the condition

Coronary heart disease (CHD) is an important cause of death worldwide. Over seven million people every year die from CHD, accounting for 12.8% of all deaths (WHO 2011). In the United Kingdom (UK) and the United States (US) it is the leading cause of death, accounting for about one-third of all deaths in people aged 35 years or over (BHF 2007; Thom 1998). Mortality rates for cardiovascular disease and CHD in men and women have fallen in most developed countries. For example, comparing the 1982 to 1992 cohort to the 1971 to 1982 cohort in the US the rate was 31% lower for mortality from cardiovascular disease, 21% lower for incidence of CHD and 28% lower for 28-day case fatality (after adjustment for age, sex and race) (Ergin 2004). The report commissioned by the UK Department of Health estimated a reduction in the case fatality rate for acute myocardial infarction (AMI) at 29 days, from 19.1% to 16.4% (Mason 2005). This reduction was associated with both a decline in the incidence of CHD and a reduction in the case fatality rate. Approximately 45% of the reduction in CHD mortality is attributable to improvement in medical therapies for coronary disease (Capewell 2000).

A common manifestation of CHD, often the first, is acute myocardial infarction (AMI). *The Third Global MI Task Force* (Thygesen 2012) defines AMI as *"*any evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischaemia.*"*

Myocardial ischaemia is usually the result of spontaneous complications of atherosclerosis (plaque rupture,ulceration, fissuring, erosion, or dissection) resulting in coronary thrombosis (type 1 AMI). Other categories of AMI include: those produced by underlying CHD with an ischaemic imbalance attributable to a wide range of factors including endothelial dysfunction, coronary spasm, coronary embolism, tachy-/brady-arrhythmias, hypo- and hyperten-

sion (type 2 AMI); sudden cardiac death induced by myocardial ischaemia (type 3 AMI); and AMI occurring in the context of invasive coronary procedures such as percutaneous coronary intervention (PCI), in-stent thrombosis, or coronary artery bypass grafting (CABG), categorised as subtypes 4a, 4b and 5 of AMI. By far the most common types of AMI are types 1 and 2, to such an extent that their incidence may be used as proxy variables to estimate the prevalence of CHD in the general population. Hereafter we will use the term 'AMI' to refer the type 1 and type 2 AMI.

Myocardial injury may be detected through: 1. Highly sensitive biochemical markers such as Troponin (I or T), or the MB fraction of the creatine kinase (CKMB); 2. Electrocardiographic changes; or 3. Imaging techniques such as echocardiography, magnetic resonance imaging (MRI) or radionuclide imaging (RI). To make the diagnosis of AMI (in a clinical context) the necessary conditions include a change (rise and/or fall) in cardiac biomarker values, together with at least one of the following criteria: ischaemic symptoms; typical electrocardiographic changes; or abnormalities in the structure or wall motion of the heart identified by imaging techniques.

Moreover, the recognition that acute coronary syndromes represent a spectrum of pathophysiological processes rather than a uniform type of 'heart attack' has led to publication of separate guidelines for AMI presenting with persistent ST-segment elevation (STEMI) and non-STEMI presentations, reflecting the different therapeutic options.

The in-hospital mortality rate of unselected STEMI patients according to the Euro Heart Survey published by the European Society of Cardiology varies between 6% and 14% (Mandelzweig 2006). The most serious complications of AMI are cardiogenic shock, heart failure, ventricular fibrillation and recurrent ischaemia. Around 8% of people with AMI develop cardiogenic shock (Babaev 2005), but this remains present in 29% of those people on admission to hospital. The Global Registry of Acute Coronary Events (GRACE) reported that heart failure occurred in 15.6% of people with STEMI and 15.7% of those with non-STEMI, but heart failure was present in only 13% of these patients on admission to hospital (Steg 2004). Ventricular fibrillation occurred in 1.9% of people with AMI (Goldberg 2008), and recurrent ischaemia in 21% of those with acute coronary syndromes (Yan 2010), of which about half presented in the first 24 hours. Other possible complications of AMI include pericarditis, mitral insufficiency, arrhythmias and conduction disturbances.

The cornerstone of contemporary management of people with STEMI is reperfusion therapy, with either primary percutaneous coronary intervention (PCI) or thrombolytic treatment. If less than 12 hours has elapsed from the onset of symptoms, recommended treatments in international guidelines include morphine, oxygen (O_2), nitrates and aspirin (MONA) (O'Connor 2010; O´ Gara 2013; Steg G 2012). Some of these treatments have a well-established research base, while others do not (Nikolaou 2012; O'Driscoll 2008; SIGN 2010).

Description of the intervention

Inhaled oxygen at normal pressure delivered by face mask or nasal cannula, at any concentration.

How the intervention might work

Myocardial infarction occurs when the flow of oxygenated blood in the heart is interrupted for a sustained period of time. The rationale for providing supplemental oxygen to a person with AMI is that it may improve the oxygenation of the ischaemic myocardial tissue and reduce ischaemic symptoms (pain), infarct size and consequent morbidity and mortality. This pathophysiological reasoning has face validity.

Why it is important to do this review

Although it is biologically plausible that oxygen is helpful, it is also biologically plausible that it may be harmful. Potentially harmful mechanisms include the paradoxical effect of oxygen in reducing coronary artery blood flow and increasing coronary vascular resistance, measured by intracoronary Doppler ultrasonography (McNulty 2005; McNulty 2007); reduced stroke volume and cardiac output (Milone 1999); other adverse haemodynamic consequences, such as increased vascular resistance from hyperoxia; and reperfusion injury from increased oxygen free radicals (Rousseau 2005).

A systematic review of human studies that included non-randomised studies did not confirm that oxygen administration diminishes acute myocardial ischaemia (Nicholson 2004). Indeed, some evidence suggested that oxygen may increase myocardial ischaemia (Nicholson 2004). Another recent narrative review of oxygen therapy (Beasley 2007) also sounded a cautionary note. It referenced a randomised controlled trial (RCT) conducted in 1976 (Rawles 1976) showing that the risk ratio of death was 2.89 (95% confidence interval (CI) 0.81 to 10.27) in participants receiving oxygen compared to those breathing air. While this suggested that oxygen may be harmful, the increased risk of death could easily have been a chance finding. A recent review (Wijesinghe 2009) looked at the effect of oxygen on infarct size in people with AMI and concluded that "There is little evidence by which to determine the efficacy and safety of high flow oxygen therapy in MI. The evidence that does exist suggests that the routine use of high flow oxygen in uncomplicated MI may result in a greater infarct size and possibly increase the risk of mortality".

Despite this lack of robust evidence of effectiveness prior to the publication of our 2010 Cochrane review of the evidence, oxygen administration was widely recommended in international guidelines (AARC 2002; AHA 2005; Anderson 2007; Antman 2002;

ILCOR 2005; Van de Werf 2008). Some guidelines were more cautious; for example, the European Guideline (Bassand 2007) did not recommend routine oxygen use in acute coronary syndrome (ACS) and the Scottish Intercollegiate Guidelines Network guidance (SIGN 2007) only recommended oxygen use in hypoxaemia (< 90% saturation), noting that there was no clinical evidence for its effectiveness and referring to animal models that showed a reduction in infarct size.

Guidelines published since the 2010 Cochrane review have tended to move to a more cautious position reflecting the lack of evidence. In 2010, for example, the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular care stated that:

"EMS providers administer oxygen during the initial assessment of patients with suspected ACS. However, there is insufficient evidence to support its routine use in uncomplicated ACS. If the patient is dyspnoeic, hypoxaemic, or has obvious signs of heart failure, providers should titrate therapy, based on monitoring of oxyhaemoglobin saturation, to 94%. (Class I, LOE)" /(O'Connor 2010).

An updated SIGN guidance states:

"A Cochrane review found no conclusive evidence from randomised controlled trials to support the routine use of inhaled oxygen in patients with acute MI. There is no evidence that routine administration of oxygen to all patients with the broad spectrum of acute coronary syndromes improves clinical outcome or reduces infarction size" (SIGN 2010).

In 2011 an Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the Management of Acute Coronary Syndromes (ACS) was published and stated that:

"There is currently insufficient evidence to formulate clear recommendations about oxygen therapy [52]. Definitive trials are needed to answer this question" (Chew 2011).

Similarly the 2012 ESC guidelines for STEMI, citing the Cochrane review, now state:

"Oxygen (by mask or nasal prongs) should be administered to those who are breathless, hypoxic, or who have heart failure.Whether oxygen should be systematically administered to patients without heart failure or dyspnoea is at best uncertain. Non-invasive. monitoring of blood oxygen saturation greatly helps when deciding on the need to administer oxygen or ventilatory support" (Steg G 2012).

The 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction have a similar change in emphasis:

"Few data exist to support or refute the value of the routine use of oxygen in the acute phase of STEMI, and more research is needed. A pooled Cochrane analysis of 3 trials showed a 3-fold higher risk of death for patients with confirmed acute MI treated with oxygen than for patients with acute MI managed on room air. Oxygen therapy is appropriate for patients who are hypoxaemic (oxygen saturation <90%) and may have a salutary placebo effect in others. Supplementary oxygen may, however, increase coronary vascular resistance. Oxygen should be administered with caution to patients with chronic obstructive pulmonary disease and carbon dioxide retention". (O´ Gara 2013).

The British Heart Foundation (BHF), in response to the doubts about oxygen use raised by Beasley 2007, originally stated in an article in The Guardian 2007 that "The current practice of giving high-flow oxygen is an important part of heart attack treatment. Best practice methods have been developed and refined over the years to ensure the best possible outcome for patients. There is not enough evidence to change the current use of oxygen therapy in heart attacks". Almost three years after the publication of the first Cochrane Review the use of oxygen in AMI and more in general in the coronary acute syndromes is still controversial (Shuvy 2013). We think that, given the evidence cited, it would have been more appropriate to conclude that despite decades of use there is inadequate clinical trial evidence to unequivocally support routine administration of oxygen. The BHF subsequently stated that the 2010 Cochrane review (BHF 2010) "highlights the need for more research into the effects of oxygen when it is given during a heart attack. Until recently, heart attack patients were routinely treated with oxygen but we simply do not have enough evidence to know if that treatment is beneficial or harmful."

With the lack of collective certainty about the use of oxygen, it is time that this treatment is re-assessed. In general, practice should not be based on tradition but on proven benefit and safety. Given that the 1976 trial (Rawles 1976) was suggestive of potential harm from oxygen in suspected AMI, it is important that the evidence base for the current guidance recommending the use of oxygen be systematically reviewed and, if necessary, further research be undertaken to clarify whether this intervention does more harm than good. If the only robust evidence is suggestive of potentially serious harm, even if the result is not statistically significant, it reinforces our opinion that this intervention should not be routinely used, however sound the underpinning pathophysiological reasoning.

