Critical Review Form
Therapy

PGY-1

Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, Cameron P, Barger B, Ellims AH, Taylor AJ, Meredith IT, Kaye DM; AVOID Investigators. Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction. Circulation. 2015 Jun 16;131(24):2143-50.

Objectives: **"to compare supplemental oxygen therapy with no oxygen therapy in normoxic patients with STEMI to determine its effect on myocardial infarct size." (p. 2144)**

Methods: **This prospective, multicenter, open-label, randomized controlled trial was conducted in Melbourne, Australia between October 2011 and July 2014. Patients with chest pain, evaluated by Ambulance Victoria and transferred to any of nine hospitals providing 24-hour percutaneous coronary intervention services were screened for enrollment by the paramedics. Patients aged 18 years or older with chest pain of < 12 hours duration and prehospital ECG evidence of STEMI were eligible for enrollment. Exclusion criteria included oxygen saturation < 94%, bronchospasms requiring nebulized beta-agonist with oxygen, oxygen administration prior to randomization, altered mental status, transport to a nonparticipating hospital, or determination that the patient did not have STEMI by the physician at the receiving hospital.**

Patients were randomized to either receive oxygen at 8 L/min via face-mask (continued until transfer from the cardiac catheterization laboratory to the cardiac care ward) or no oxygen. Patients in the no oxygen arm were administered oxygen if O_2 saturation fell below 94%, with a goal to keep this value at 94% or above. Cardiac troponin I (cTnI) and creatine kinase (CK) levels were checked at baseline and every 6 hours for the first 24 hours, then every 12 hours for the next 48 hours. Contrast-enhanced cardiac MRI (CMR) was offered to all patients at 6 months following STEMI.

The primary endpoint was myocardial injury, measured by peak cTnI and CK levels. Secondary endpoints included ST-segment resolution on ECG, mortality, major adverse cardiac events (death, recurrent MI, repeat vascularization, stroke), and infarct size on CMR at 6 months.

Out of 836 patients screened for enrollment, 638 were randomized by paramedics. Fifty were excluded for prehospital protocol violations, refusal of consent, and repeat enrollment; another 118 were deemed not to have STEMI by the treating physician in the ED; and another 29 were excluded after failure to confirm STEMI on coronary angiography. In the final analysis, there were 441 patients, 218 in the oxygen group and 223 in the no oxygen group. The mean age was around 63 years and 79% were male.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	Yes. Patients were randomized to either receive oxygen at 8 L/min via face-mask (continued until transfer from the cardiac catheterization laboratory to the cardiac care ward) or no oxygen.
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. "Computer-generated block randomization was performed with ambulances carrying opaque envelopes numbered externally, concealing treatment assignment." (p. 2144)
3.	Were patients analyzed in the groups to which they were randomized?	Yes and no. Patients in the no oxygen group could receive oxygen, by protocol, if their O_2 saturation fell below 94%. Per the authors, "The primary analysis was performed on an intention-to-treat basis for all patients with confirmed STEMI after emergent coronary angiogram." (p. 2145) Of patients randomized to no oxygen, 7.7% received oxygen; of patients randomized to receive oxygen, 0.5% did not. However, as the authors excluded patients initially enrolled by EMS who were eventually deemed not to have an AMI, this was not a trued intention to treat analysis. Such patients, although excluded from the final analysis, would receive oxygen if it were deemed to be beneficial, and any effects on them should be considered.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Mostly yes. Patients were similar with respect to age, gender, BMI, past medical history (with slightly higher rate of PVD in no oxygen group at 4.9% vs. 1.8%), baseline vital signs, culprit artery on PCI, and TIMI flow before and after the procedure. Two patients (0.9%) in the oxygen received thrombolysis compared to none in the no oxygen arm; three patients (1.3%) in the no oxygen arm required intubation, compared to none in the oxygen arm.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	

