Critical Review Form
Therapy

PGY-3

Hofmann R, James SK, Jernberg T, et al; DETO2X–SWEDEHEART Investigators. Oxygen Therapy in Suspected Acute Myocardial Infarction. N Engl J Med. 2017 Aug 28.

Objectives: **"to evaluate the effect of oxygen therapy on all-cause mortality at 1 year among patients with suspected myocardial infarction who did not have hypoxemia at baseline." (p. 2)**

Methods: **This multicenter, open-label, randomized, controlled trial was conducted using the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry for enrollment and data collection. Thirty-five hospitals participated, and patients were enrolled between April 13, 2013 and December 30, 2015. Patients aged 30 years or older, presenting to the ambulance services, emergency departments (ED), coronary care units, or cardiac catheterization laboratories of participating hospitals with symptoms suggestive of myocardial infarction were eligible, assuming they had symptoms for less than 6 hours, had an oxygen saturation of 90% or more, had electrocardiographic findings of ischemia or elevated troponin T or I levels, and were Swedish citizens. Patients already receiving supplemental oxygen and those with cardiac arrest were excluded.**

Patients were randomly assigned in a 1:1 fashion to either receive supplemental oxygen (6 L/min by face mask for 6 to 12 hours) or ambient air. All other treatments were at the discretion of the treating physicians. Supplemental oxygen could be given if necessary outside of the treatment protocol, and patients were analyzed according to the intention to treat principle.

The primary outcome was death from any cause within 1 year of randomization. Secondary outcomes included death from any cause at 30 days, rehospitalization with MI, rehospitalization with heart failure, and cardiovascular death at 30 days and 1 year, as well as a composite of these outcomes. Data on mortality were obtained from the Swedish National Population Registry.

A total of 6629 patients with suspected MI were enrolled, with 3311 assigned to receive oxygen and 3318 assigned to receive ambient air. Among those with data available, the median time from symptom onset to randomization was 245 minutes in the oxygen group and 250 minutes in the ambient air group. The median age in both groups was 68 years, and around 69% were male. A final diagnosis of MI was made in 5010 (75.6%) patients.

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. "Unrestricted 1:1 randomization following a computer-generated list was performed with the use of an online randomization module embedded in SWEDEHEART." (p. 3)
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. The online randomization module should have been sufficient to prevent subversion of the randomization process, but the authors do not provide details regarding group allocation and concealment following the generation of the lists.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. "If it was deemed clinically necessary… supplemental oxygen outside the protocol was provided…" (p. 3). A total of 316 patients (4.8%) received oxygen outside of the trial due to hypoxemia, including 254 patients (7.7%) assigned to ambient air. There were also 403 patients (6.1%) who did not complete participation in the trial, including 297 in the oxygen group who declined to continue oxygen therapy. These patients were analyzed according to their group assignment, in keeping with the intention to treat principle.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, BMI, medical comorbidities (including previous cardiovascular disease), relevant medication usage, duration of symptoms, baseline vital signs, and final diagnosis.
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	Yes. "...double blinding was not considered to be feasible or ethical, because there is no pressurized air in Swedish ambulances, and the avail- able closed Hudson masks might have put patients at risk for carbon dioxide retention if they had been used as a sham comparator." (p. 7)

		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. 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?	Uncertain. The authors do not specify whether outcome assessors were blinded to group allocation. The outcomes were very objective, however, (especially mortality) and it is unlikely that observer bias would affect the assessment of outcomes.
4.	Was follow-up complete?	Yes. While 9% of patients in the oxygen group and 3% in the ambient air group did not complete participation in the study, outcome data was available for all patients who were randomized.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• For the primary outcome: all-cause mortality at one year was similar between groups, with 5.0% dying in the oxygen group and 5.1% dying in the ambient air group, hazard ratio (HR) 0.97 (95% CI 0.79 to 1.21). • One-year mortality in a per protocol analysis was also similar between groups, at 4.7% (141 of 3014) in the oxygen group and 5.1% (163 of 3212) in the ambient air group: HR 0.91 (95% CI 0.72 to 1.14). • Rehospitalization with MI within one year occurred in 3.8% of patients in the oxygen group and 3.3% of patients in the ambient air group: HR 1.13 (95% CI 0.88 to 1.46). • The composite of death or rehospitalization with MI at one year occurred in 8.3% of patients in the oxygen group and 8.0% in the ambient air group: HR 1.03 (95% CI 0.87 to 1.22). • There were no differences in either of the outcomes, or the composite outcome, at 30 days.
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 at multiple hospitals in Sweden. 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 was mortality, which is certainly a relevant patient-centered outcome. It would also have been more useful to evaluate the long-term effects of oxygen therapy on some measure of infarct size or 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 suspected MI does not seem to have any significant effect on mortality or hospital readmission for MI. While it would have been helpful to look at some measure of infarct size or cardiac function (especially a measure of quality of life in cardiac failure), this was not addressed, and the preponderance of evidence shows no benefit.

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. **While oxygen therapy does not appear to have any effect on mortality, it could potentially have an effect on other patient-centered outcomes such as cardiac function and hence quality of life.**

3. **The study was conducted in Sweden. While it seems likely that patients with suspected MI in this study would be similar to those treated in the US, differences in racial make-up and medical comorbidities could have some affect on the results (external validity).**

Bottom Line:

This large, unblinded, randomized trial, conducted at several hospitals in Sweden, demonstrated no significant effect on mortality or rehospitalization for MI at either 1 year or 30 days with the administration of oxygen vs. ambient air in patients without

hypoxia. The study was limited by lack of blinding and lack of additional outcomes (such as quality of life), but was otherwise robust and methodologically sound.