OBJECTIVES

To determine if routinely giving oxygen (O_2) to people with suspected and proven acute myocardial infarction (AMI) (ST-segment elevation (STEMI) and non-STEMI) does more good than harm by reviewing the evidence from randomised controlled trials using patient-centred outcomes, in particular death and pain.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), in any language, with any length of follow-up, and any publication status (full publication, abstract only or unpublished).

Types of participants

Adults of any age treated, in a pre-hospital or a hospital setting, for suspected or proven AMI (STEMI or non-STEMI), within less than 24 hours after onset of symptoms, regardless of any co-therapy (for example a reperfusion therapy) provided this is the same in both arms of the trial.

Types of interventions

The intervention is routinely-given inhaled oxygen administered by any device at normal pressure for one hour or more within the first 24 hours after the onset of symptoms of AMI. The comparators are air, or air with titrated oxygen in the event of desaturation. Excluded interventions are hyperbaric oxygen or aqueous oxygen therapy (unless the studies include arms with air or oxygen at normal pressure).

Types of outcome measures

We sought only clinically relevant outcomes. The primary outcome for the systematic review was prespecified as mortality; the secondary outcomes were pain and any other complications (such as heart failure, pericarditis and rhythm disorders). Other indirect clinical outcomes such as infarct size estimated through different methods (electrocardiogram (ECG), cardiac enzymes, Troponin T, Brain Natriuretic Peptide (BNP), or magnetic resonance imaging (MRI)) were also employed.
Surrogate outcomes, such as reperfusion arrhythmias and arterial oxygen saturation, were not included as these may not necessarily correlate well with clinically important outcomes.

Search methods for identification of studies

Electronic searches

We searched the following bibliographic databases (from start of database to 17 July 2012):

- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*);
- MEDLINE (Ovid);
- MEDLINE In-Process (Ovid);
- EMBASE (Ovid);
- CINAHL (EBSCO);
- Web of Science (ISI).

We also searched LILACS (Latin American and Caribbean Health Sciences Literature) and the PASCAL database in May 2013. ZETOC was last searched in February 2010.
A RCT search filter as recommended in the *Cochrane Handbook for Reviews of Systematic Interventions* (Cochrane Handbook) has been applied to the 2012 searches of MEDLINE and EMBASE and adaptations of these to CINAHL and Web of Science.
We searched the following databases for ongoing trials:

- Current Controlled Trials metaRegister http://www.controlled-trials.com/mrct/;
- International Clinical Trials Registry Platform (ICTRP), World Health Organization. http://www.who.int/ictrp/network/en/

Details of the database search strategies are in Appendix 1 (for 2010) and Appendix 2 (for 2012).

Searching other resources

We searched proceedings of annual meetings and conferences of professional bodies (American Heart Association, British Cardiovascular Society, European Society of Cardiology and American College of Cardiology) for relevant abstracts.
We contacted experts in the field to locate any unpublished studies, and checked citations from key references.
No date or language restrictions were applied to the searches.

Data collection and analysis

We used the standard methods of The Cochrane Collaboration as described in the Cochrane Handbook so that the review methods are consistent with current recommendations. We used Review Manager 5 (RevMan) for the analysis.

Selection of studies

Two authors independently reviewed the titles and abstracts of studies identified in the searches to see if they met the above inclusion criteria. We obtained study reports in full text when inclusion could not be decided from the title or abstract.

Data extraction and management

Two authors independently evaluated the methodological quality and undertook independent data extraction using an agreed data extraction form. We resolved differences by discussion. The data were entered into Review Manager 5 by one review author and checked by two others.

Assessment of risk of bias in included studies

Risk of bias in individual studies

We used the two-part tool described in Section 8.5 of the Cochrane Handbook. We explored the six specific domains of: sequence generation; allocation concealment; blinding (participants, personnel and outcome assessors); incomplete outcome data; selective outcome reporting; and other potential threats to validity.
For each trial, two review authors independently first described the design characteristics relating to each domain and then judged the risk of bias associated with the main outcome. A nominal scale was used for the judgement: low, high or unclear risk of bias.

Risk of bias across studies

We did an overall assessment of risk of bias for every outcome within the review for each domain and using a similar scale: low risk of bias in all domains, unclear risk of bias for one or more domains, and high risk of bias for one or more domains.
When meta-analysis was undertaken we summarised the risk of bias for the main outcomes, across studies. We resolved disagreements between review authors in the description or in the judgement by consensus without the need for recourse to a third review author.

Measures of treatment effect

We looked at the risk ratio (RR) of death and report this in preference to risk difference. This was because the trials were old (the main trial was undertaken in the era before thrombolysis was routine) and we anticipated that there would be higher control event rates than would be expected today. We also looked for differences in mean pain scores. These were not given, and we therefore used the risk ratio of opiate use as a proxy for pain. We used the differences in mean for continuous measurement of infarct size such as cardiac enzymes, Troponin T, BNP or MRI.

Unit of analysis issues

In the main trial (Rawles 1976), 200 participants with AMI were randomised but the results were only analysed for the 157 who were later confirmed to have had an AMI. Similarly in the most recent trial (Ranchord 2012) the five participants in which AMI was not confirmed and another seven withdrawn participants were excluded from the analysis. It is legitimately open to debate as to whether people who did not have an AMI should be included in a study of the benefits of oxygen in AMI. Theoretically diagnosis may be more certain today, but not at the beginning of symptoms. On the other hand, we treat suspected MIs and these represent some of the people to whom a treatment would be given. We have therefore performed two analyses: one in participants who had confirmed MI in Rawles 1976 and Ranchord 2012, and a second that also covered all participants from the other two trials in a strict intention-to-treat (ITT) analysis that included the 43 participants from the Rawles trial who did not have an AMI confirmed and the 12 withdrawn participants from the Ranchord study. This was to preserve the strict randomisation process and to minimise selection bias.

Dealing with missing data

We conducted an ITT analysis whenever possible. We contacted study authors for missing data.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the outcomes tables and using the I^2 statistic (where an $I^2 < 60\%$ was considered to demonstrate moderate heterogeneity) (Higgins 2003).

Assessment of reporting biases

As there were only four studies that met the inclusion criteria, it was not possible to explore reporting bias using funnel plots or the Begg (Begg 1994) and Egger (Egger 1997) tests.

Data synthesis

We undertook meta-analyses where data were available and it was clinically sensible to do so, using both fixed-effect and random-effects models. We reported the results using both models because we recognise that readers may have different perspectives (for example priors, values or contexts) and different people may wish to see the results with the different mathematical assumptions.

Subgroup analysis and investigation of heterogeneity

The data were too sparse to permit adequate exploration of all the subgroups that had been prespecified for analysis (such as timing and duration of oxygen therapy; pre-existing levels of hypoxaemia; other measures of severity of infarction). We undertook an analysis including only the trials undertaken during the reperfusion era, as these reflect today's clinical practice.

Sensitivity analysis

Similarly, our intention to explore the effect of trial quality in a sensitivity analysis was limited by the number of trials and the quality of reporting. We undertook separate analyses using the confirmed AMI population and the ITT population, and undertook a 'best-case' scenario, 'worst-case' scenario sensitivity analysis for the missing data on deaths (Wilson 1997).

RESULTS

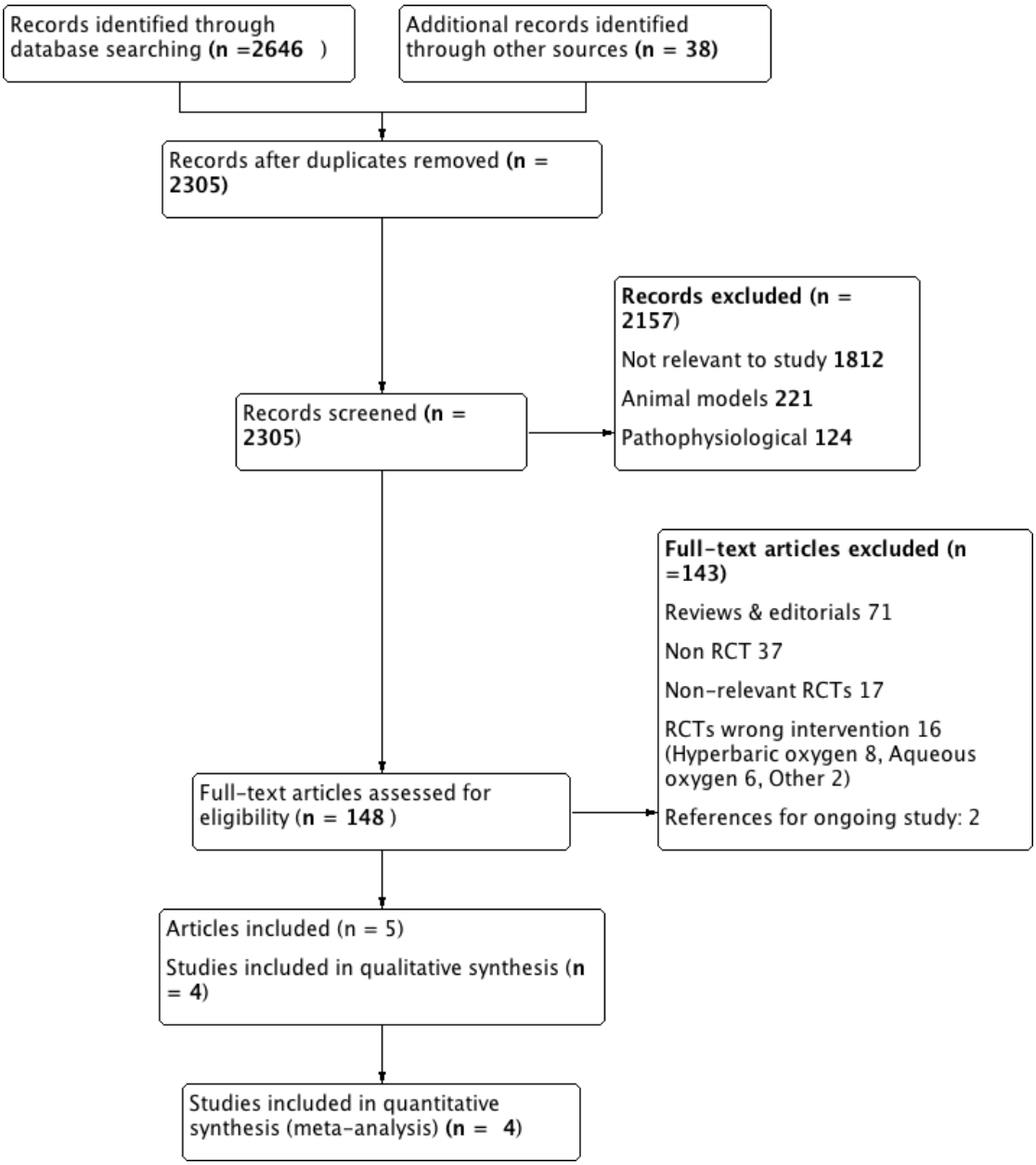
Description of studies

Results of the search

We identified 115 new articles with the updated search in July 2012. The removal of duplicates left 77 new articles for screening. One new randomised controlled trial (RCT) was eligible for inclusion (Ranchord 2012).

