Critical Review Form
Meta-analysis

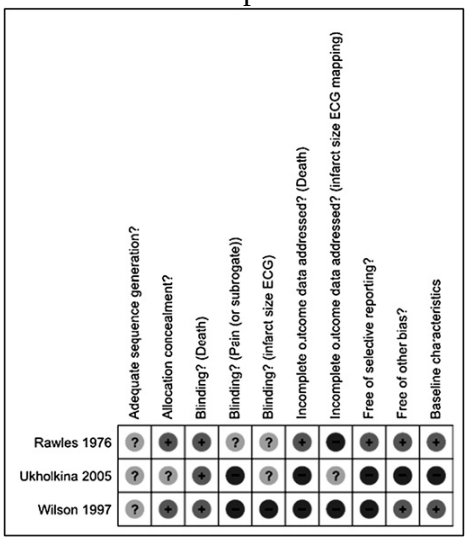
Burls A, Cabello JB, Emparanza JI, et al. Oxygen therapy for acute myocardial infarction: a systematic review and meta-analysis. Emerg Med J 2011 28: 917-923

Objectives: **"A systematic review and meta-analysis were performed to determine whether inhaled oxygen in acute myocardial infarction (AMI) improves pain or the risk of death."**

Methods: **A systematic review of the literature was conducted searching for randomized controlled trials (RCTs) evaluating the use of inhaled oxygen, at normal pressure, for one hour or longer compared to room air within 24 hours of the onset of AMI. An extensive list of the databases searched is provided; additionally annual meetings and conferences of the American College of Cardiology, American Heart Association, British Cardiovascular Society and European Society of Cardiology were searched for relevant research. Two authors independently reviewed titles and abstract identified for inclusion. The primary outcome was specified *a priori* as mortality, with secondary outcomes of pain (rated by opiate use), quality of life, or any other reported patient-important outcome.**

Of 2529 studies identified by the search strategy, three were selected for inclusion (Rawles 1976, Wilson 1997, Ukholkina 2005). Risk of bias within and between studies was evaluated using the Cochrane Collaboration two-part tool (Higgins 2008) which assesses 6 domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential threats to validity. Mortality was assessed using relative risk (RR), and evaluation was performed for both cases of confirmed AMI and using intention to treat (ITT) analysis for all included patients. A best-case, worst-case sensitivity analysis was performed for patients in whom mortality outcome data was not available.

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes. The review attempted to determine the affect of supplemental oxygen (at atmospheric pressure) compared to room air on mortality (primary outcome), pain, and quality of life in AMI. Current guidelines provide inconsistent recommendations regarding administration of supplemental oxygen (Kallstrom 2002, Antman 2004, Van de Werk 2008), likely due to a paucity of clear evidence of benefit and the potential for harm.
2.	Was the search for relevant studies detailed and exhaustive?	Yes. The authors searched the Cochrane CENTRAL Register of Controlled Trials, MEDLINE, MEDLINE In-Process, EMBASE, CINAHL, LILACS and PASCAL, UK National Research Register (NRR) to 2007, the NRR Archive and NIHR CRN portfolio, Current Controlled Trials metaRegister and http://Clin-icalTrials.gov/, Library ZETOC, Web of Science, ISI Proceedings, annual meetings and conferences of the American College of Cardiology, American Heart Association, British Cardiovascular Society and European Society of Cardiology. Databases were searched from their start date to February 2010.
3.	Were the primary studies of high methodological quality?	No. While all 3 studies were parallel design RCTs, only one (Rawles 1976) was blinded. Blinding in this study involved shrouds over the oxygen/air canisters, which could be compromised and hence lead to performance bias. None of the studies described the process of randomization sequence generation, and one study (Ukholkina 2005) did not state whether allocation was concealed. One study (Wilson 1997) excluded 8 patients from analysis and provided incomplete outcome data on these patients; one death was recorded in the study, but this patient was excluded from the study and it is not noted to which arm the patient was randomized. Another study (Ukholkina 2005) failed to report data on patients excluded post-randomization due to failed revascularization; there appears to be missing data on 2 patients in the air group and 4 in the oxygen