1.	Were patients aware of group allocation?	Presumably yes. No attempt was made to blind the patients to group allocation, and sham oxygen therapy was not used. Patients receiving O_2 would know that they had a mask placed. It is doubtful, however, that performance bias on the part of the patient would have affected outcomes.
2.	Were clinicians aware of group allocation?	Yes. "Individuals involved with the delivery of oxygen therapy before hospital arrival and in hospital were not blinded to treatment assignment." (p. 2144) It is possible, though unlikely, that performance bias on the part of paramedics and clinicians could have affected the outcomes.
3.	Were outcome assessors aware of group allocation?	No. "Six-month follow-up of all patients was performed by a central coordinator blinded to treatment assignment. Investigators undertaking data analysis were masked to treatment assignment for primary end points and 6-month telephone follow-up." (p. 2144)
4.	Was follow-up complete?	No. cTnI data was not available in 18 patients in each group. CK data was not available in 1 patient in each group. CMR was only performed in 61 patients in the oxygen group (28%) and 66 patients in the no oxygen group (30%).
II.	**What are the results ?**	
1.	How large was the treatment effect?	• There was no significant difference in the geometric mean peak cTnI in the O_2 group compared to the no O_2 group, with a ratio of 1.20 (95% CI 0.92-1.56). • There was an increase in the geometric mean peak CK in the O_2 group compared to the no O_2 group, with a ratio of 1.26 (95% CI 1.05 to 1.52). • In-hospital mortality was not statistically significant between the groups: 1.8% in the O_2 group vs. 4.5% in the no O_2 group, p = 0.11. • The rate of in-hospital recurrent MI was higher in the O_2 group: 5.5% vs. 0.9%, p = 0.006. • Major cardiac dysrhythmias (ventricular or atrial tachycardia) occurred more frequently during the hospital stay in the O_2 group: 40.4% vs. 31.4%, p = 0.05. • On 6-month CMR, the median infarct size was larger in the O_2 group (20.3 g vs. 13.1 g, p = 0.04), but there was no difference in left

		ventricular dimensions or ejection fraction.
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Uncertain. This study was conducted in a large, urban EMS system that is similar to ours, and included hospitals that perform 24-hour cardiac catheterization, which ours does. Likely these patients were similar to ours, but racial difference would likely exist, as well as possible differences in baseline comorbidities. Overall, it makes sense that the results of this study would apply to our patient population (external validity).
2.	Were all clinically important outcomes considered?	No. The primary outcome of the study, infarct size based on peak cardiac enzyme levels, is a surrogate outcome. Several other short-term outcomes were assessed, including in-hospital mortality, arrhythmias, and recurrent MI, but the authors failed adequately to look at long-term outcomes. They performed CMR only on a small subset of patients (less than a third). Clinically relevant patient-centered outcomes would have been more useful to evaluate the long-term effects of oxygen on cardiac function, including any of several measures of quality of life in patients with heart failure (e.g. the Chronic Heart Failure Questionnaire (CHQ), the Minnesota Living with Heart Failure Questionnaire (LHFQ), and the General Health Survey Short-form-12 (SF-12)).
3.	Are the likely treatment benefits worth the potential harm and costs?	No. Supplemental oxygen in patients with STEMI undergoing percutaneous coronary intervention caused an increase in geometric mean peak CK levels with no effect on cTnI levels. Patients receiving O_2 also had an increased incident of in-hospital recurrent MI and dysrhythmia, with no effect on mortality. At 6-month follow-up, in a small subset of patients, cardiac MR demonstrated no difference in ejection fraction or left ventricular dimensions, with higher infarct size in the O_2 group. While this difference was statistically significant, it is unclear if it was clinically significant. Essentially, O_2 had either no effect on the outcomes measured or caused some degree of worse outcomes. The primary outcome was not a patient-centered outcome, as were many of the secondary outcomes,

		but overall, it does not seem that O_2 therapy is beneficial in normoxic patients with STEMI.

Limitations:

1. **This study was not blinded. While the early outcome measure (elevation of cardiac enzymes) was objective, and hence not subject to observer bias, significant performance bias would have affected the results.**

2. **The primary outcome measured was a surrogate outcome. Clinically relevant patient-centered outcomes would have been more useful to evaluate the long-term effects of oxygen on cardiac function.**

3. **The authors did not perform a true intention to treat analysis, as they excluded a significant number of patients with suspected STEMI who were later deemed not to have a STEMI.**

4. **Primary outcome data was missing for 18 patients in each group (8.3% and 8.7% for the two groups) (attrition bias), and CMR was only performed in a fraction of patients (selection bias).**

Bottom Line:

This prospective, open-label, multicenter trial of normoxic patients with confirmed STEMI comparing administration of supplemental oxygen to ambient air found no significant difference in peak cTnI levels, with an increased in peak CK in patients receiving oxygen. There was no difference in mortality, but a higher rate of recurrent MI and dysrhythmia was seen in the oxygen group. In a small, select group of patients undergoing CMR, infarct size was larger in the oxygen group, but no difference in LV size or systolic function was observed. The primary outcome in this study was, unfortunately, a surrogate outcome, and the data from patients undergoing CMR was at high risk of selection bias.