Including the papers identified in the previous version of the review, we retrieved a total of 2646 articles and screened 2305 (after the removal of duplicates) (Figure 1). Based on title and abstract, 2157 were excluded and 148 full papers retrieved. A further 125 were not RCTs or were RCTs not related to our review. Of the remaining 23 papers, 16 were excluded for various reasons and two are references for an ongoing study. This leaves five papers reporting four trials that met the inclusion criteria (Ranchord 2012; Rawles 1976; Ukholkina 2005; Wilson 1997). The process with reasons for exclusions is described in Figure 1 and the list of the excluded trials given in the table Characteristics of excluded studies.

Figure 1. Study flow diagram.



We identified in the trials registers three ongoing trials (July 2012), two of which have begun recruitment.(Characteristics of ongoing studies). All three are parallel designs to compare oxygen (O_2) versus air (or titrated oxygen) in people with suspected acute myocardial infarction (AMI). In two studies the primary outcome is infarct size estimated by echocardiography, magnetic resonance imaging (MRI) or biochemical markers; in the third one the main outcome is in-hospital mortality (this study, despite having been registered in 2009, has yet to begin recruitment).

Included studies

The four included trials were reported between 1976 and 2012 (Ranchord 2012; Rawles 1976; Ukholkina 2005; Wilson 1997). Two were conducted in the UK (Rawles 1976; Wilson 1997) one in Russia (Ukholkina 2005) and one in New Zealand (Ranchord 2012). All four studies were parallel-design, randomised controlled trials. One was double-blind (Rawles 1976) and the other three were open-label.

Population: a total of 535 participants were recruited, of whom 73.2% were men. Participants with suspected AMI were recruited in two studies (Ranchord 2012; Rawles 1976) and only people with confirmed AMI in the other two. The mean ages in years (and standard errors where given) of the included participants in each group were as follows: Rawles 1976: air 50.8 (2.4), O_2 51.3 (1.7); Wilson 1997: air 64, O_2 65; Ukholkina 2005: air 53.5 (1.06), O_2 55.6 (1.33); Ranchord 2012: air 60 (12.8), O_2 62.1 (12.5).

Intervention: in all four included trials the intervention was inhaled oxygen at 4 to 6 L/min. This was given by mask in three studies and by a nasal cannula in the other study. The comparator was air in three studies, breathed normally in the two open-label studies and given at 4 to 6 L/min by facial mask in the double-blind study. In the remaining study the comparison was titrated oxygen delivered by nasal prongs or mask adjusting the flow-rate to achieve an oxygen saturation of 93% - 96%.

Outcomes: death was reported in all four studies. Pain or analgesic use (as a proxy for pain) was reported in two studies. Two studies included infarct size estimated by electrocardiogram (ECG), biochemical markers (creatine kinase (CK),T troponin, BNP) or MRI as an indirect clinical outcome.

The main characteristics of the included studies are in the table Characteristics of included studies.

Excluded studies

Of the 125 excluded articles, 71 did not report original data; 37 were not RCTs; 17 were RCTs of interventions which were not relevant to our study; and 16 papers reported studies which had a different oxygen intervention (eight used hyperbaric oxygen, six aqueous oxygen, one oxygen associated with haemoglobin, and one oxygen combined with nitric oxide versus placebo for pain control). The two remaining papers were the protocol and the pilot of an ongoing trial (NCT01272713). The main characteristics of the excluded studies are in the table Characteristics of excluded studies.

Risk of bias in included studies

Randomisation

There was no description of how the sequence for allocation was generated in three studies (Rawles 1976; Ukholkina 2005; Wilson 1997). In Ranchord 2012 a random number sequence was generated by a computer programme. This study was undertaken in two centres and randomisation was not stratified by centre.

Allocation concealment

In three studies allocation was concealed using numbered sealed envelopes (Ranchord 2012; Rawles 1976; Wilson 1997). The method of allocation concealment was not reported in Ukholkina 2005. In Ranchord 2012 (two centres) there is no description of how the envelopes were distributed to each centre.

Blinding

Only Rawles 1976 was blinded. This was done by using shrouded cylinders but there is no information about how effective this was. Nursing staff were not aware that the record of opiate administration would be used as a proxy measure of pain. We think that the use of shrouded cylinders left blinding potentially compromised and that therefore the possibility of performance and observer bias cannot be excluded. However, while this could affect the assessment of the surrogate outcomes for pain, it is much less likely to have affected the primary outcome of this review, which was death (Wood 2008). We have no clear information whether infarct size measurement (through ECG, enzymes or BNP) was done blind (though we presume that it was). Finally in Ranchord 2012 the cardiologist who measured the infarct size through MRI was blinded to treatment received by the participant and to biomarkers data.

Performance and observer biases were possible in the three unblinded studies, which may have affected the evaluation of the surrogate outcome for pain in Wilson 1997 (this outcome was not reported in the Ukholkina and Ranchord trials). The assessment of the primary outcome (death) and the other secondary outcome

of complications such as recurrent ischaemia or AMI, heart failure, arrhythmias and pericarditis were less likely to be subject to significant observer bias. On the other hand the methods used for infarct size estimation (ECG, creatine kinase, Troponin T, or MRI) are quite robust to observer bias, so these measures may be considered free of observer bias.

Incomplete outcome data addressed

All participants were followed to discharge in Rawles 1976 but randomisation was undertaken before the diagnosis was confirmed. AMI was not confirmed in 21.5% of those with suspected AMI. Although this may appear high, it is not inconsistent with diagnostic techniques in the 1970s. Of the 105 people randomised to oxygen and the 95 to air, AMI was not confirmed in 25 and 18 participants respectively. The characteristics of those in whom AMI was not confirmed were similar in both groups and there were no deaths among the excluded individuals.

In Wilson 1997 , it was unclear for how long participants were followed up. Eight people were excluded from the analysis: one death, one stroke, four who withdrew consent and two because data were incomplete. This is 16% of the participants and the expected effect on the results for the primary event was very low; the risk of bias was therefore high, but its direction is unknown.

In Ukholkina 2005 the outcomes were measured for 10 days and no participants were lost to follow-up. However, no explicit data were provided about the participants who were excluded post-randomisation because of failed revascularisation or the relative number of failed revascularisations in each group. The mismatch between the numbers reported in the tables and the text suggest that two participants may have been excluded from the air group and four from the oxygen group, but we cannot be certain. Consequently we could not include these participants in the intention-to-treat analysis. We therefore think there is a high risk of bias for the outcomes we measured.

In Ranchord 2012 12 participants were excluded **after** randomisation (four in the experimental group and eight in the control group). The outcomes of these participants were not reported and they were excluded from the analysis in the published study report. The reasons for withdrawal were: in five cases the absence of formal consent; in five cases a wrong diagnosis of STEMI (two cases of acute pericarditis and three cases with normal coronary arteries); and two people had cardiogenic shock which was an exclusion criterion for the study. The group to which these participants had been allocated was not reported.

We contacted authors to try and find out to which groups the 12 withdrawn participants had been allocated and their vital status, so that we could include them in an intention-to-treat (ITT) analysis. Although the authors replied, the information provided was contradictory and of limited value. Initially we were told that five people had been withdrawn because they did not consent and that the other seven had not been randomised. When we enquired further about this because it contradicted the published report, we were told that these seven had been randomised. Of concern to us was the fact that the distribution of their allocation to groups subsequently provided was not consistent with the numbers in the published trial report. The authors declined to provide the mortality outcomes for the participants who had alternative diagnoses, stating that "Although they are described as 'randomised and withdrawn' in the manuscript, they received no study treatment. For these reasons we are firmly of the view that these subjects should not be included in the mortality analysis." This failure to appreciate the nature of ITT analysis compounded our concerns raised by the inconsistencies in the allocation information. The authors felt unable to tell us the mortality status of the five participants who did not consent on the grounds that "if they have not consented then we can collect no further details about them". While we understand that trial-specific data could not be collected on these people, mortality can be known by public methods, and we believe therefore that providing us with this information would not have been an ethical breach. However we appreciate that others may judge this differently. The only information of use was that the three participants withdrawn because they had normal coronary arteries, were alive at the end of the study period.

The two cases excluded from the analysis by cardiogenic shock merit special comment. While cardiogenic shock was an exclusion criterion of the study, it is important to recognise that this is a dynamic clinical condition which is present on admission to hospital only in 29% of those who go on to develop this complication. It is not reported in the paper whether the participants had cardiogenic shock when they arrived at the hospital or not. If cardiogenic shock developed after randomisation but before treatment, then the exclusion of these participants could bias the results since people with cardiogenic shock have a higher mortality rate. This illustrates the importance of ITT analysis.

As we were unable to include these participants in the ITT analysis because mortality data were withheld, we undertook a sensitivity analysis with a 'worst-case' scenario in which we tested the robustness of the current estimate by assuming that both participants received oxygen but died.

Selective outcome reporting

No study protocols were available. Rawles 1976 was the best-quality study and we believe that the report probably included all the prespecified variables. In Wilson 1997 the primary purpose was to look at the incidence and degree of hypoxaemia and the effect of oxygen on hypoxaemia, rather than this review's primary outcome of death; the participant who died was excluded from the analysis. Despite contacting the authors, we were unable to establish in which group the death occurred and this study could not be included in the meta-analysis. We carried out a sensitivity analysis to assess the potential risk of bias.

In Ukholkina 2005, ECGs were mapped to estimate the surrogate

outcome of infarct size but only in a subset of 31 participants in the oxygen group; there was no information for the air group. We therefore believe that meaningful conclusions cannot be drawn about infarct size. We do not think the pain and death outcomes were subject to selective reporting.

In Ranchord 2012 the infarct size, estimated by MRI, was undertaken only in a small subgroup of 71 participants (Selective reporting of subgroup). In addition neither the protocol nor the trial report give any defined criteria on whether or not to perform MRI, so this analysis should be considered a non-randomised comparison. On the other hand, given that the MRI was performed four to six weeks after AMI, this specific subgroup represents a cohort of survivors, which also needs to be taken into account in the infarct size comparison.