		group. Finally, one of the studies (Rawles 1976) randomized patients prior to confirmation of the diagnosis of AMI, then excluded from analysis those patients in whom the diagnosis was not confirmed.
4.	Were the assessments of the included studies reproducible?  Figure 2 Risk of bias.	Yes. The authors provide a detailed assessment of the methodological quality of the individual studies using the Cochrane Collaboration two-part tool (Higgins 2008) which assesses 6 domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential threats to validity. This data is summarized in Figure 2.
II.	***What are the results?***	
1.	What are the overall results of the study?	The meta-analysis showed a RR of death for patients in the oxygen group of 3.03 (95% CI 0.93 to 9.83) in confirmed AMI and 2.88 (95% CI 0.88 to 9.38) in the ITT population. The meta-analysis for analgesic use gives a RR of 0.99 (95% CI 0.83 to 1.18) in confirmed AMI and 0.97 (95% CI 0.78 to 1.20; figure 4) in the ITT population. In the sensitivity analysis for missing information on the arm in which the death occurred in the trial by Wilson and Channer: the worst-case scenario assumes that the patient who died was in the oxygen arm and gives a RR of death of 2.88 (95% CI 0.88 to 9.38) using ITT analysis; the best-case scenario assumes that the patient who died received air, giving a RR of death of 2.06 (95% CI 0.67 to 6.37) using ITT analysis.
2.	How precise are the results?	See above.
3.	Were the results similar from study	Mostly. There was little heterogeneity when

	to study?	assessing mortality rates between studies (χ^2=0.05, dF=1 (P=0.82), I^2=0%), though this is difficult to assess with such a small number of studies. In the meta-analysis for analgesic use in confirmed AMI there was moderate heterogeneity (I^2=54%) but it disappeared in the ITT analysis.
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	It is very difficult to apply these results given the low statistical power of the analysis. While the data show a trend towards increased mortality in those patients receiving oxygen, the wide 95% CI does cross 1.0. A large number of subjects would be needed to attain the necessary power to show a difference in mortality between the groups with statistical significance (if one truly exists). Given the paucity of evidence to justify the routine administration of oxygen in patients with MI, it is reasonable to reserve supplemental oxygen for those patients with hypoxia (as determined by pulse-oximetry) or those with shortness of breath in whom supplemental oxygen provides subjective relief.
2.	Were all patient important outcomes considered?	No. Future studies should consider the incidence of long-standing arrhythmias requiring treatment, conduction defects requiring pacemaker placement, hospital length of stay, and cost. Additionally, the use of validated Health-Related Quality of Life (HQRL) instruments such as the Kansas City Cardiomyopathy Questionnaire and the Quality of Life after Myocardial Infarction (QLMI) instrument would help assess the long-term impacts of oxygen use.
3.	Are the benefits worth the costs and potential risks?	Uncertain. Based on the current evidence, there does not appear to be any benefit from the use of supplemental oxygen, however the small sample size and limited patient-important outcomes precludes drawing any firm conclusions. The cost of supplemental oxygen administration is low, and if future large studies showed any reduction of mortality or other patient-oriented outcomes, this would justify its use.

Limitations:

1) **The low number of total subjects results in a lack of statistical power to detect a statistically significant difference in the primary outcome (mortality) despite the high estimate of effect size (RR 3.03).**
2) **The included studies were of overall poor methodological quality, and the results of a meta-analysis of such studies are difficult to interpret.**
3) **The included studies (and meta-analysis) failed to address many patient important outcomes, such as functional status, hospital length of stay, and cost.**
4) **Only three trials were identified for meta-analysis in this systematic review. Assessments of heterogeneity can be difficult to interpret when the number of studies is low (Higgins 2002, Hardy 1998).**

Bottom Line:

This meta-analysis of the current literature describes a non-statistically significant trend towards increased mortality with the use of supplemental oxygen in AMI with a RR of death of 3.03 (95% CI 0.93 to 9.83) in confirmed AMI and 2.88 (95% CI 0.88 to 9.38) in the ITT population. The overall small sample size and the poor methodological quality of the included studies preclude any conclusions being drawn from this analysis. The authors note that a clinical trial with 10,000 patients in each arm would be needed to address the question of whether oxygen improves or increases mortality, though they do not provide the details of this power analysis. They found no clinically significant difference in analgesia use.