Baseline characteristics

Overall, the two groups appeared similar after randomisation in Rawles 1976 and Wilson 1997. In Ukholkina 2005 the two groups appeared similar in age, smoking, hypertension, unstable angina and cholesterol. There was a difference (not statistically significant) in the Killip stage, with more Killip II in the oxygen group than in the air group; time to revascularisation was 41 minutes shorter in the air group (P = 0.052), which even if due to chance may have important clinical implications for our outcomes of interest. In Ranchord 2012 the two groups appear similar in age, sex, body mass index, diabetes, hyperlipidaemia, hypertension and previous coronary artery bypass grafting (CABG). There were differences in the number of previous percutaneous coronary interventions (PCIs), and in the infarct territory, with less anterior infarction in the experimental group that in the control group (18% versus 31%).

Other biases

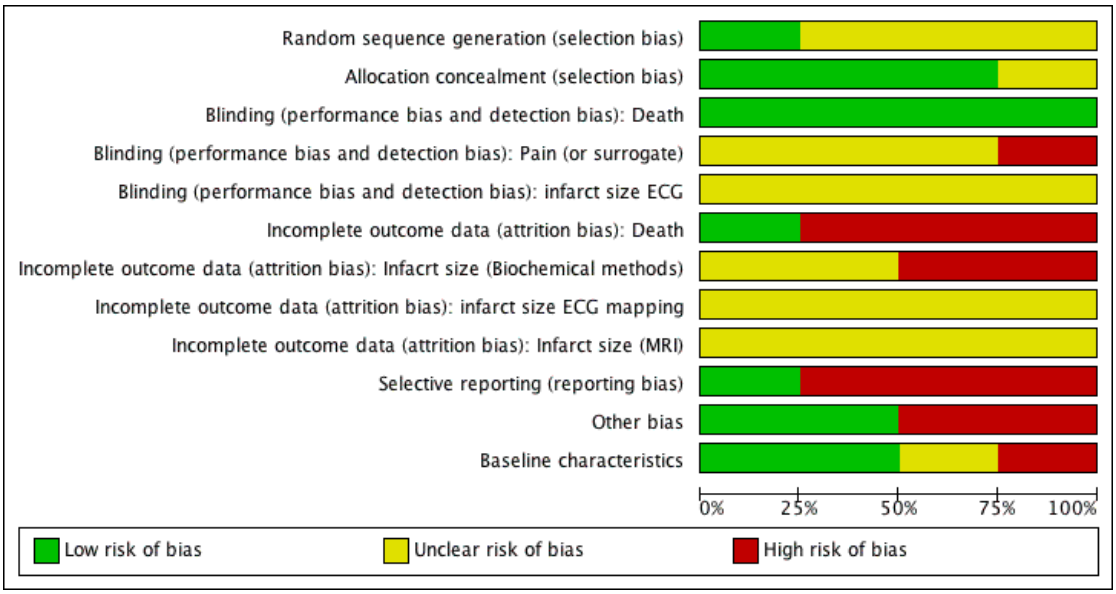
No other biases were identified in Rawles 1976 or Wilson 1997. Ukholkina 2005 reported differences in infarct size between the two interventions but the authors did not specify the time after symptom onset when creatine phosphokinase M and B isoenzymes (MB-CPK) were measured; they were not measured at the same time in all participants. In addition, no information was provided about the consistency and validity of the method used to map myocardial damage (number and blinding of observers; reliability and repeatability of their measurements; whether there were disagreements and, if so, how these were resolved). While these methodological weaknesses call into question the reliability of the estimation of myocardial damage, they do not affect the main outcomes of this review. Only Ukholkina 2005 reported complications but there was an inconsistency between the data in the table and the text. We recalculated complication rates and used these data in our analysis.

In Ranchord 2012 before randomisation pre-hospital oxygen was administered to the experimental and control groups (86.8% and 63% respectively). If the effect of oxygen is truly determinant on the outcome, then this prerandomisation intervention could have produced a bias in effect estimation toward the null hypothesis (i.e. a reduction of the study power).

Summary of risk of bias

Death as an outcome had a low risk of bias in Rawles 1976, was not reported adequately in Wilson 1997 and had a high risk of bias in Ukholkina 2005. There are also the 'withdrawn' participants from Ranchord 2012, for which we had no outcome data and do not therefore know their vital status. We therefore consider the overall risk of bias for mortality in the meta-analyses to be high. For pain we consider the risk of bias in Rawles 1976 to be unclear and that there is a high risk of bias in Wilson 1997. Consequently we consider the risk of bias in the meta-analysis for pain to be high (Figure 2; Figure 3).

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



Effects of interventions

Mortality

All four trials reported the observed mortality. Rawles 1976 found more deaths in the group randomised to oxygen than in the air group, both for all randomised participants (suspected AMI) and for those with confirmed AMI. Wilson 1997 described one death but did not report in which group this occurred. We contacted both of the authors of the original paper, who confirmed that they no longer had the trial data and did not remember in which arm the death and the stroke had occurred; however, they stated that 25 participants had been randomised into each group. In Ukholkina 2005, only one person out of 58 died in the oxygen group and none out of 79 participants in the air group. In Ranchord 2012 one participant out of 68 died in the high oxygen group and two out 68 in the titrated group. Twelve participants (four in the high oxygen group and eight in the titrated group) were withdrawn after randomisation, with the mortality data for these 12 people not reported in the paper. We contacted the authors of the trial, but they were unable to provide the missing data for these cases.

Only the results from three of the four studies (Ranchord 2012; Rawles 1976; Ukholkina 2005) could be combined. When the data were pooled, twice as many people on oxygen died as in the group given air. This suggests that oxygen may be harmful but, because of the small numbers of people in the trials, this may simply be due to chance. The complete results are given numerically below, and a sensitivity analysis for the missing data from Wilson 1997 and Ranchord 2012 studies are also presented.

Meta-analysis for mortality in participants with confirmed AMI: risk ratio (RR) 2.11 (95% confidence interval (CI) 0.78 to 5.68; I^2 = 0%, fixed-effect model) (Analysis 1.1). This remained unchanged when applying a random-effects model (Analysis 1.2).

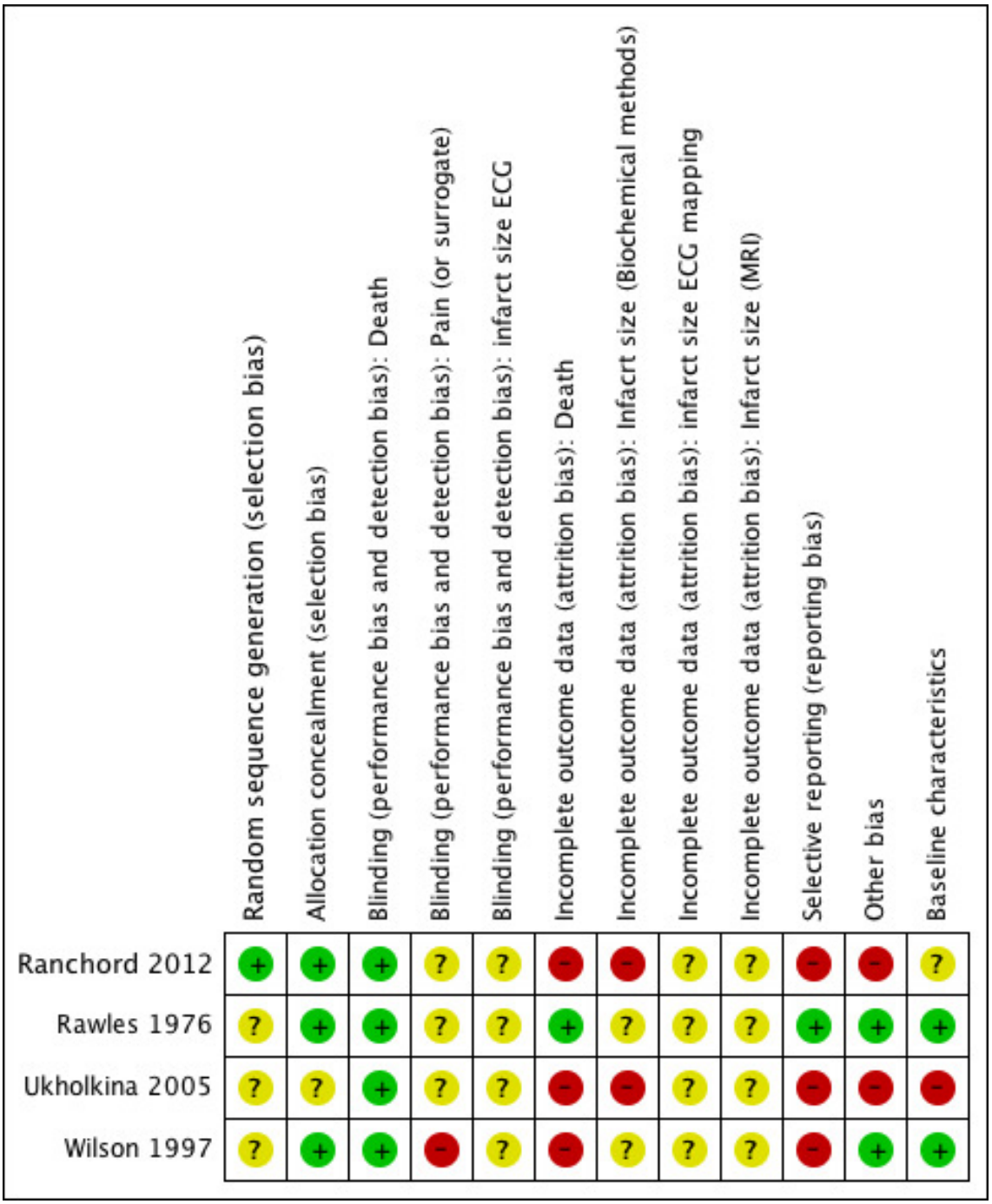
Meta-analysis for mortality in an ITT population (including those who did not have AMI): RR 2.05 (0.75 to 5.58; I^2 = 0%, fixed-effect model) (Analysis 1.3).This remained unchanged when applying a random-effects model (Analysis 1.4).

Sensitivity analysis for missing information about the arm in which the death occurred in the Wilson trial (ITT analysis): a 'worst-case' scenario assuming that the participant who died was in the oxygen arm gave a RR of death of 2.88 (95% CI 0.88 to 9.38). A 'best-case' scenario assuming that the participant who died was in the air arm gave a RR of death of 2.06 (95% CI 0.67 to 6.37). In both cases we used a fixed-effect model. Sensitivity analysis for missing information about the group in which the two participants with cardiogenic shock were allocated: assuming that both participants died, a 'worst-case' scenario in which both were in the oxygen arm gave a RR of 2.42 (95% CI 0.91 to 6.41), and a 'best-case' assuming that the participants were in the control arm gave a RR of 0.26 (95% CI 0.03 to 2.31).

The subgroup analysis, including only the two reperfusion era trials, gave a RR of death of 1.60 (95% CI 0.21 to 6.32). Unfortunately, despite being recent, these two studies did not meet current standards of trial design and conduct and have a high risk of bias

(see Risk of bias in included studies and Figure 3).

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



Pain

Pain was not explicitly measured but the authors reported diamorphine use as a proxy for pain. In Rawles 1976, a similar proportion of participants from both groups received analgesia. The total dosage was similar: 54.3% of randomised participants (71.3% of those with confirmed AMI) in the oxygen group received analgesia, with an average of 2.1 doses (standard deviation (SD) 1.5), but it was not clear whether the denominator was participants who used diamorphine or all participants; 54.7% of randomised participants (67.5% of those with confirmed AMI) in the air group received analgesia, with an average of 2.0 doses (SD 1.4), but again the denominator population was not clearly defined. In Wilson 1997 the authors reported opiate use as a proxy for pain. Although 50 people were randomised, results were only reported for 42, as follows: 16 of 22 participants (72.7%) in the oxygen group used opiates; 18 of 20 participants (90%) in the air group used opiates. Ukholkina 2005 did not measure pain or analgesic use.

Thus we can only combine results from two studies. There was no difference in analgesic use between the oxygen and the air groups. The complete results are given numerically below.

Meta-analysis for analgesic use in confirmed AMI: RR 0.99 (95% CI 0.83 to 1.18; I^2 = 54%, fixed-effect model) (Analysis 1.5). This was slightly altered when

a random-effects model was applied: RR 0.94 (95% CI 0.72 to 1.23; I^2 = 54%) (Analysis 1.6).

Meta-analysis for analgesic use in the ITT population (including those who did not have an AMI): RR 0.97 (95% CI 0.78 to 1.20; I^2 = 0%, fixed-effect model) (Analysis 1.7). This remained unchanged using a random-effects model: RR 1.01 (95% CI 0.75 to 1.34; I^2 = 0%) (Analysis 1.8).

Complications

Ukholkina 2005 explored complications such as heart failure, pericarditis and rhythm disorders. The RR of complications (excluding recurrent ischaemia) was 0.68 (95% CI 0.45 to 1.03) (Analysis 1.9).

Infarct size estimation

Three of the four studies explored the effect of oxygen on the infarct size (Ranchord 2012; Rawles 1976; Ukholkina 2005). As they used quite different methods to estimate the infarct size it was not possible to synthesise the findings (qualitatively or quantitatively).

DISCUSSION

Summary of main results

We identified four studies meeting our inclusion criteria. None demonstrated that oxygen therapy in people with AMI does more good than harm, based on clinical outcomes. In both the intention-to-treat meta-analysis and the confirmed AMI meta-analysis, there were more deaths among those people on oxygen than among those on air, although these results did not reach statistical significance and could simply be a chance occurrence. There was no clinically or statistically significant difference in analgesia use between the two treatments. Finally there was no clear effect of the intervention in reducing infarct size estimated through different methods in subsets of patients.

Overall completeness and aplicability of evidence

Regarding the applicability of the evidence three aspects should be pointed out:

Firstly, the Rawles and Wilson (Rawles 1976; Wilson 1997) studies were undertaken before the reperfusion era (primary percutaneous coronary intervention (PPCI) or thrombolysis) and also before the use of treatments such as beta-blockers, aspirin, angiotensin-converting enzyme inhibitors or modern antiplatelet therapies, and thus their results may not be applicable in today's context. While the two trials in the sensitivity analysis including only the reperfusion era trials were at high risk of bias, the result risk ratio (RR) of death of 1.60 (95% confidence interval (CI) 0.21 to 6.32) should nevertheless be taken into account when planning further studies (for example, in calculating sample sizes).

Moreover the reported case fatality rates from AMI have fallen in recent decades (Koopman 2012, Schmidt 2012, Smolina 2012, Yeh 2010). In the included studies for this review, hospital mortality among control participants was only 1.7%. This rate is lower than that observed in contemporary routinely collected data (Babaev 2005, Movahed 2009). While this may be explained by the fact that only lower-risk participants were recruited, it could also be due to a chance deficit of deaths in the control arm, which would have contributed to the apparent difference between the oxygen and control groups. This aspect should be considered to inform selection criteria of patients in future studies.

A further issue to consider when assessing the contemporary relevance and applicability of the earlier studies in our review is that the definition of AMI has changed several times in the intervening years, reflecting better understanding of underlying pathophysiological processes and developments in diagnostic techniques such as the high sensitivity troponins. Furthermore, it is now recognised that acute coronary syndromes represent a spectrum of pathophysiological processes rather than a uniform type of 'heart attack'. Notably, there are now separate guidelines for STEMI and non-STEMI presentations, reflecting the different therapeutic options. Supplementary oxygen is under investigation in STEMI patients currently, but we have not identified any trials (reported, ongoing or in development) of oxygen in non-STEMI patients. This spec-

trum of ACS should be considered in further studies.

Quality of the evidence

The evidence (published and unpublished) in support of such a widespread practice is surprisingly sparse and scattered. The quality of the included studies was generally poor and the risk of bias was high for both our main outcomes. Two of the studies (Rawles 1976; Wilson 1997) were not recent and were carried out prior to the improvements in trial design, conduct and reporting that have taken place in the last decade; unfortunately the two recent studies were not conducted or reported in full accord with these advances. Therefore the risk of bias for death and pain across studies is high, and with regard these outcomes the results must be interpreted with caution. Other surrogate outcomes such as infarct size have been measured inappropriately or in a subset of the study population that represents a cohort of survivors of AMI.

Potential biases in the overview process

We were unable to determine if there was any publication bias using formal methods, as we found only four studies for inclusion. The possibility cannot be excluded that there are unpublished or ongoing studies, especially in foreign languages, that were not indexed in the electronic databases we searched.
Regarding heterogeneity, in the meta-analysis for analgesic used in confirmed AMI we found moderate heterogeneity (I^2 = 54%), which disappeared in the intention-to-treat analysis. While the two studies used in the meta-analysis had differences in their design (for example, blinded versus open-label) and attrition rates (much higher in Wilson 1997), it was not possible to investigate the heterogeneity further with only two trials.

Agreement or disagreements with other studies or reviews

The result is consistent with other published reviews and with the previous version of this review.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence in this area is sparse, of poor quality, and predates the advances in reperfusion techniques and trial methods of recent years. The evidence available is suggestive of harm but lacks power, so this could be due to chance. Current evidence neither supports nor clearly refutes the routine use of oxygen in people with AMI.

Implications for research

As long ago as 1950, it was demonstrated that the administration of pure oxygen via a facial mask not only failed to reduce the duration of angina pain but also prolonged the electrocardiographic changes indicative of an AMI (Russek 1950). This finding was explicitly identified as requiring further research over three decades ago (Salzman 1975). Given that Rawles 1976 subsequently suggested possible harm, it is surprising that a definitive study has not been done to rule out the possibility that oxygen may do more harm than good.

Part of the reason for the failure to fund such an essential study may be the strong a priori belief (Cabello 2009, Danchin 2009), based on pathophysiological reasoning, that oxygen administration must reduce both the oxygen deficit in ischaemic myocardial tissue and consequent tissue death. Indeed, both the medical profession and the public are so familiar with the use of oxygen that the general attitude may be that even if it is not doing any good it is not going to be of any harm. However, in recent years oxygen has been increasingly recognised as a "vasoactive substance". In summary ,while there are pathophysiological reasons to believe that it may have the potential to reduce tissue damage, it is also biologically plausible that oxygen is doing harm (see above under 'Why it is important to do this review').

There are three registered ongoing trials and two of them are currently recruiting participants (NCT01272713; NCT01423929). Both studies focus on the effect of oxygen on the infarct size estimated by biochemical markers and magnetic resonance imaging (MRI) (see Characteristics of ongoing studies) and focus on patients with STEMI. There are no ongoing trials seeking to address as a primary outcome the question of whether routine use of oxygen for AMI reduces pain or death.

Given the widespread use of oxygen for AMI, the inconsistencies in recommendations about when and to whom it should be given, and the fact that the best current evidence is suggestive of potential clinically significant harm, we believe there is an urgent need for an adequately powered randomised controlled trial to establish the effectiveness of, or harm from, the administration of oxygen to people with AMI. That trial must incorporate contemporary standards in design, conduct, analysis and reporting of trials and address the spectrum, population and sample size mentioned above to reflect contemporary diagnosis and care of the patient with AMI.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Rawles 1976

Methods	Double-blind, randomised controlled trial
Participants	People with suspected AMI presenting within 24 hours after onset of symptoms. Sample size 200
Interventions	Oxygen or compressed air administered by MC mask at 6 L/min over 24 hours Comparator: air at normal pressure given at 6 L/min by MC mask
Outcomes	Death, arrhythmias, use of analgesics, maximum serum aspartate aminotransferase levels, length of stay, systolic ejection time, hypoxaemia
Exclusions	People with heart failure, bronchitis, emphysema, or other respiratory problems
Length of follow-up	Discharge
Clinical Context and parallel care	Prethrombolysis period
Notes	Clinical setting: single site coronary care unit in the UK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	There was no description of how the sequence was generated
Allocation concealment (selection bias)	Low risk	Numbered sealed envelopes
Blinding (performance bias and detection bias) Death	Low risk	Double-blinded using shrouded cylinders (but likely that the blinding could have been compromised)
Blinding (performance bias and detection bias) Pain (or surrogate)	Unclear risk	Double-blinded using shrouded cylinders (but likely that the blinding could have been compromised and this may affect the assessment of this outcome: pain or surogate)
Blinding (performance bias and detection bias) infarct size ECG	Unclear risk	Not applicable in this trial

Rawles 1976 (*Continued*)

Incomplete outcome data (attrition bias) Death	Low risk	There were post-randomisation exclusions due to unconfirmed AMI (19% air group and 24% O_2 group)
Incomplete outcome data (attrition bias) Infacrt size (Biochemical methods)	Unclear risk	Not applicable in this trial
Incomplete outcome data (attrition bias) infarct size ECG mapping	Unclear risk	Not applicable in this trial
Incomplete outcome data (attrition bias) Infarct size (MRI)	Unclear risk	Not applicable in this trial
Selective reporting (reporting bias)	Low risk	There was no protocol published but we judged that there was no bias in reporting the primary outcome
Other bias	Low risk	Other biases have been not identified
Baseline characteristics	Low risk	Consecutive participants, similar age, sex

Wilson 1997

Methods	Randomised, open-label, controlled trial
Participants	People with confirmed AMI presenting within 24 hours of onset of symptoms. Sample size 50
Interventions	Oxygen by face mask at 4 L/min or normal air over 24 hours
Outcomes	Hypoxaemia, arrhythmias, cardiac enzymes
Exclusions	People with heart failure, cyanosis central or pulmonary disease requiring O_2
Length of follow-up	Discharge
Clinical Context and parallel care	Thrombolysis period
Notes	Single-site coronary care unit in the UK. The primary purpose of this trial was to look at the effect of oxygen on hypoxaemia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated

Wilson 1997 (*Continued*)

Allocation concealment (selection bias)	Low risk	Sealed envelopes for randomisation
Blinding (performance bias and detection bias) Death	Low risk	This was an open-label trial (but the absence of blinding is unlikely to introduce bias in this outcome)
Blinding (performance bias and detection bias) Pain (or surrogate)	High risk	This was an open-label trial, therefore the risk of bias in this outcome cannot be ruled out
Blinding (performance bias and detection bias) infarct size ECG	Unclear risk	Not relevant to this study
Incomplete outcome data (attrition bias) Death	High risk	Eight out of 50 missing data (group not specified); one death, one stroke, four withdrew consent, two with incomplete data
Incomplete outcome data (attrition bias) Infacrt size (Biochemical methods)	Unclear risk	Not relevant in this study
Incomplete outcome data (attrition bias) infarct size ECG mapping	Unclear risk	Not relevant in this study
Incomplete outcome data (attrition bias) Infarct size (MRI)	Unclear risk	Not relevant in this study
Selective reporting (reporting bias)	High risk	The main variables of the study were incidence and degree of hypoxaemia and the effect of oxygen administration. The main outcome of this review (death) was not reported, and in fact the only participant who died was not included in the analysis
Other bias	Low risk	Other biases were not identified
Baseline characteristics	Low risk	Consecutive participants, similar age, smoking and diabetes

Ukholkina 2005

Methods	Randomised, open-label, controlled trial
Participants	Confirmed AMI within 12 hours of onset of symptoms. Sample size 137
Interventions	Oxygen for three hours administered via nasal cannulae 3 - 6 L/min (FiO_2 30 - 40%)

Ukholkina 2005 (*Continued*)

Outcomes	Death, arrhythmias within one hour after reperfusion, surgery during hospital stay, recurrent AMI, post-infarction angina, hypoxaemia, heart failure, pericarditis, area of tissue damage measured by ECG mapping and cardiac enzymes	
Exclusions	People with complicated AMI, congestive heart failure, pulmonary disease, or anaemia	
Length of follow-up	10 days	
Clinical Context and parallel care	Context of primary PCI	
Notes	Single-site coronary care unit in Russia	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) Death	Low risk	This was an open-label trial (but absence of blinding unlikely to introduces bias in this outcome)
Blinding (performance bias and detection bias) Pain (or surrogate)	Unclear risk	Not applicable in this trial (pain was not a variable evaluated in the study)
Blinding (performance bias and detection bias) infarct size ECG	Unclear risk	This was an open-label trial (but the absence of blinding unlikely to introduce bias in this outcome)
Incomplete outcome data (attrition bias) Death	High risk	While mortality was adequately reported for included participants, there was inadequate description of exclusion post-randomisation in each group (e.g. failed revascularisation)
Incomplete outcome data (attrition bias) Infacrt size (Biochemical methods)	High risk	There was inadequate description of exclusion post-randomisation in each group
Incomplete outcome data (attrition bias) infarct size ECG mapping	Unclear risk	Inadequate description of exclusion post-randomisation in each group (e.g. failed revascularisation). Consequently, these participants are not included in the infarct size comparison. There were problems of consistency in the measurement process of ECG mapping done to estimate infarct size

Ukholkina 2005 (*Continued*)

Incomplete outcome data (attrition bias) Infarct size (MRI)	Unclear risk	Not applicable in this trial
Selective reporting (reporting bias)	High risk	We have no information about the protocol, but the infarct size estimation was only reported in 31 patients in the oxygen group and no information in the air group
Other bias	High risk	See baseline imbalances
Baseline characteristics	High risk	The groups were different at baseline in two important variables: 1. Clinical class Killip and Kimball (Killip II 10% O_2 versus 1% air group, P = 0.08) 2. Time to revascularisation 41 minutes shorter in the air group

Ranchord 2012

Methods	Open randomised controlled trial
Participants	People with ischaemic symptoms + ST-segment elevation (0.1 mV) in two contiguous leads STEMI or elevation (0.2 mV) in more of two precordial leads (STEMI), or with ischaemic symptoms + new onset left bundle branch block. Sample size 148
Interventions	Intervention: oxygen high flow 6 L/mit by concentration mask Comparator: oxygen titrated delivered by nasal prongs or mask adjusting the flow-rate to achieve an oxygen saturation of 93% - 96%
Outcomes	30 days mortality, complications, infarct size estimated by troponin T level measured 66 to 78 hours, infarct mass (absolute and as percentage) documented by MRI (measured in 4 - 6 weeks after AMI only in a subset of participants), por-BNP measured 24 hours after randomisation. As composite variable major cardiaca event (death, reinfarction, target vessel revascularisation) at 30 days was used
Exclusions	Previous myocardial infarction, chronic obstructive pulmonary disease (COPD), type II respiratory failure, cardiogenic shock, oxygen desaturation below 85%; pregnancy, bleomycin treatment or participation in another trial
Length of follow-up	30 days for mortality, Troponin T and BNP, 4 - 5 weeks after AMI for MRI
Clinical Context and parallel care	The study was undertaken exclusively in-hospital patients therefore the pre-hospital phase of AMI was not considered Primary percutaneous coronary intervention (PPCI) was the first-choice treatment in one centre, while in the other PPCI or thrombolysis was the treatment, depending on the hour of hospital admission

Notes	The study was conducted in two centres.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The sequence was undertaken by a computer programme.
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias) Death	Low risk	There is no threat for this outcome
Blinding (performance bias and detection bias) Pain (or surrogate)	Unclear risk	Not applicable in this trial
Blinding (performance bias and detection bias) infarct size ECG	Unclear risk	Not applicable in this trial
Incomplete outcome data (attrition bias) Death	High risk	There are 12 post-randomisation exclusions for which there are no 30-day mortality data reported
Incomplete outcome data (attrition bias) Infacrt size (Biochemical methods)	High risk	There are 12 post-randomisation exclusions in which there are no reported biochemical data
Incomplete outcome data (attrition bias) infarct size ECG mapping	Unclear risk	Not applicable in this trial
Incomplete outcome data (attrition bias) Infarct size (MRI)	Unclear risk	By definition, the primary outcome (30 days mortality) implies that MRI was not performed (by protocol performed 4 - 5 weeks after AMI). Data therefore not available
Selective reporting (reporting bias)	High risk	MRI was performed only in a subgroup of participants (selective reporting of subgroup)
Other bias	High risk	Prerandomisation oxygen was administered in experimental and control group (86.8% and 63% respectively). This prerandomisation intervention may have produced a bias in effect estimation towards the null hypothesis The comparison of infarct size measured by MRI between the two groups should be considered a non-randomised comparison therefore prone to the

Ranchord 2012 (*Continued*)

		bias of observational studies
Baseline characteristics	Unclear risk	There were differences in previous PCI, and in the infarct territory: anterior infarction was less frequent in the experimental group (18%) than in the control group (31%)

ABBREVIATIONS:
STEMI = ST-segment elevation myocardial infarction
CHD = coronary heart disease
AMI = myocardial infarction
ACS = acute coronary syndrome
STEMI: ST-elevation acute myocardial infarction
SIGN = Scottish Intercollegiate Guidelines Network
RCT = randomised controlled trial
RR = risk ratio
ECG = electrocardiogram
LOE = level of evidence
MRI = magnetic resonance imaging
BNP = brain natriuretic peptide
SD = standard deviation
SE = standard error
ITT = intention-to-treat analysis

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

Study	Reason for exclusion
AMIHOT 2003	Wrong intervention: aqueous oxygen therapy in STEMI
Dekleva 2004	Wrong intervention: hyperbaric oxygen versus air in participants after thrombolysis in AMI
Dotsenko 2007	Wrong intervention: hyperbaric oxygen versus air in conventionally treated participants with AMI
Haude 2007	Wrong intervention: supersaturated oxygen therapy after percutaneous coronary intervention in AMI
Kerr 1975	Different intervention: nitrous oxide 50% with or without oxygen 50% versus air in participants with AMI
Shandling 1997	Wrong intervention: hyperbaric oxygen
Slagboom 2005	Wrong intervention: haemoglobin-based oxygen therapeutics in elective PCI

AMI = acute myocardial infarction

PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction

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

ACTRN12609000466246

Trial name or title	A randomised controlled trial comparing controlled oxygen therapy versus high flow oxygen therapy for acute myocardial infarctions in the prehospital setting (no specific name available)
Methods	Randomised controlled trial, parallel design with open label and allocation concealment
Participants	People with chest pain and suspicion of acute coronary syndrome attended by Tasmanian ambulance service in the Launceston region
Interventions	High flow oxygen 8 - 15 L/min by non-breather mask compared to oxygen therapy to maintain oxygen saturation between 92% - 96%
Outcomes	Primary outcome: Mortality during ambulance or in the hospital stay. Secondary outcomes: 1.Time to resolution of chest pain using a 0 - 10 scale and an electronic system for reporting data 2. Length of hospital stay
Starting date	Theoretically January 2012
Contact information	Dr Michael Austin, Menzies Research Institute (Private Bag 23) Hobart TAS 7001. maaustin@utas.edu.au
Notes	Not recruiting yet (register visited last time January 1st 2013)

NCT01272713

Trial name or title	Air Versus Oxygen in myocarDial infarction study **(AVOID)**
Methods	Multicentric open-label randomised controlled trial
Participants	Participants uncomplicated acute ST-elevation myocardial infarction (STEMI) or ischaemic pain + left bundle branch block
Interventions	Oxygen by mask 8 L/min versus air. If the oxygen saturation falls below 94% then titrated oxygen was administered to achieve an oxygen saturation of 94%
Outcomes	Infarct size evaluated by cTnl and CK (peak and area under curve) at 72 hours of reperfusion. Survival to hospital discharge, Infarct size on MRI (in a subset of participants), Major adverse cardiac events (MACE) at six months
Starting date	Octorer 2011
Contact information	Dion Stub. d.stub@alfred.org.au

NCT01272713 (*Continued*)

Notes	The protocol and a feasibility study have been published (see studies awaiting for classification)

NCT01423929

Trial name or title	Suplemental Oxygen in Catheterization Coronary Emergency Reperfusion (**SOCCER)**
Methods	Multicentre single-blind randomised controlled trial
Participants	Normoxic STEMI ambulance patients with symptom duration less than six hours
Interventions	Oxygen 10 L/min by oxymask™ versus room air
Outcomes	Infarct size estimated by MRI at day four, myocardial salvage index by MRI, echocardiography (acute and six months after AMI), pro-BNP, dose of opioids
Starting date	January 2012
Contact information	Mahin Akbarzadeh (Skåne University Hospital at Lund)
Notes	Three hospitals with PPCI capabilities.

DATA AND ANALYSES

Comparison 1. Oxygen versus air

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death in hospital for participants with acute MI	3	430	Risk Ratio (M-H, Fixed, 95% CI)	2.11 [0.78, 5.68]
2 Death in hospital for participants with acute MI (random-effects)	3	430	Risk Ratio (M-H, Random, 95% CI)	2.12 [0.74, 6.10]
3 Death in hospital for all participants (including those who did not have an AMI)	3	485	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.75, 5.58]
4 Death in hospital for all participants (including those who did not have an AMI)(random-effects)	3	485	Risk Ratio (M-H, Random, 95% CI)	2.05 [0.71, 5.92]
5 Opiate use (as a proxy measure for pain) for participants with an AMI	2	199	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.83, 1.18]
6 Opiate use (as a proxy measure for pain) for participants with an AMI (random-effects)	2	199	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.72, 1.23]
7 Opiate use (as a proxy measure for pain) for all participants on ITT (including those who did not have an AMI)	2	250	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.20]
8 Opiate use (as a proxy measure for pain) for all participants on ITT (including those who did not have an AMI) (random-effects	2	250	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.78, 1.38]
9 Complications of AMI	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.45, 1.03]
10 Death in hospital for all participants (including those who did not have an AMI) trials done in the revascularization era	2	285	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.21, 6.32]

Analysis 1.1. Comparison 1 Oxygen versus air, Outcome 1 Death in hospital for participants with acute MI.

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 1 Death in hospital for participants with acute MI

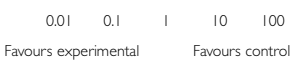
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rawles 1976	9/80	3/77		55.8 %	2.89 [0.81, 10.27]
Ukholkina 2005	1/58	0/79		7.7 %	4.07 [0.17, 98.10]
Ranchord 2012	1/68	2/68		36.5 %	0.50 [0.05, 5.39]
Total (95% CI)	**206**	**224**		**100.0 %**	**2.11 [0.78, 5.68]**

Total events: 11 (Experimental), 5 (Control)

Heterogeneity: Chi^2 = 1.81, df = 2 (P = 0.40); I^2 =0.0%

Test for overall effect: Z = 1.48 (P = 0.14)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 Oxygen versus air, Outcome 2 Death in hospital for participants with acute MI (random-effects).

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 2 Death in hospital for participants with acute MI (random-effects)

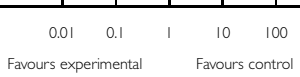
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Rawles 1976	9/80	3/77		69.3 %	2.89 [0.81, 10.27]
Ukholkina 2005	1/58	0/79		11.0 %	4.07 [0.17, 98.10]
Ranchord 2012	1/68	2/68		19.7 %	0.50 [0.05, 5.39]
Total (95% CI)	**206**	**224**		**100.0 %**	**2.12 [0.74, 6.10]**

Total events: 11 (Experimental), 5 (Control)

Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.81, df = 2 (P = 0.40); I^2 =0.0%

Test for overall effect: Z = 1.40 (P = 0.16)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Oxygen versus air, Outcome 3 Death in hospital for all participants (including those who did not have an AMI).

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 3 Death in hospital for all participants (including those who did not have an AMI)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rawles 1976	9/105	3/95		57.1 %	2.71 [0.76, 9.73]
Ukholkina 2005	1/58	0/79		7.7 %	4.07 [0.17, 98.10]
Ranchord 2012	1/72	2/76		35.3 %	0.53 [0.05, 5.70]
Total (95% CI)	**235**	**250**		**100.0 %**	**2.05 [0.75, 5.58]**

Total events: 11 (Experimental), 5 (Control)

Heterogeneity: $Chi^2 = 1.61$, df = 2 (P = 0.45); $I^2 = 0.0\%$

Test for overall effect: Z = 1.40 (P = 0.16)

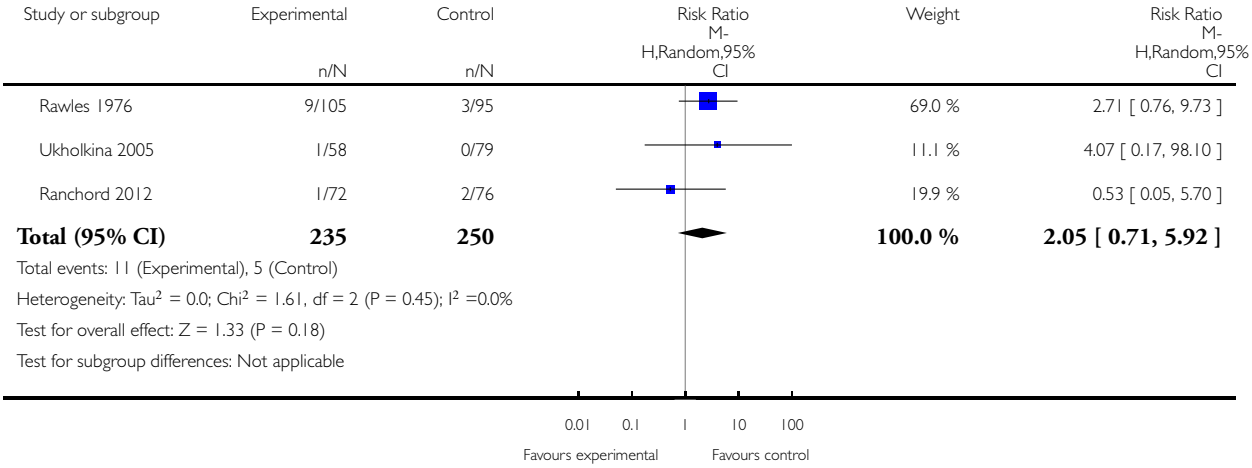
Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Oxygen versus air, Outcome 4 Death in hospital for all participants (including those who did not have an AMI)(random-effects).

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 4 Death in hospital for all participants (including those who did not have an AMI)(random-effects)



Analysis 1.5. Comparison 1 Oxygen versus air, Outcome 5 Opiate use (as a proxy measure for pain) for participants with an AMI.

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 5 Opiate use (as a proxy measure for pain) for participants with an AMI

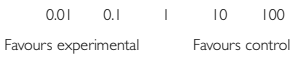
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wilson 1997	16/22	18/20		26.2 %	0.81 [0.60, 1.08]
Rawles 1976	57/80	52/77		73.8 %	1.06 [0.86, 1.30]
Total (95% CI)	**102**	**97**		**100.0 %**	**0.99 [0.83, 1.18]**

Total events: 73 (Experimental), 70 (Control)

Heterogeneity: Chi^2 = 2.18, df = 1 (P = 0.14); I^2 =54%

Test for overall effect: Z = 0.11 (P = 0.91)

Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1 Oxygen versus air, Outcome 6 Opiate use (as a proxy measure for pain) for participants with an AMI (random-effects).

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 6 Opiate use (as a proxy measure for pain) for participants with an AMI (random-effects)

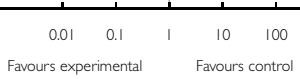
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Rawles 1976	57/80	52/77		57.6 %	1.06 [0.86, 1.30]
Wilson 1997	16/22	18/20		42.4 %	0.81 [0.60, 1.08]
Total (95% CI)	**102**	**97**		**100.0 %**	**0.94 [0.72, 1.23]**

Total events: 73 (Experimental), 70 (Control)

Heterogeneity: Tau^2 = 0.02; Chi^2 = 2.18, df = 1 (P = 0.14); I^2 =54%

Test for overall effect: Z = 0.44 (P = 0.66)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 Oxygen versus air, Outcome 7 Opiate use (as a proxy measure for pain) for all participants on ITT (including those who did not have an AMI).

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 7 Opiate use (as a proxy measure for pain) for all participants on ITT (including those who did not have an AMI)

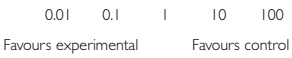
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rawles 1976	57/105	52/95		75.2 %	0.99 [0.77, 1.28]
Wilson 1997	16/25	18/25		24.8 %	0.89 [0.61, 1.30]
Total (95% CI)	**130**	**120**		**100.0 %**	**0.97 [0.78, 1.20]**

Total events: 73 (Experimental), 70 (Control)

Heterogeneity: Chi^2 = 0.22, df = 1 (P = 0.64); I^2 =0.0%

Test for overall effect: Z = 0.32 (P = 0.75)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 Oxygen versus air, Outcome 8 Opiate use (as a proxy measure for pain) for all participants on ITT (including those who did not have an AMI) (random-effects.

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 8 Opiate use (as a proxy measure for pain) for all participants on ITT (including those who did not have an AMI) (random-effects

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio(Non-event) M-H,Random,95% CI	Weight	Risk Ratio(Non-event) M-H,Random,95% CI
Rawles 1976	57/105	52/95		87.9 %	1.01 [0.75, 1.37]
Wilson 1997	16/25	18/25		12.1 %	1.29 [0.57, 2.91]
Total (95% CI)	**130**	**120**		**100.0 %**	**1.04 [0.78, 1.38]**
Total events: 73 (Experimental), 70 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.30$, df = 1 (P = 0.59); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.27 (P = 0.79)					
Test for subgroup differences: Not applicable					

Analysis 1.9. Comparison 1 Oxygen versus air, Outcome 9 Complications of AMI.

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 9 Complications of AMI

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ukholkina 2005	20/58	40/79		100.0 %	0.68 [0.45, 1.03]
Total (95% CI)	**58**	**79**		**100.0 %**	**0.68 [0.45, 1.03]**
Total events: 20 (Experimental), 40 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.81 (P = 0.070)					
Test for subgroup differences: Not applicable					

Analysis 1.10. Comparison 1 Oxygen versus air, Outcome 10 Death in hospital for all participants (including those who did not have an AMI) trials done in the revascularization era.

Review: Oxygen therapy for acute myocardial infarction

Comparison: 1 Oxygen versus air

Outcome: 10 Death in hospital for all participants (including those who did not have an AMI) trials done in the revascularization era

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ukholkina 2005	1/58	0/79		17.9 %	4.07 [0.17, 98.10]
Ranchord 2012	1/72	2/76		82.1 %	0.53 [0.05, 5.70]
Total (95% CI)	**130**	**155**		**100.0 %**	**1.16 [0.21, 6.32]**
Total events: 2 (Experimental), 2 (Control)					
Heterogeneity: Chi^2 = 1.02, df = 1 (P = 0.31); I^2 =2%					
Test for overall effect: Z = 0.17 (P = 0.86)					
Test for subgroup differences: Not applicable					

APPENDICES

Appendix 1. Search strategies 2010

CENTRAL on The Cochrane Library

#1 MeSH descriptor Myocardial Infarction explode all trees
#2 myocardial next infarct*
#3 heart next infarct*
#4 (acute near/3 coronary)
#5 (coronary near/3 syndrome*)
#6 heart next attack*
#7 MeSH descriptor Coronary Thrombosis this term only
#8 coronary near/3 thrombosis
#9 ami
#10 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)

#11 MeSH descriptor Oxygen Inhalation Therapy explode all trees
#12 oxygen
#13 (#10 and #12)

MEDLINE on Ovid

1 exp Myocardial Infarction/
2 myocardial infarct$.tw.
3 heart attack$.tw.
4 heart infarct$.tw.
5 (coronary adj3 syndrome$).tw.
6 acute coronary.tw.
7 Coronary Thrombosis/
8 coronary thrombosis.tw.
9 ami.tw.
10 or/1-9
11 Oxygen Inhalation Therapy/
12 (oxygen adj3 (therapy or treat$ or effect$ or admin$ or inhal$)).tw.13 oxygen.ti. or Oxygenotherapy/
14 or/11-13
15 10 and 14
16 randomized controlled trial.pt.
17 controlled clinical trial.pt.
18 randomized controlled trials.sh.
19 random allocation.sh.
20 double blind method.sh.
21 single-blind method.sh.
22 or/16-21
23 (animals not humans).sh.
24 22 not 23
25 clinical trial.pt.
26 exp clinical trials/
27 (clin$ adj25 trial$).ti,ab.
28 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
29 placebos.sh.
30 placebo$.ti,ab.
31 random$.ti,ab.
32 research design.sh.
33 or/25-32
34 33 not 23
35 34 not 24
36 comparative study.sh.
37 exp evaluation studies/
38 follow up studies.sh.
39 prospective studies.sh.
40 (control$ or prospectiv$ or volunteer$).ti,ab.
41 or/36-40
42 41 not 23
43 42 not (24 or 35)
44 24 or 35 or 43
45 15 and 44

EMBASE on Ovid

1 exp Heart Infarction/
2 Coronary Artery Thrombosis/
3 myocardial infarct$.tw.
4 heart attack$.tw.
5 heart infarct$.tw.
6 (coronary adj3 syndrome$).tw.
7 acute coronary.tw.
8 coronary thrombosis.tw.
9 ami.tw.
10 or/1-9
11 oxygen therapy/
12 (oxygen adj3 (therapy or treat$ or effect$ or admin$ or inhal$)).tw.
13 oxygen.ti.
14 or/11-13
15 10 and 14

Pascal

1 oxygen.mp. [mp=abstract, descriptors - english, descriptors - french, descriptors - spanish, heading words, identifiers - english, identifiers - french, identifiers - spanish, title, translated title]
2 myocardial infarction.mp. [mp=abstract, descriptors - english, descriptors - french, descriptors - spanish, heading words, identifiers - english, identifiers - french, identifiers - spanish, title, translated title]
3 acute coronary syndrome.mp. [mp=abstract, descriptors - english, descriptors - french, descriptors - spanish, heading words, identifiers - english, identifiers - french, identifiers - spanish, title, translated title]
4 2 or 3
5 1 and 4
6 random$.mp. [mp=abstract, descriptors - english, descriptors - french, descriptors - spanish, heading words, identifiers - english, identifiers - french, identifiers - spanish, title, translated title]
7 5 and 6

CINAHL (EBSCO)

(heart attack* or MI or AMI or heart infarct* or myocardial infarct* or coronary syndrome or coronary thrombosis) AND ((oxygen) AND (random* or control* or trial*)

LILACS (BIREME)

(heart or MI or AMI or myocardial or coronary) AND (oxygen) AND (random* or control* or trial*)

ISI Proceedings (Web of Knowledge)

(heart or MI or AMI or myocardial or coronary) AND (oxygen) AND (random* or control* or trial*)

Appendix 2. Search strategies 2012

CENTRAL

#1(preoperative physical therapy):ti
#2MeSH descriptor Myocardial Infarction explode all trees
#3(myocardial infarct*)
#4(heart attack*)
#5(heart infarct*)
#6(coronary near/3 syndrome*)
#7"acute coronary"
#8MeSH descriptor Coronary Thrombosis, this term only
#9 "coronary thrombosis"
#10(ami)
#11(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
#12MeSH descriptor Oxygen Inhalation Therapy, this term only
#13(oxygen near/3 (therapy or treat* or effect* or admin* or inhal*))
#14(oxygen):ti
#15(oxygenotherapy)
#16(#12 OR #13 OR #14 OR #15)
#17(#11 AND #16), from 2010 to 2012

MEDLINE (OVID)

1 exp Myocardial Infarction/
2 myocardial infarct$.tw.
3 heart attack$.tw.
4 heart infarct$.tw.
5 (coronary adj3 syndrome$).tw.
6 acute coronary.tw.
7 Coronary Thrombosis/
8 coronary thrombosis.tw.
9 ami.tw.
10 or/1-9
11 Oxygen Inhalation Therapy/
12 (oxygen adj3 (therapy or treat$ or effect$ or admin$ or inhal$)).tw.
13 oxygen.ti. or Oxygenotherapy.tw.
14 or/11-13
15 10 and 14
16 randomized controlled trial.pt.
17 controlled clinical trial.pt.
18 randomized.ab.
19 placebo.ab.
20 drug therapy.fs.
21 randomly.ab.
22 trial.ab.
23 groups.ab.
24 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25 exp animals/ not humans.sh.
26 24 not 25
27 15 and 26
28 limit 27 to yr="2010 -Current"

EMBASE (OVID)

1 exp Myocardial Infarction/
2 myocardial infarct$.tw.
3 heart attack$.tw.
4 heart infarct$.tw.
5 (coronary adj3 syndrome$).tw.
6 acute coronary.tw.
7 Coronary Thrombosis/
8 coronary thrombosis.tw.
9 ami.tw.
10 or/1-9
11 Oxygen Inhalation Therapy/
12 (oxygen adj3 (therapy or treat$ or effect$ or admin$ or inhal$)).tw.
13 oxygen.ti. or Oxygenotherapy.tw.
14 or/11-13
15 10 and 14
16 random$.tw.
17 factorial$.tw.
18 crossover$.tw.
19 cross over$.tw.
20 cross-over$.tw.
21 placebo$.tw.
22 (doubl$ adj blind$).tw.
23 (singl$ adj blind$).tw.
24 assign$.tw.
25 allocat$.tw.
26 volunteer$.tw.
27 crossover procedure/
28 double blind procedure/
29 randomized controlled trial/
30 single blind procedure/
31 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 (animal/ or nonhuman/) not human/
33 31 not 32
34 15 and 33
35 limit 34 to yr="2010 -Current"

CINAHL

S19 S14 and S17 Limiters - Published Date from: 20100101-20120731
S18 S14 and S17
S17 S15 or S16
S16 (MH "Randomized Controlled Trials")
S15 random* or blind* or allocat* or trial* or placebo* or crossover* or cross-over*
S14 S10 and S13
S13 S11 or S12
S12 oxygen or oxygenotherapy
S11 (MH "Oxygen Therapy+")
S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S9 ami
S8 coronary N3 thrombosis
S7 (MH "Coronary Thrombosis")
S6 (heart attack*)

S5 (coronary N3 syndrome*)
S4 (acute N3 coronary)
S3 (heart infarct*)
S2 (myocardial infarct*)
S1 (MH "Myocardial Infarction+")

Web of Science

#14 #13 AND #12 AND #8
#13 Topic=((random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*))
#12 #11 OR #10 OR #9
#11 Topic=(oxygenotherapy)
#10 Title=((oxygen near/3 (therapy or treat* or effect* or admin* or inhal*)))
#9 Title=(oxygen)
#8 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#7 Topic=(ami)
#6 Topic=(coronary near/3 thrombosis)
#5 Topic=((heart attack*))
#4 Topic=((coronary near/3 syndrome*))
#3 Topic=((acute near/3 coronary))
#2 Topic=((heart infarct*))
#1 Topic=((myocardial infarct*))

WHAT'S NEW

Last assessed as up-to-date: 17 July 2012.

Date	Event	Description
7 April 2013	New search has been performed	The updated search was conducted in May 2013, and identified one new trial for inclusion and three ongoing trials
7 April 2013	New citation required but conclusions have not changed	One new study included

CONTRIBUTIONS OF AUTHORS

Juan Cabello provided expert advice, co-wrote the protocol and helped with quality assessment, data extraction, writing the discussion and entering data into RevMan.

Amanda Burls co-wrote the protocol, contacted authors for further information and contributed to quality assessment, data extraction, analysis, writing the discussion, and entering data into Review Manager 5.

Sue Bayliss undertook the electronic searches, helped obtain papers and proofread the review.

Jose Emparanza Knorr co-wrote the protocol and contributed to quality assessment, data extraction, analysis and writing the discussion.

Tom Quinn provided expert advice, contacted experts to find unpublished studies and contributed to quality assessment, data extraction and writing the discussion.

DECLARATIONS OF INTEREST

None on starting this review. After starting this systematic review some of the authors have put together, with other clinical colleagues, a proposal for a randomised controlled trial in the UK of oxygen for AMI in the pre-hospital setting.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- None, Not specified.

No financial support was received for this review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Data were too sparse to permit adequate analysis of the subgroups that had been prespecified for exploration.

We made two changes:

1. One minor change in the search strategy to improve the sensitivity, i.e. the inclusion of the text word 'oxygenotherapy' in the title (the original search failed to pick up the Russian article and we looked to see if it was in MEDLINE and, if so, why the search strategy had missed it);

2. After the protocol was published, a new version of the Cochrane Handbook recommended a new approach to assessment of risk of bias, so we changed our method of assessment to be consistent with the recommendations.

INDEX TERMS

Medical Subject Headings (MeSH)

*Oxygen Inhalation Therapy [adverse effects; mortality]; Air; Analgesics [therapeutic use]; Myocardial Infarction [mortality; *therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans