

## Air Versus Oxygen in ST-Segment Elevation Myocardial Infarction

**Running title:** *Stub et al.; AVOID Study*

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## Abstract

**Background**—Oxygen is commonly administered to patients with ST-elevation myocardial infarction (STEMI) despite previous studies suggesting a possible increase in myocardial injury due to coronary vasoconstriction and heightened oxidative stress.

**Methods and Results**—We conducted a multicenter, prospective, randomized, controlled trial comparing oxygen (8 L/min) with no supplemental oxygen in patients with STEMI diagnosed on paramedic 12-lead electrocardiogram. Of 638 patients randomized, 441 were confirmed STEMI patients who underwent primary endpoint analysis. The primary endpoint was myocardial infarct size as assessed by cardiac enzymes, troponin (cTnI) and creatine kinase (CK). Secondary endpoints included recurrent myocardial infarction, cardiac arrhythmia and myocardial infarct size assessed by cardiac magnetic resonance (CMR) imaging at 6 months. Mean peak troponin was similar in the oxygen and no oxygen groups (57.4 mcg/L vs. 48.0 mcg/L; ratio, 1.20; 95% confidence interval [CI], 0.92 to 1.56;  $P=0.18$ ). There was a significant increase in mean peak CK in the oxygen group compared to the no oxygen group (1948 U/L vs. 1543 U/L; means ratio, 1.27; 95% CI, 1.04 to 1.52;  $P=0.01$ ). There was an increase in the rate of recurrent myocardial infarction in the oxygen group compared to the no oxygen group (5.5% vs. 0.9%,  $P=0.006$ ) and an increase in frequency of cardiac arrhythmia (40.4% vs. 31.4%;  $P=0.05$ ). At 6-months the oxygen group had an increase in myocardial infarct size on CMR ( $n=139$ ; 20.3 grams vs. 13.1 grams;  $P=0.04$ ).

**Conclusions**—Supplemental oxygen therapy in patients with STEMI but without hypoxia may increase early myocardial injury and was associated with larger myocardial infarct size assessed at six months.

**Clinical Trial Registration Information**—clinicaltrials.gov. Identifier: NCT01272713.

**Key words:** myocardial infarction, ST-segment elevation myocardial infarction, oxygen

## Introduction

Following the first report of supplemental oxygen for angina in 1900,<sup>1</sup> oxygen therapy has been commonly used in the initial treatment of patients with ST-elevation myocardial infarction (STEMI). This is based on the belief that supplemental oxygen may increase oxygen delivery to ischemic myocardium and hence reduce myocardial injury, and is supported by laboratory studies,<sup>2,3</sup> an older clinical trial,<sup>4</sup> the apparent benefit of hyperbaric oxygen,<sup>5</sup> and clinical trials of intracoronary aqueous oxygen.<sup>6</sup> Other studies, however, have suggested a potential adverse physiologic effect of supplemental oxygen, with reduced coronary blood flow,<sup>7</sup> increased coronary vascular resistance,<sup>8</sup> and the production of reactive oxygen species contributing to vasoconstriction and reperfusion injury.<sup>9, 10</sup> A recent meta-analysis of three small randomized trials suggested a possible increase in adverse outcomes with supplemental oxygen administration.<sup>11</sup> More recently, a study comparing high concentration oxygen with titrated oxygen in patients with suspected acute myocardial infarction (AMI) found no difference in myocardial infarct size on cardiac magnetic resonance imaging (CMR).<sup>12</sup> Importantly, there are no studies evaluating the effects of supplemental oxygen therapy in the setting of contemporary therapy for STEMI, specifically acute coronary intervention.

Taken together, there remains considerable uncertainty over the utility of routine supplemental oxygen in uncomplicated AMI, with no clear recommendation regarding oxygen therapy in normoxic patients in the latest American Heart Association STEMI guidelines.<sup>13</sup> Despite its potential adverse physiological effects, supplemental oxygen continues to be administered to almost 90% of patients with suspected AMI.<sup>14</sup> The aim of this study was to compare supplemental oxygen therapy with no oxygen therapy in normoxic patients with STEMI to determine its effect on myocardial infarct size.

## Methods

### Study Design

The Air Versus Oxygen in Myocardial Infarction (AVOID) study was a multicentre, prospective, open label, randomised trial. The study was conducted by Ambulance Victoria and nine metropolitan hospitals that provide 24 hour percutaneous coronary intervention (PCI) services in Melbourne, Australia between October 2011 and July 2014. The trial design was registered with clinicaltrials.gov (NCT01272713) and has been reported previously.<sup>15</sup>

### Study Oversight

The study conformed to the Australian National Health and Medical Research Council framework for the conduct of clinical trials in the emergency setting. The study was approved by the Human Research Ethics Committees of all participating hospitals utilizing a process of delayed consent. Prior to pre-hospital enrolment, patients were given brief information and the opportunity to opt out of the trial. Informed consent by the patient or next of kin was sought after stabilization in hospital. The study was designed by the authors, who wrote all drafts of the manuscript and vouch for the integrity and completeness of the data and analyses and for the fidelity of this report. None of the sponsors had access to the study data or had any role in the design or implementation of the study or the reporting of the data. All primary efficacy and safety outcome measures including mortality, cardiac arrest, and unplanned intubations were assessed by an independent data safety monitoring committee (DSMC) (Supplementary Appendix List of investigators). The DSMC performed an interim analysis after 405 randomizations and recommended continuing the trial to the planned target.

### Patient Population

Paramedics screened patients with chest pain to determine their eligibility for enrolment. Patients

were included if they were adults  $\geq 18$  years of age, had chest pain commencing less than 12 hours prior to assessment, with prehospital electrocardiography (ECG) evidence of STEMI, as determined by the paramedic, defined as ST-segment elevation of  $\geq 0.1$  mV in two contiguous limb leads, or  $\geq 0.2$  mV in two contiguous chest leads, or new left bundle branch block pattern. Patients were excluded if any of the following were present: oxygen saturation  $< 94\%$  measured on pulse oximeter,<sup>16</sup> bronchospasm requiring nebulized salbutamol therapy using oxygen, oxygen administration prior to randomization, altered conscious state, or planned transport to a non-participating hospital. Patients who met inclusion criteria in the field and were allocated to a treatment arm were excluded after arrival at hospital if physician assessment indicated that the patient did not have a STEMI.



### **Randomization and Masking**

Computer-generated block randomization was performed, with ambulances carrying opaque envelopes numbered externally, concealing treatment assignment. Individuals involved with the delivery of oxygen therapy pre-hospital and in-hospital were not blinded to treatment assignment. 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 endpoints and six-month telephone follow-up.

### **Procedures**

In the oxygen group patients were administered supplemental oxygen via face mask at 8 L/min by paramedics, and this therapy continued until transfer from the cardiac catheterization laboratory to the cardiac care ward. Patients randomized to the no oxygen arm received no oxygen unless oxygen saturation fell below 94% in which case oxygen was administered via nasal cannula (4 L/min) or face mask (8 L/min) to achieve an oxygen saturation of 94%. All

patients received Aspirin 300 mg orally by paramedics. Additional anti-platelet therapy, choice of anticoagulation and percutaneous intervention strategy was at the discretion of the treating interventional cardiologist, according to hospital protocol. Blood sampling was done at baseline and then six hourly for the first 24 hours and 12 hourly out to 72 hours after admission to assess troponin (cTnI) and creatine kinase (CK) concentration. Contrast enhanced CMR at 6 months was offered to all patients with confirmed STEMI, who were agreeable to travel to the core site for scanning, and had no contraindications for CMR.

Data were collected from patient case notes and electronic records into trial-specific case record forms. All randomized patients were accounted for using daily audits of pre-hospital and hospital data to crosscheck against all cardiac catheterization laboratory activations at each institution.

### Statistical analysis

For the baseline characteristics, variables that approximated a normal distribution were summarized as mean  $\pm$  SD, and groups compared using Student's t-tests. Non-normal variables were represented as median and first and third quartiles (Q1, Q3), and groups were compared using Wilcoxon rank sum test with exact inference. Binomial variables were expressed as proportions and 95% confidence intervals (CI) and groups compared by  $\chi^2$  tests. Definitions of the endpoints used in this study are provided in **Supplemental Table 1**. The primary endpoint was myocardial injury, measured by peak cTnI and CK. The area under the curve (AUC<sub>72</sub>) for cTnI and CK concentration in serum were also measured. Secondary endpoints, measured at hospital discharge and 6 months, included ECG ST-segment resolution; mortality; major adverse cardiac events (death, recurrent myocardial infarction, repeat revascularization and stroke), and; myocardial infarct size on CMR (n=139) at 6 months. For the primary endpoint, we calculated

geometric means and ratios (95% CI) for cTnI and CK release, and a Student's t-test was carried out on the log-transformed data with comparison of groups obtained after back-transformation. To estimate the AUC<sub>72</sub> for cTnI and CK release we used trapezoidal integration, with multiple imputation using the Markov Chain Monte Carlo method for patients with one or more missing biomarker assays (**Supplemental Figure 1**) (**Supplemental Table 2**).<sup>17, 18</sup>

The robustness of our AUC<sub>72</sub> estimations were assessed using a series of sensitivity analyses. Firstly we conducted trapezoidal integration for area under the curve measurement as above, and also considered additional covariates for the imputation model as follows: age, gender, TIMI flow pre procedure, LAD culprit artery, symptom to intervention time and procedural success. In the second sensitivity analysis, a repeated measures analysis was used to estimate the overall profile of cTnI/CK release over the 72 hour window. All available biomarker data were analyzed using linear mixed-effects regression with patient as a random effect together with treatment group, time of assay, and an interaction term between treatment group and time of assay included as fixed effects. For this analysis, the non-significant interaction term between treatment group and time of assay was removed from the model. In the final sensitivity analysis, trapezoidal integration was used for the estimation of area under the curve. Patients with one or more missing biomarker assays were replaced by linear interpolation and extrapolation.

(**Supplemental Table 2**).<sup>19</sup> Infarct size assessed by CMR at six-months was compared across groups using the Student's t-test on the log-transformed data with comparison of groups obtained after back-transformation. Group differences in the median CMR infarct size was also compared across groups using the Wilcoxon rank sum test. Finally, we used spearman rank correlations to assess the relationship between cTnI, CK, and CMR infarct size (**Supplemental Table 3**).

For the primary endpoint we hypothesized that withholding oxygen may influence



myocardial injury by 20%.<sup>20, 21</sup> Assuming a mean peak cTnI level of  $75 \pm 35$  mcg/L,<sup>22</sup> for a statistical power of 90% and a probability of a type I error of 0.01 using a 2-sided test, a sample size of 326 (163 in each group) was calculated. This sample was increased to allow for the positive predictive value of prehospital diagnosis of STEMI to be <100%, and protocol violations. The final recruitment target was 600 pre-hospital randomizations, with 490 (245 patients in each arm) meeting inclusion criteria on arrival to hospital.

The primary analysis was performed on an intention to treat basis for all patients with confirmed STEMI following emergent coronary angiogram. Analysis of all randomized patients was also performed to examine differences in baseline characteristics (**Supplemental Table 4**). Analysis of primary endpoint and all cardiac biomarker analyses was performed by an independent statistician, blinded to treatment allocation. We assessed whether the distribution of the main clinical variables was similar between groups, taking into account whether they later fulfilled eligibility criteria (**Supplemental Table 5**). To examine possible bias due to exclusion after randomization of patients with an alternative diagnosis to STEMI, and possible effect of the intervention on the diagnosis itself, we compared baseline and procedural characteristics, and secondary endpoints available in patients included in the analysis versus those who were excluded (**Supplemental Table 6**). Similarly, to examine whether missing data introduced selection bias, we compared baseline and procedural characteristics and secondary endpoints between included patients and patients who did not undergo 6 month CMR (**Supplemental Table 7**).

## Results

The study profile is shown in **Figure 1**. Of 836 adult patients with chest pain screened for the trial, 638 patients were randomized by paramedics. Of these, 50 were subsequently excluded due



to: pre-hospital protocol violations (35 patients), patient refused consent for trial participation (14 patients) and repeat enrollment (1 patient). After arrival at the emergency department, a further 118 patients were excluded from the analysis of primary endpoint, after physician assessment of patient and ECG indicated an alternative diagnosis to STEMI.

The remaining 470 patients who were eligible to continue in the study underwent emergent coronary angiography. Primary endpoint data are reported on the 441 patients (oxygen group, 218 patients; no oxygen group, 223 patients) with confirmed STEMI.

The baseline characteristics and vital signs between the treatment groups were well matched (**Table 1**). Patient treatments after randomization are shown in **Table 2**. Patient reported pain scores, opioid requirements and hemodynamics were similar between the two groups (**Supplemental Table 8**). The majority (99.5%) of patients allocated to oxygen received oxygen at 8 L/min, whilst a small proportion (7.7%) of patients in the no oxygen group required oxygen at 4 L/min either before or upon arrival to the cardiac catheterization laboratory (**Supplemental Figure 2**). There was a significant difference in oxygen saturations ( $P<0.001$ ) during the intervention period (**Supplemental Figure 3**).

The time from onset of symptoms to intervention was similar in the two groups with a median time of 150.5 minutes (interquartile range, 125.0 to 213.8) in the oxygen group compared with 162.0 minutes (interquartile range, 130.0 to 240.0) in the no oxygen group ( $P=0.09$ ). Procedural details including infarct related artery, site of arterial access, use of thrombus aspiration, administration of glycoprotein IIb/IIIa antagonists and stent implantation were similar between the groups (**Table 2**).

In patients with confirmed STEMI, the geometric mean peak troponin I was 57.4 mcg/L (95% CI, 48.0 to 68.6) in the oxygen group compared to 48.0 mcg/L (95% CI, 39.6 to 58.1) in

the no oxygen group, with a ratio of oxygen to no oxygen of 1.20 (95% CI, 0.92 to 1.56;  $P=0.18$ ). Similar findings were obtained for  $AUC_{72}$  (**Table 3**). In the repeated measures analysis, an approximate 20% difference in the geometric mean for cTnI was consistent across all assay times ( $p$ -value for group\*time interaction=0.93) (**Fig. 2**). The ratio for oxygen to no oxygen cTnI based on the model that ignores the group\*time interaction was highly significant, 1.28 (95% CI, 1.04 to 1.56;  $P=0.02$ ) (**Supplemental Table 2**).

There was a significant increase in the geometric mean peak CK in the oxygen group compared to no oxygen group, 1948 U/L (95% CI, 1721 to 2205) compared with 1543 U/L (95% CI, 1341 to 1776), with a ratio of oxygen to no oxygen of 1.26 (95% CI, 1.05 to 1.52;  $P=0.01$ ). Significant findings were also found for geometric mean  $AUC_{72}$  (**Table 3**). The results of the repeated measures analysis were similar to cTnI, a consistent 20% increase in the geometric mean CK was found in the oxygen group irrespective of assay time (**Fig. 3**), which was significant when collapsed over time (ratio of oxygen to no oxygen, 1.20; 95% CI, 1.05 to 1.38;  $P=0.007$ ) (**Supplemental Table 2**). Peak cTnI and CK measurements were highly correlated ( $r=0.87$ ,  $p<0.001$ ) (**Supplemental Table 3**), with a similar trend across clinically relevant subgroups (**Supplemental Figure 4**).

Clinical endpoints in-hospital and at 6-months were monitored for safety (**Table 4**). By hospital discharge there were four (1.8%) deaths in the oxygen group compared with 10 (4.5%) in the no oxygen group ( $P=0.11$ ). In the oxygen group, there was an increase in the rate of in-hospital recurrent myocardial infarctions (5.5% vs. 0.9%;  $P=0.006$ ) and major cardiac arrhythmias, defined as sustained and non-sustained ventricular and atrial tachyarrhythmia (40.4% vs. 31.4%;  $P=0.05$ ). At 6-month follow-up, the rate of adverse outcomes did not differ between the groups, with appropriate medical therapy in both groups (**Supplemental Table 9**).

CMR was performed on 139 patients (32%) at 6 months. Baseline characteristics of those patients in the oxygen (n=65) and no oxygen (n=74) groups were similar (**Supplemental Table 10**), as were the characteristics of those patients who did and did not undergo CMR (**Supplemental Table 8**). No patient had evidence of a myocardial infarction in two arterial territories or myocardial scarring in a non-ischemic pattern. Left ventricular dimensions and ejection fraction were similar between the two groups. Median infarct size was increased in the oxygen group compared to the no oxygen group, (20.3 grams [interquartile range, 9.6 to 29.6] vs. 13.1 grams [interquartile range, 5.2 to 23.6];  $P=0.04$ ). When expressed as a proportion of left ventricular mass, the difference in median infarct size was 12.6% (interquartile range, 6.7 to 19.2) in the oxygen group compared with 9.0% (interquartile range, 4.1 to 16.3) in the no oxygen group ( $P=0.08$ ), with the ratio of geometric means approaching significance: 1.38 (95% CI, 0.99 to 1.92;  $P=0.06$ ). Troponin and CK measurements taken at the index admission were significantly correlated with infarct size at six months (**Supplemental Table 3**).

## Discussion

The AVOID study was conducted to determine whether the routine administration of supplemental oxygen for patients with STEMI in both the pre-hospital and early in-hospital setting is associated with beneficial or harmful effects. We demonstrated that in normoxic patients, routine oxygen administration was not associated with a reduction in symptoms or a diminution in infarct size according to the troponin I and CK profile. Rather, our data suggest that routine high flow oxygen supplementation may be accompanied by harm, as reflected by a significant rise in CK and larger infarct size determined by CMR at 6 months.

Whilst there have been significant advances in therapies for AMI, our findings are similar

to those reported by Rawles and Kenmure over 40 years ago. In their study, inhaled oxygen therapy at 6L/minute, increased myocardial injury as measured by aspartate aminotransferase release in patients with AMI.<sup>20</sup> Our results differ from a recent study by Ranchord and colleagues of high flow oxygen (6L/minute) compared to titrated oxygen in patients with STEMI.<sup>12</sup> In their study of 136 patients, there was no difference in infarct size by troponin or CMR. One limitation of that study was that randomization and allocation to different levels of oxygen therapy occurred only after hospital presentation, and most subjects had routinely received oxygen therapy by paramedics for an average of 60 minutes.<sup>12</sup>

It has been suggested that oxygen may provide both psychological and physiological benefits to anxious patients during an AMI.<sup>23</sup> Our data suggest there was no difference in chest pain scores or the requirement for additional opioid analgesics in the pre-hospital period in patients not administered oxygen. There are, however, proposed mechanisms that support our finding of increased myocardial infarct size in patients administered high flow oxygen.<sup>24</sup> High flow oxygen has been shown to reduce epicardial coronary blood flow,<sup>7</sup> increase coronary vascular resistance,<sup>8</sup> and impact the microcirculation leading to functional oxygen shunting.<sup>25</sup>

Our results also suggest that withholding routine oxygen therapy is safe in normoxic patients with an AMI. A previous study reported a rate of hypoxia in AMI patients of 70%,<sup>26</sup> however our study found that only 7.7% of patients allocated to no oxygen, on arrival to the cardiac catheterisation laboratory required oxygen supplementation for an oxygen saturation of <94%.

Our study was not powered for clinical endpoints. The statistical differences noted for in-hospital recurrent myocardial infarctions and major cardiac arrhythmias, and the non-significant difference in mortality, will need to be confirmed. The currently enrolling Swedish registry

based randomized trial of oxygen in AMI is powered for mortality, and will provide evidence for the effects of supplemental oxygen on cardiovascular morbidity and mortality<sup>27</sup>. The AVOID trial was also not designed to assess the impact of lower concentrations of supplemental oxygen that may be administered via nasal cannulae. Patients in the oxygen arm received 8 L/minute of oxygen therapy via face mask, and this was chosen to maintain consistency with existing EMS treatment protocols in Australia. Although the dose of 8 L/minute is substantially lower than those used in other EMS systems<sup>28</sup> and earlier physiological studies<sup>29</sup>, the dose is similar to what has been used in earlier clinical trials.<sup>12, 30</sup>

The AVOID study was a pragmatic clinical trial, which by design required randomisation in the pre-hospital setting by paramedics, prior to detailed patient consent. The use of delayed consent in clinical trials in patients with STEMI has been the subject of significant recent controversy<sup>31</sup>, but deemed to be a suitable method of conducting ethical pragmatic comparative effectiveness trials of emergency interventions<sup>32</sup>. Our process of consent was approved by the Human Research Ethics Committees of all participating hospitals and was well received by patients.

Our study has several limitations. First, treatment allocation was not blinded to paramedics, patients or in-hospital cardiology teams. However, the analysis of the primary endpoint was performed by a statistician who was blinded to treatment group. Our study was powered to detect group differences in initial myocardial injury as reflected by the cardiac biomarker profiles, rather than major adverse cardiac events. Given the relatively low mortality observed in our trial, an outcomes-based study would require much larger numbers of patients. The study had a pragmatic design facilitating pre-hospital enrolment by paramedics, which led to a number of patients excluded from primary endpoint analysis following randomization, who did

not have STEMI. The proportion of excluded patients was comparable to other pre-hospital STEMI trials,<sup>33, 34</sup> and the characteristics of excluded patients compared to those included in the analysis were similar, suggesting that substantial selection bias did not occur. Also, not all patients in our study underwent CMR at 6 months post infarct, due to contraindications and availability of CMR at a single central site that made travel difficult for many patients. Given this limited availability it was not feasible to perform, the originally planned CMR scan during index presentation to measure myocardial salvage, and infarct size as a proportion of area at risk. All cardiac enzymes were performed using the same cTnI and CK assays, we did not utilize a core laboratory for all enzyme analysis or analysis of angiographic data. However, our findings suggest a strong correlation between both sets of cardiac biomarker data.

Whilst oxygen therapy is appropriate in hypoxemic patients with complicated AMI, it should be noted that oxygen is a drug with possible significant side effects. To date, clinical trial data supporting its routine use in normoxemic patients with AMI has not been robust enough to inform clinical guidelines with sufficient levels of evidence, particularly in the setting of contemporary interventional reperfusion practices. In conclusion our study, does not demonstrate any significant benefit of routine oxygen therapy for reducing myocardial infarct size, improving patient hemodynamics or alleviating symptoms. Instead, we identified some evidence for increased myocardial injury when oxygen was administered during uncomplicated AMI.

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**Conflict of Interest Disclosures:** None.

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**Table 1.** Baseline characteristics of patients with confirmed STEMI.

| Characteristic                        | Oxygen Arm<br>N=218  | No Oxygen Arm<br>N=223 |
|---------------------------------------|----------------------|------------------------|
| Age in years, mean (SD)               | 63.0 (11.9)          | 62.6 (13.0)            |
| Males, n (%)                          | 174 (79.8)           | 174 (78.0)             |
| Body mass index, median (IQR)*        | 27.4 (25.1, 31.1)    | 27.7 (24.7, 30.8)      |
| Past history and risk factors, n (%)  |                      |                        |
| Diabetes mellitus                     | 37 (17.0)            | 41 (18.4)              |
| Hypertension                          | 130 (59.6)           | 123 (55.2)             |
| Dyslipidemia                          | 121 (55.5)           | 118 (52.9)             |
| Current or ex-smoker†                 | 141 (65.3)           | 165 (74.3)             |
| Peripheral vascular disease           | 4 (1.8)              | 11 (4.9)               |
| Stroke                                | 11 (5.0)             | 15 (6.7)               |
| Ischemic Heart Disease                | 38 (17.4)            | 40 (17.9)              |
| Previous PCI                          | 24 (11.0)            | 26 (11.7)              |
| Previous CABG                         | 4 (1.8)              | 3 (1.3)                |
| Medication only                       | 8 (3.7)              | 12 (5.4)               |
| Creatinine > 120 µmol/L               | 17 (7.8)             | 19 (8.5)               |
| Status on arrival of paramedics       |                      |                        |
| Heart rate, median (IQR)              | 74.0 (61.0, 84.0)    | 72.0 (60.0, 80.3)      |
| Systolic blood pressure, median (IQR) | 130.0 (105.0, 150.0) | 130.0 (110.0, 150.0)   |
| Oxygen saturation, median (IQR)       | 98.0 (97.0, 99.0)    | 98.0 (97.0, 99.0)      |
| Pain score, median (IQR)              | 7.0 (5.0-9.0)        | 7.0 (5.0-8.0)          |

SD denotes standard deviation, PCI percutaneous coronary intervention, CABG coronary artery bypass grafting, IQR interquartile range.

\* Available in 280 of 441 patients.

† P for difference < 0.05.

**Table 2.** Procedural details of patients with confirmed STEMI.

| Characteristic  | Oxygen Arm<br>N=218  | No Oxygen Arm<br>N=223 |
|---|----------------------|------------------------|
| <b>Status on arrival at the catheterization laboratory</b>              |                      |                        |
| Oxygen saturation, median (IQR) <sup>†</sup>                            | 100.0 (99.0, 100.0)  | 98.0 (96.0, 99.0)      |
| Oxygen being administered, n (%) <sup>†</sup>                           | 208 (95.9)           | 17 (7.7)               |
| Oxygen dose, median (IQR) <sup>†</sup>                                  | 8.0 (8.0, 8.0)       | 4.0 (2.0, 8.0)         |
| Pre-intervention oxygen duration in minutes, median (IQR)* <sup>†</sup> | 79.0 (59.3, 94.0)    | 51.5 (41.3, 91.8)      |
| Cardiac arrest, n (%)   | 10 (4.6)             | 8 (3.6)                |
| Inotrope use, n (%)   | 11 (5.0)             | 12 (5.4)               |
| Intubation, n (%)   | 0                    | 3 (1.3)                |
| Thrombolysis, n (%)   | 2 (0.9)              | 0                      |
| Killip Class ≥ II, n (%)  | 23 (11.1)            | 27 (12.7)              |
| <b>Culprit artery, n (%)</b>  |                      |                        |
| LAD   | 82 (38.0)            | 74 (33.8)              |
| LCx   | 21 (9.7)             | 31 (14.2)              |
| RCA   | 100 (46.3)           | 101 (46.1)             |
| Other   | 11 (5.1)             | 15 (6.8)               |
| <b>Extent of coronary disease, n (%)</b>                                |                      |                        |
| Single vessel   | 95 (43.8)            | 84 (37.7)              |
| Multi-vessel  | 122 (56.2)           | 139 (62.3)             |
| LMCA Involvement  | 9 (4.1)              | 7 (3.1)                |
| <b>Pre-procedural TIMI flow 0/1, n (%)</b>                              | 191 (89.3)           | 191 (88.0)             |
| <b>Post-procedural TIMI flow 2/3, n (%)</b>                             | 208 (98.1)           | 211 (95.9)             |
| <b>Procedural details, n (%)</b>  |                      |                        |
| Radial intervention   | 72 (33.2)            | 74 (33.3)              |
| Stent implanted   | 202 (92.7)           | 201 (90.1)             |
| Drug-eluting stent  | 112 (51.4)           | 114 (51.1)             |
| Glycoprotein IIb/IIIa inhibitor   | 97 (44.5)            | 90 (40.4)              |
| Thrombus aspiration   | 107 (49.1)           | 105 (47.1)             |
| Intra-aortic balloon pump   | 7 (3.2)              | 12 (5.4)               |
| CABG  | 5 (2.3)              | 9 (4.0)                |
| <b>Time intervals (minutes), median (IQR)</b>                           |                      |                        |
| Call to hospital arrival  | 55.0 (46.0, 69.0)    | 56.5 (48.0, 68.8)      |
| Paramedic on scene to hospital arrival                                  | 45.0 (35.0, 55.0)    | 46.0 (38.0, 57.0)      |
| Symptom to intervention   | 150.5 (125.0, 213.8) | 162.0 (130.0, 240.0)   |
| Hospital arrival to intervention  | 54.0 (39.0, 66.3)    | 56.0 (42.0, 70.8)      |
| <b>Length of stay (days), median (IQR)</b>                              | 4.0 (4.0, 5.0)       | 4.0 (3.0, 5.0)         |

LAD denotes left anterior descending, LCx left circumflex, RCA right coronary artery, TIMI thrombolysis in myocardial infarction, CABG coronary artery bypass grafting, IQR, interquartile range.

\* Duration on oxygen therapy from randomization to first procedural intervention (e.g. aspiration, ballooning) measured in patients who received oxygen therapy.

<sup>†</sup> P for difference <0.05.

**Table 3.** Measures of infarct size in patients with confirmed STEMI.

| End point  | Oxygen Arm<br>N=218      | No Oxygen Arm<br>N=223   | Ratio of means<br>(Oxygen/No Oxygen) | P-Value |
|--|--------------------------|--------------------------|--------------------------------------|---------|
| <b>Troponin I, mcg/L</b>   |                          |                          |                                      |         |
| Sample size  | 200                      | 205                      |                                      |         |
| Median Peak (IQR)  | 65.7 (30.1, 145.1)       | 62.1 (19.2, 144.0)       |                                      |         |
| Geometric Mean Peak (95% CI)   | 57.4 (48.0 – 68.6)       | 48.0 (39.6 – 58.1)       | 1.20 (0.92 – 1.55)                   | 0.18    |
| Median AUC <sub>72</sub> (IQR)   | 2336.4 (965.6, 5043.1)   | 1995.5 (765.7, 4426.0)   |                                      |         |
| Geometric Mean AUC <sub>72</sub> (95% CI)  | 2000.4 (1692.8 – 2363.9) | 1647.9 (1380.1 – 1967.6) | 1.21 (0.95 – 1.55)                   | 0.12    |
| <b>Creatine kinase, U/L</b>  |                          |                          |                                      |         |
| Sample size  | 217                      | 222                      |                                      |         |
| Median Peak (IQR)  | 2073 (1065, 3753)        | 1727 (737, 3598)         |                                      |         |
| Geometric Mean Peak (95% CI)   | 1948 (1721 – 2205)       | 1543 (1341 – 1776)       | 1.26 (1.05 – 1.52)                   | 0.01    |
| Median AUC <sub>72</sub> (IQR)   | 64620 (35751, 107066)    | 51757 (29141, 106029)    |                                      |         |
| Geometric Mean AUC <sub>72</sub> (95% CI)  | 60395 (54185 – 67316)    | 50726 (44861 – 57358)    | 1.19 (1.01 – 1.40)                   | 0.04    |
| <b>Infarct size on CMR*</b>  |                          |                          |                                      |         |
| Sample size  | 61                       | 66                       |                                      |         |
| Median (IQR), grams  | 20.3 (9.6, 29.6)         | 13.1 (5.2, 23.6)         |                                      | 0.04    |
| Geometric Mean (95% CI), grams   | 14.6 (11.3 – 18.8)       | 10.2 (7.7 – 13.4)        | 1.43 (0.99 – 2.07)                   | 0.06    |
| Median (IQR) proportion of LV mass   | 12.6 (6.7, 19.2)         | 9.0 (4.1, 16.3)          |                                      | 0.08    |
| Geometric Mean (95% CI) proportion of LV mass  | 10.0 (8.1 – 12.5)        | 7.3 (5.7 – 9.3)          | 1.38 (0.99 – 1.92)                   | 0.06    |
| <b>ECG ST-segment resolution &gt; 70%,<br/>measured one day after hospital admission</b> | 132 (62.0)               | 149 (69.6)               |                                      | 0.10    |

CI denotes confidence interval, IQR interquartile range, LV left ventricular.

\* CMR conducted at six-month follow-up in 139 of 441 patients.

**Table 4.** Adverse clinical end points at hospital discharge and six-month follow-up in patients with confirmed STEMI.

| Clinical End Point                    | Oxygen Arm<br>N=218 | No Oxygen Arm<br>N=223 | P-Value |
|---------------------------------------|---------------------|------------------------|---------|
| <b>At hospital discharge, n (%)</b>   |                     |                        |         |
| Mortality, any cause                  | 4 (1.8)             | 10 (4.5)               | 0.11    |
| <i>Cardiac cause</i>                  | 4 (1.8)             | 7 (3.1)                | -       |
| <i>Massive hemorrhage</i>             | 0                   | 2 (0.8)                | -       |
| <i>Sepsis</i>                         | 0                   | 1 (0.4)                | -       |
| Recurrent myocardial infarction       | 12 (5.5)            | 2 (0.9)                | 0.006   |
| Stroke or transient ischemic attack   | 3 (1.4)             | 1 (0.4)                | 0.30    |
| Cardiogenic shock                     | 20 (9.2)            | 20 (9.0)               | 0.94    |
| Coronary artery bypass grafting       | 5 (2.3)             | 9 (4.0)                | 0.30    |
| Major bleeding                        | 9 (4.1)             | 6 (2.7)                | 0.41    |
| Arrhythmia                            | 88 (40.4)           | 70 (31.4)              | 0.05    |
| <b>At six-month follow-up, n (%)*</b> |                     |                        |         |
| Mortality, any cause                  | 8 (3.8)             | 13 (5.9)               | 0.32    |
| <i>Cardiac cause</i>                  | 6 (2.9)             | 9 (4.1)                | -       |
| <i>Massive hemorrhage</i>             | 0                   | 2 (0.9)                | -       |
| <i>Sepsis</i>                         | 0                   | 1 (0.5)                | -       |
| <i>Renal failure</i>                  | 1 (0.5)             | 0                      | -       |
| <i>Cancer</i>                         | 0                   | 1 (0.5)                | -       |
| Recurrent myocardial infarction       | 16 (7.6)            | 8 (3.6)                | 0.07    |
| Stroke or transient ischemic attack   | 5 (2.4)             | 3 (1.4)                | 0.43    |
| Repeat revascularization              | 23 (11.0)           | 16 (7.2)               | 0.17    |
| Major adverse cardiac event†          | 46 (21.9)           | 34 (15.4)              | 0.08    |

\* 14 of 441 were lost-to-follow-up.

† MACE denotes all-cause mortality, recurrent myocardial infarction, repeat revascularization, stroke..

**Figure Legends:**

**Figure 1.** Patient selection and randomisation flow-chart.

**Figure 2.** Geometric mean (95% CI) for TnI release (mcg/L) over 72 hours in patients with confirmed STEMI. \* \*A repeated measures analysis was used to estimate the overall profile of cTnI release over the 72 hour window. All available biomarker data were analyzed using linear mixed-effects (LMM) regression with patient as a random effect together with treatment group, time of assay, and an interaction term between treatment group and time of assay included as fixed effects.



**Figure 3.** Geometric mean (95% CI) for CK release (U/L) over 72 hours in patients with confirmed STEMI. \* \*A repeated measures analysis was used to estimate the overall profile of CK release over the 72 hour window. All available biomarker data were analyzed using linear mixed-effects (LMM) regression with patient as a random effect together with treatment group, time of assay, and an interaction term between treatment group and time of assay included as fixed effects.



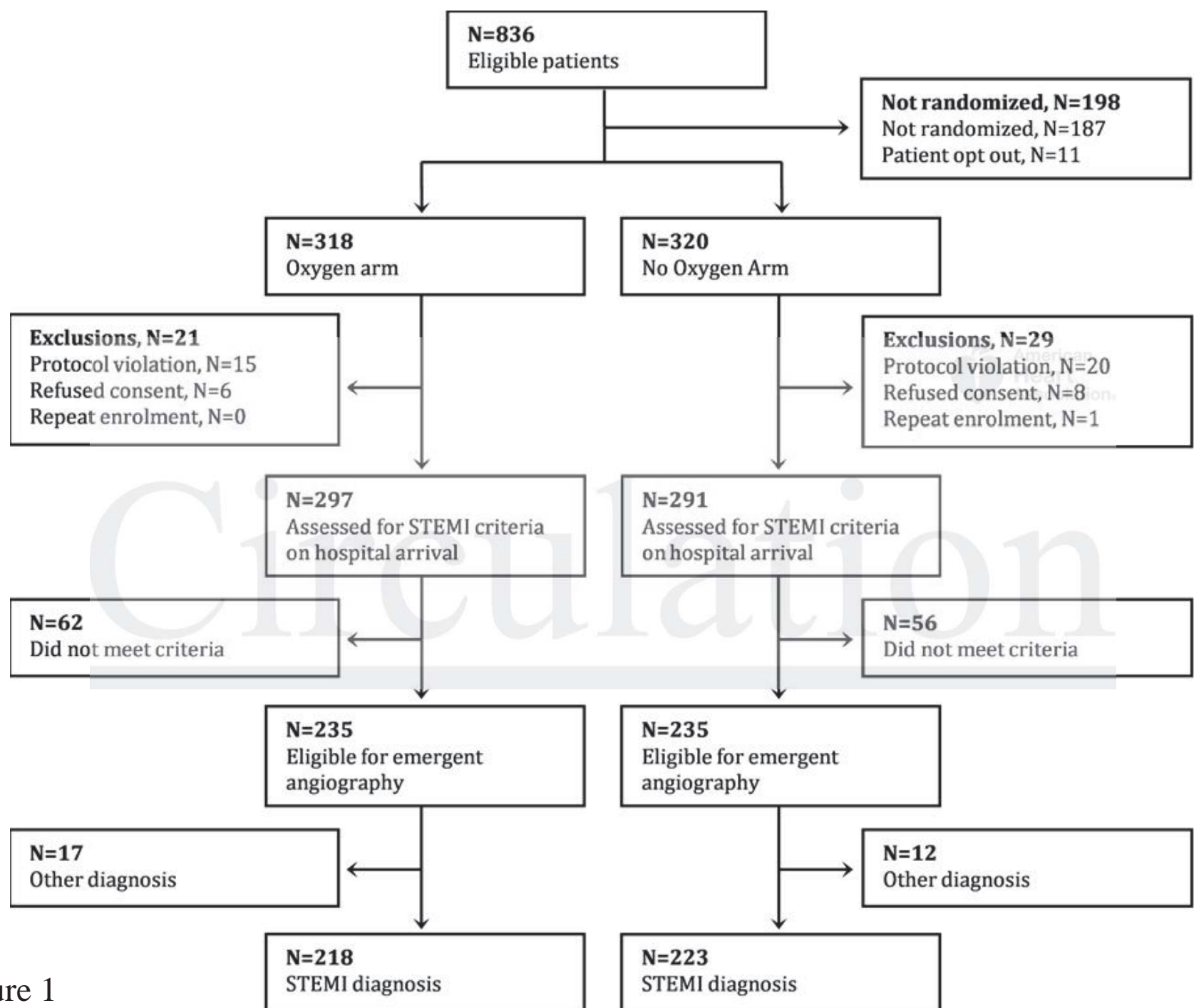


Figure 1

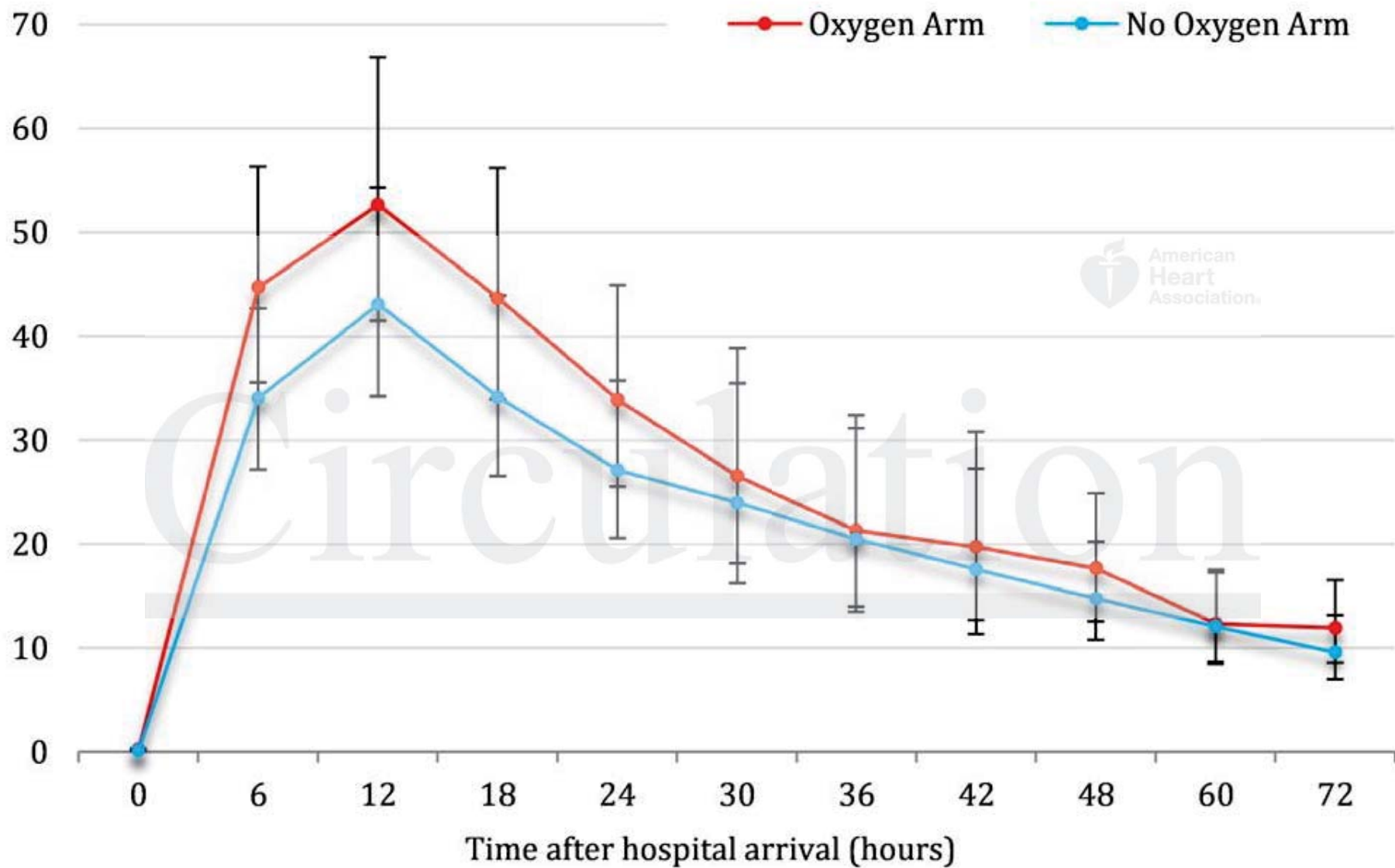


Figure 2

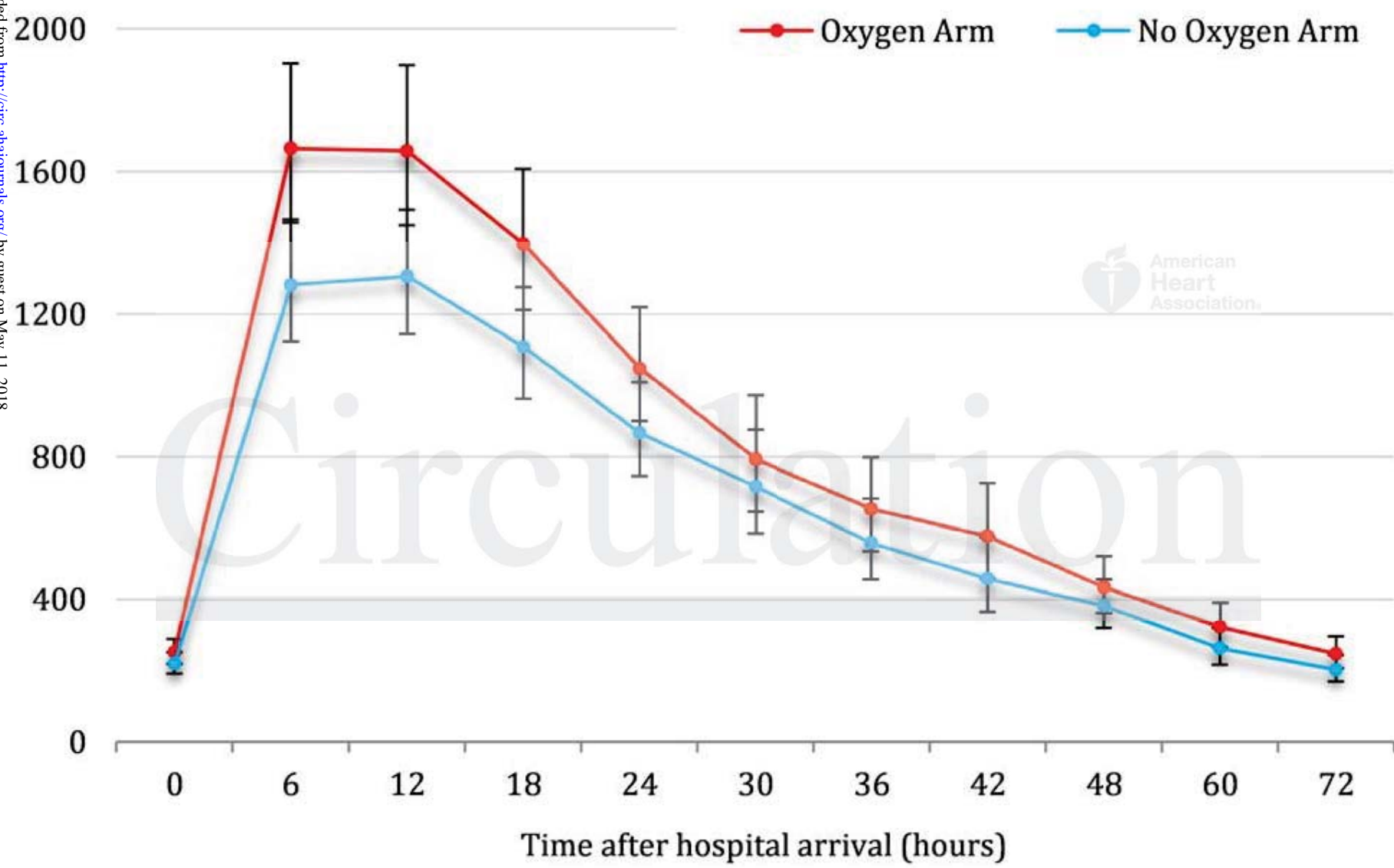


Figure 3

## Air Versus Oxygen in ST-Segment Elevation Myocardial Infarction

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on behalf of the AVOID Investigators

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# Supplementary Appendix

## *Air Versus Oxygen In ST-Elevation Myocardial Infarction*

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**Table S1. Definitions of outcomes used in the AVOID study.**

|   |  |
|---|--|
| <b>Death</b>  | Deaths were classified as cardiac or non-cardiac. Examples of cardiac death included myocardial infarction, cardiogenic shock, arrhythmia, or dissection. A non-cardiac cause of death was the result of sepsis, pneumonia, cancer or non-cardiac haemorrhaging. Non-cardiac causes of death which occurred after the index admission were classified as non-cardiac deaths. Causes of death were verified through medical records and autopsy findings (if necessary). Deaths occurring after the index admission were verified through telephone follow-up with the patient's next-of-kin.   |
| <b>Recurrent myocardial infarction</b>                | <p>The diagnosis of recurrent myocardial infarction was made using the following criteria:</p> <ol style="list-style-type: none"> <li>1. Occurred after the index admission; <b>AND</b></li> <li>2. Recurrence of ischemic chest discomfort and/or new ST segment elevation, in at least two contiguous limbs leads (<math>\geq 1</math> mm) or chest leads (<math>\geq 2</math>mm), or new left bundle branch block (LBBB) pattern; <b>AND</b></li> <li>3. A 50% increase in the serum cardiac enzyme level in a patient with a previously established peak value, and where the result is greater than <math>3 \times 99</math>th percentile Upper Reference Limit (URL) <b>OR</b></li> <li>4. Angiographic evidence of new thrombus, or either complete or partial vessel occlusion.</li> </ol> |
| <b>Stroke or transient ischemic attack</b>            | Neurological deficits classified by a clinician as stroke or transient ischaemic attack. Strokes were classified as haemorrhagic or ischaemic on the basis of brain imaging.   |
| <b>Major adverse cardiac event</b>                    | A major adverse cardiac event was defined as death from any cause, recurrent myocardial infarction, recurrent revascularisation, and stroke.   |
| <b>Cardiogenic shock</b>                              | Evidence of inadequate tissue perfusion in the setting of adequate intravascular volume, characterised by persistent hypotension (systolic blood pressure $\leq 90$ mm Hg), with or without altered mental status and peripheral hypoperfusion, requiring either pharmacologic or mechanical circulatory support.  |
| <b>Major bleeding</b>                                 | <p>Clinically overt bleeding associated with either one of the following:</p> <ol style="list-style-type: none"> <li>1. A drop in haemoglobin of <math>&gt; 3</math> g/dL;</li> <li>2. Haemodynamic compromise;</li> <li>3. Requires blood transfusion;</li> <li>4. Intracranial haemorrhage.</li> </ol> <p>Bleeding occurring after the index admission was classified as major bleeding when associated with death, hospital admission, blood transfusion, or intracranial haemorrhage.</p>  |
| <b>Repeat revascularization</b>                       | Any subsequent revascularisation (i.e. percutaneous coronary intervention or coronary artery bypass grafting) of any lesion which occurs after the index admission and verified at 6 months follow-up.   |
| <b>Target vessel revascularization</b>                | Any subsequent revascularisation (i.e. percutaneous coronary intervention or coronary artery bypass grafting) which occurs after the index admission, and involves the target lesion treated at the index admission.   |
| <b>Readmissions</b>                                   | Re-hospitalisations occurring for any reason after the index admission.  |
| <b>ST segment resolution at 1 day after admission</b> | The reduction in ST-segment elevation one day after the admission as a proportion of the initial pre-procedural ECG.   |
| <b>Major Cardiac Arrhythmia</b>                       | Defined as sustained and non-sustained ventricular and atrial tachyarrhythmia requiring medical intervention   |



**Table S2. Sensitivity analyses of area under the curve estimation for cTnI and CK release in patients with confirmed STEMI.**

|   | Oxygen Arm               | No Oxygen Arm            | Ratio of Means<br>(Oxygen/No Oxygen) | P-Value |
|---|--------------------------|--------------------------|--------------------------------------|---------|
| <b>Geometric Mean AUC<sub>72</sub> (95% CI) cTnI, mcg/L</b> |                          |                          |                                      |         |
| Primary analysis*   | 2000.4 (1692.8 – 2363.9) | 1647.9 (1380.1 – 1967.6) | 1.21 (0.95 – 1.55)                   | 0.12    |
| Sensitivity analysis 1†                                     | 1978.3 (1683.6-2324.6)   | 1620.2 (1354.2-1938.5)   | 1.22 (0.96 – 1.55)                   | 0.10    |
| Sensitivity analysis 2‡                                     | NA                       | NA                       | 1.28 (1.04 – 1.56)                   | 0.02    |
| Sensitivity analysis 3§                                     | 2164.4 (1824.8 – 2567.2) | 1820.4 (1518.1 – 2183)   | 1.19 (0.93 – 1.53)                   | 0.17    |
| <b>Geometric Mean AUC<sub>72</sub> (95% CI) CK, U/L</b>     |                          |                          |                                      |         |
| Primary model*  | 60395 (54185 - 67316)    | 50726 (44861 - 57358)    | 1.19 (1.01 – 1.40)                   | 0.04    |
| Sensitivity analysis 1†                                     | 60749 (5414 - 67699)     | 51168 (45232 - 57883)    | 1.19 (1.01 – 1.40)                   | 0.04    |
| Sensitivity analysis 2‡                                     | NA                       | NA                       | 1.20 (1.05 – 1.38)                   | 0.007   |
| Sensitivity analysis 3§                                     | 69937 (62494 – 78266)    | 58760 (51891 – 66538)    | 1.19 (1.01 – 1.41)                   | 0.04    |

NA denotes not applicable.

\* Trapezoidal integration was used for the estimation of AUC<sub>72</sub>. Data for patients with one or more missing biomarker assays were replaced by multiple imputation using the Markov Chain Monte Carlo (MCMC) method. Analyses were conducted on the log-transformed data, with comparisons obtained by back-transformation.

† Trapezoidal integration was used for the estimation of AUC<sub>72</sub>, as per the primary analysis. For this sensitivity analysis, the imputation model included additional baseline covariates were associated with cTnI/CK release and missingness of data. The imputation model considered additional covariates as follows: age, gender, TIMI flow pre procedure, LAD culprit artery, symptom to intervention time and procedural success.

‡ A repeated measures analysis was used to estimate the overall profile of cTnI/CK release over the 72 hour window. All available biomarker data were analyzed using linear mixed-effects (LMM) regression with patient as a random effect together with treatment group, time of assay, and an interaction term between treatment group and time of assay included as fixed effects. For this analysis, the non-significant interaction term between treatment group and time of assay was removed from the model.

§ Trapezoidal integration was used for the estimation of AUC<sub>72</sub>, as per the primary analysis. Patients with one or more missing biomarker assays were replaced by linear interpolation and extrapolation.

**Table S3. Spearman's rank correlation coefficient between derived endpoints\***

|                              | <b>Peak CK</b> | <b>AUC<sub>72</sub> CK</b> | <b>Peak cTnI</b> | <b>AUC<sub>72</sub> cTnI</b> |
|------------------------------|----------------|----------------------------|------------------|------------------------------|
| <b>AUC<sub>72</sub> CK</b>   | 0.95           | -                          | -                | -                            |
| <b>Peak cTnI</b>             | 0.87           | 0.81                       | -                | -                            |
| <b>AUC<sub>72</sub> cTnI</b> | 0.89           | 0.86                       | 0.97             | -                            |
| <b>CMRI Infarct size</b>     | 0.65           | 0.59                       | 0.68             | 0.70                         |

\* All correlations are significant (p<0.001).

**Table S4. Baseline characteristics of all randomized patients.\***

| Characteristic  | Oxygen Arm<br>N=312  | No Oxygen Arm<br>N=312 | P-Value |
|---|----------------------|------------------------|---------|
| Age in years, median (IQR)                                  | 63.5 (54.0, 73.0)    | 62.0 (53.0, 71.0)      | 0.28    |
| Males, n (%)  | 240 (76.9)           | 242 (77.6)             | 0.85    |
| Body mass index, median (IQR) †                             | 27.4 (25.0, 31.0)    | 27.5 (24.7, 30.1)      | 0.80    |
| <b>Status on arrival of paramedics</b>                      |                      |                        |         |
| Heart rate, median (IQR)                                    | 76.0 (64.0, 88.0)    | 72.0 (62.0, 84.0)      | 0.28    |
| Systolic blood pressure (mmHg), median (IQR)                | 130.0 (108.0, 150.0) | 130.0 (110.0, 150.0)   | 0.57    |
| Oxygen saturation (%), median (IQR)                         | 98.0 (97.0, 99.0)    | 98.0 (97.0, 99.0)      | 0.50    |
| Pain score, median (IQR)                                    | 6.0 (4.8, 8.0)       | 6.0 (4.0, 8.0)         | 0.17    |
| <b>Status on arrival at hospital</b>                        |                      |                        |         |
| Heart rate, median (IQR)                                    | 75.0 (64.0, 84.5)    | 74.0 (63.0, 84.0)      | 0.48    |
| Systolic blood pressure (mmHg), median (IQR)                | 130.0 (118.3, 148.8) | 130.0 (115.0, 145.0)   | 0.13    |
| Oxygen saturation (%), median (IQR)                         | 99.0 (99.0, 100.0)   | 98.0 (97.0, 99.0)      | <0.001  |
| Pain score, median (IQR)                                    | 2.0 (0.0, 4.0)       | 2.0 (0.5, 3.5)         | 0.77    |
| <b>Hospital diagnosis, n (%) ‡</b>                          |                      |                        |         |
| ST elevation myocardial infarction                          | 220 (75.1)           | 227 (78.0)             | 0.41    |
| Non-ST elevation myocardial infarction                      | 11 (3.8)             | 13 (4.5)               | 0.66    |
| Unstable angina   | 4 (1.4)              | 3 (1.0)                | 0.71    |
| Pericarditis  | 9 (3.1)              | 6 (2.1)                | 0.44    |
| Apical ballooning   | 4 (1.4)              | 8 (2.7)                | 0.24    |
| Chest pain, non-specific                                    | 20 (6.8)             | 13 (4.5)               | 0.22    |
| Arrhythmia  | 4 (1.4)              | 5 (1.7)                | 0.73    |
| Syncope   | 6 (2.0)              | 7 (2.4)                | 0.77    |
| Other   | 15 (5.1)             | 9 (3.1)                | 0.22    |
| <b>All-cause mortality during hospital admission, n (%)</b> | 5 (1.6)              | 11 (3.5)               | 0.13    |

IQR denotes interquartile range.

\* Excludes 14 of 638 patients who did not consent for participation in the trial.

† Available in 302 of 624 patients.

‡ Available in 584 of 624 patients.

**Table S5. Baseline characteristics of randomized patients by enrolment criteria.\***

| Characteristic  | All randomized patients<br>N=624 | Assessed for STEMI criteria on hospital arrival<br>N=588 | Confirmed STEMI on emergent coronary angiogram<br>N=441 |
|---|----------------------------------|--|---|
| <b>Age in years, median (IQR)</b>                           | 63.0 (54.0, 72.0)                | 63.0 (54.0, 72.0)  | 63.0 (54.0, 71.0)                                       |
| <b>Males, n (%)</b>   | 482 (77.2)                       | 457 (77.7)   | 348 (78.9)  |
| <b>Body mass index, median (IQR) †</b>                      | 27.4 (24.9, 30.8)                | 27.4 (24.9, 30.8)  | 27.5 (24.9, 30.9)                                       |
| <b>Status on arrival of paramedics</b>                      |                                  |  |   |
| Heart rate, median (IQR)                                    | 74.0 (62.5, 84.0)                | 74.0 (62.0, 84.5)  | 72.0 (60.0, 84.0)                                       |
| Systolic blood pressure (mmHg), median (IQR)                | 130.0 (110.0, 150.0)             | 130.0 (110.0, 150.0)                                     | 130.0 (110.0, 150.0)                                    |
| Oxygen saturation (%), median (IQR)                         | 98.0 (97.0, 99.0)                | 98.0 (97.0, 99.0)  | 98.0 (97.0, 99.0)                                       |
| Pain score, median (IQR)                                    | 6.0 (4.0, 8.0)                   | 6.0 (5.0, 8.0)   | 7.0 (5.0, 8.0)  |
| <b>Status on arrival at hospital</b>                        |                                  |  |   |
| Heart rate, median (IQR)                                    | 74.0 (64.0, 84.0)                | 74.0 (64.0, 84.0)  | 72.5 (64.0, 84.0)                                       |
| Systolic blood pressure (mmHg), median (IQR)                | 130.0 (115.8, 146.0)             | 130.0 (116.3, 145.8)                                     | 130.0 (120.0, 148.0)                                    |
| Oxygen saturation (%), median (IQR)                         | 99.0 (99.0, 100.0)               | 99.0 (98.0, 100.0)                                       | 99.0 (98.0, 100.0)                                      |
| Pain score, median (IQR)                                    | 2.0 (0.0, 4.0)                   | 2.0 (0.0, 4.0)   | 2.0 (1.0, 4.0)  |
| <b>Hospital diagnosis, n (%) ‡</b>                          |                                  |  |   |
| ST elevation myocardial infarction                          | 447 (76.5)                       | 443 (76.4)   | 441 (100.0)   |
| Non-ST elevation myocardial infarction                      | 24 (4.1)                         | 24 (4.1)   | 0   |
| Unstable angina   | 7 (1.2)                          | 7 (1.2)  | 0   |
| Pericarditis  | 15 (2.6)                         | 15 (2.6)   | 0   |
| Apical ballooning   | 12 (2.1)                         | 12 (2.1)   | 0   |
| Chest pain, non-specific                                    | 33 (5.7)                         | 33 (5.7)   | 0   |
| Arrhythmia  | 9 (1.5)                          | 9 (1.6)  | 0   |
| Syncope   | 13 (2.2)                         | 13 (2.2)   | 0   |
| Other   | 24 (4.1)                         | 24 (4.1)   | 0   |
| <b>All-cause mortality during hospital admission, n (%)</b> | 16 (2.6)                         | 15 (2.6)   | 14 (3.2)  |

IQR denotes interquartile range.

\* Excludes 14 of 638 patients who did not consent for participation in the trial.

† Available in 302 of 624 patients.

‡ Available in 584 of 624 patients.

**Table S6. Baseline characteristics of patients included in the primary endpoint analysis and those excluded after randomization.\***

| Characteristic  | Confirmed STEMI on emergent coronary angiogram<br>N=441 | Excluded after randomization<br>N=183 | P-Value |
|---|---|---------------------------------------|---------|
| Age in years, median (IQR)                                  | 63.0 (54.0, 71.0)                                       | 63.0 (50.0, 73.0)                     | 0.86    |
| Males, n (%)  | 348 (78.9)  | 134 (73.2)                            | 0.12    |
| Body mass index, median (IQR) †                             | 27.5 (24.9, 30.9)                                       | 26.8 (24.4, 29.4)                     | 0.30    |
| <b>Status on arrival of paramedics</b>                      |   |                                       |         |
| Heart rate, median (IQR)                                    | 72.0 (60.0, 84.0)                                       | 77.0 (66.0, 89.3)                     | 0.003   |
| Systolic blood pressure (mmHg), median (IQR)                | 130.0 (110.0, 150.0)                                    | 130.0 (110.0, 150.0)                  | 0.36    |
| Oxygen saturation (%), median (IQR)                         | 98.0 (97.0, 99.0)                                       | 98.0 (97.0, 99.0)                     | 0.60    |
| Pain score, median (IQR)                                    | 7.0 (5.0, 8.0)  | 5.0 (1.0, 8.0)                        | <0.001  |
| <b>Status on arrival at hospital</b>                        |   |                                       |         |
| Heart rate, median (IQR)                                    | 72.5 (64.0, 84.0)                                       | 76.0 (64.0, 84.0)                     | 0.41    |
| Systolic blood pressure (mmHg), median (IQR)                | 130.0 (120.0, 148.0)                                    | 125.0 (111.3, 145.0)                  | 0.06    |
| Oxygen saturation (%), median (IQR)                         | 99.0 (98.0, 100.0)                                      | 99.0 (98.0, 100.0)                    | 0.61    |
| Pain score, median (IQR)                                    | 2.0 (1.0, 4.0)  | 1.0 (0.0, 2.0)                        | <0.001  |
| <b>Hospital diagnosis, n (%) ‡</b>                          |   |                                       |         |
| ST elevation myocardial infarction                          | 441 (100.0)   | 6 (4.2)                               | <0.001  |
| Non-ST elevation myocardial infarction                      | 0   | 24 (16.8)                             | <0.001  |
| Unstable angina   | 0   | 7 (4.9)                               | <0.001  |
| Pericarditis  | 0   | 15 (10.5)                             | <0.001  |
| Apical ballooning   | 0   | 12 (8.4)                              | <0.001  |
| Chest pain, non-specific                                    | 0   | 33 (23.1)                             | <0.001  |
| Arrhythmia  | 0   | 9 (6.3)                               | <0.001  |
| Syncope   | 0   | 13 (9.1)                              | <0.001  |
| Other   | 0   | 24 (16.8)                             | <0.001  |
| <b>All-cause mortality during hospital admission, n (%)</b> | 14 (3.2)  | 2 (1.1)                               | 0.13    |

SD denotes standard deviation; IQR, interquartile range.

\* Excludes 14 of 638 patients who did not consent for participation in the trial.

† Available in 302 of 624 patients.

‡ Available in 584 of 624 patients.

**Table S7. Baseline characteristics and procedural details of patients with confirmed STEMI with and without CMRI data at six months follow-up.**

| Characteristic  | Patients without MRI data<br>N=302 | Patients with MRI data<br>N=139 | P-Value |
|---|------------------------------------|---------------------------------|---------|
| Age in years, median (IQR)                            | 64.0 (55.0, 74.0)                  | 60.0 (53.0, 65.0)               | <0.001  |
| Males, n (%)  | 231 (76.5)                         | 117 (84.2)                      | 0.07    |
| Body mass index, median (IQR)*                        | 27.4 (24.7, 31.1)                  | 27.7 (25.9, 30.7)               | 0.60    |
| Previous IHD, n (%)                                   | 54 (17.9)                          | 24 (17.3)                       | 0.88    |
| Diabetes mellitus, n (%)                              | 59 (19.5)                          | 19 (13.7)                       | 0.13    |
| Current or ex-smoker, n (%)                           | 209 (69.9)                         | 97 (69.8)                       | 0.98    |
| <b>Status on arrival of paramedics</b>                |                                    |                                 |         |
| Heart rate, median (IQR)                              | 72.0 (60.0, 84.0)                  | 72.0 (60.0, 84.0)               | 0.90    |
| Systolic blood pressure, median (IQR)                 | 130.0 (108.5, 150.0)               | 135.0 (110.0, 154.0)            | 0.51    |
| Oxygen saturation, median (IQR)                       | 98.0 (97.0, 99.0)                  | 98.0 (97.0, 99.0)               | 0.11    |
| Pain score, median (IQR)                              | 7.0 (5.0, 8.0)                     | 7.0 (5.0, 8.0)                  | 0.59    |
| <b>Procedural details, n (%)</b>                      |                                    |                                 |         |
| LAD Culprit artery                                    | 101 (34.1)                         | 55 (39.6)                       | 0.27    |
| Multi-vessel coronary disease                         | 180 (59.8)                         | 81 (58.3)                       | 0.76    |
| Pre-procedural TIMI flow 0/1                          | 259 (88.7)                         | 123 (88.5)                      | 0.95    |
| Post-procedural TIMI flow 0/1                         | 12 (4.1)                           | 1 (0.7)                         | 0.06    |
| Radial intervention                                   | 105 (35.0)                         | 42 (30.2)                       | 0.32    |
| Stent implanted                                       | 270 (89.4)                         | 133 (95.7)                      | 0.03    |
| Glycoprotein IIb/IIIa inhibitor                       | 118 (39.1)                         | 69 (49.6)                       | 0.04    |
| Thrombus aspiration                                   | 139 (46.0)                         | 73 (52.5)                       | 0.21    |
| Length of stay (days), median (IQR)                   | 4.0 (4.0, 5.0)                     | 4.0 (3.0, 5.0)                  | 0.09    |
| Symptom-to-intervention time in minutes, median (IQR) | 158.0 (127.0, 230.0)               | 156.0 (123.5, 219.8)            | 0.43    |
| Geometric Mean Peak cTnI (95% CI), mcg/L              | 53.3 (45.3 – 62.7)                 | 50.5 (40.5 – 62.9)              | 0.71    |
| Geometric Mean Peak CK (95% CI), U/L                  | 1719 (1530 – 1931)                 | 1760 (1498 – 2066)              | 0.82    |

IHD denotes ischemic heart disease, TIMI thrombolysis in myocardial infarction, LAD left anterior descending, IQR interquartile range, CI confidence interval.

\* Available in 280 of 441 patients.

**Table S8. Paramedic treatment of patients with confirmed STEMI.**

|  | Oxygen Arm<br>N=218  | No Oxygen Arm<br>N=223 | P-Value |
|--|----------------------|------------------------|---------|
| <b>Status on arrival of paramedics</b>       |                      |                        |         |
| Heart rate, median (IQR)                     | 74.0 (61.0, 84.0)    | 72.0 (60.0, 80.3)      | 0.24    |
| Systolic blood pressure (mmHg), median (IQR) | 130.0 (105.0, 150.0) | 130.0 (110.0, 150.0)   | 0.29    |
| Oxygen saturation (%), median (IQR)          | 98.0 (97.0, 99.0)    | 98.0 (97.0, 99.0)      | 0.51    |
| Pain score, median (IQR)                     | 7.0 (5.0, 9.0)       | 7.0 (5.0, 8.0)         | 0.08    |
| <b>Status on arrival at hospital</b>         |                      |                        |         |
| Heart rate, median (IQR)                     | 75.0 (64.0, 86.0)    | 72.0 (62.5, 84.0)      | 0.32    |
| Systolic blood pressure (mmHg), median (IQR) | 130.0 (120.0, 148.0) | 130.0 (118.0, 147.8)   | 0.45    |
| Oxygen saturation (%), median (IQR)          | 100.0 (99.0, 100.0)  | 98.0 (97.0, 99.0)      | <0.001  |
| Pain score, median (IQR)                     | 2.0 (1.0-4.0)        | 2.0 (1.0-4.0)          | 0.59    |
| Oxygen being administered, n (%)             | 215 (99.5)           | 10 (4.5)               | <0.001  |
| Oxygen dose (L/min), median (IQR)            | 8.0 (8.0, 8.0)       | 4.0 (2.8, 8.0)         | < 0.001 |
| Morphine administered, n (%)                 | 192 (89.3)           | 204 (91.5)             | 0.44    |
| Morphine dose total (mg), median (IQR)       | 12.5 (8.0, 20.0)     | 11.3 (7.5, 15.0)       | 0.33    |
| Fentanyl administered, n (%)                 | 20 (9.3)             | 21 (9.4)               | 0.97    |
| Fentanyl dose total (mcg), median (IQR)      | 137.5 (63.8, 218.8)  | 100.0 (80.0, 150.0)    | 0.45    |
| Nitrates administered, n (%)                 | 46 (21.3)            | 54 (24.2)              | 0.47    |
| Nitrates dose total (mg), median (IQR)       | 0.6 (0.3, 1.3)       | 0.6 (0.3, 0.9)         | 0.44    |

IQR denotes interquartile range.



**Table S9. Medical therapy at six months follow-up.**

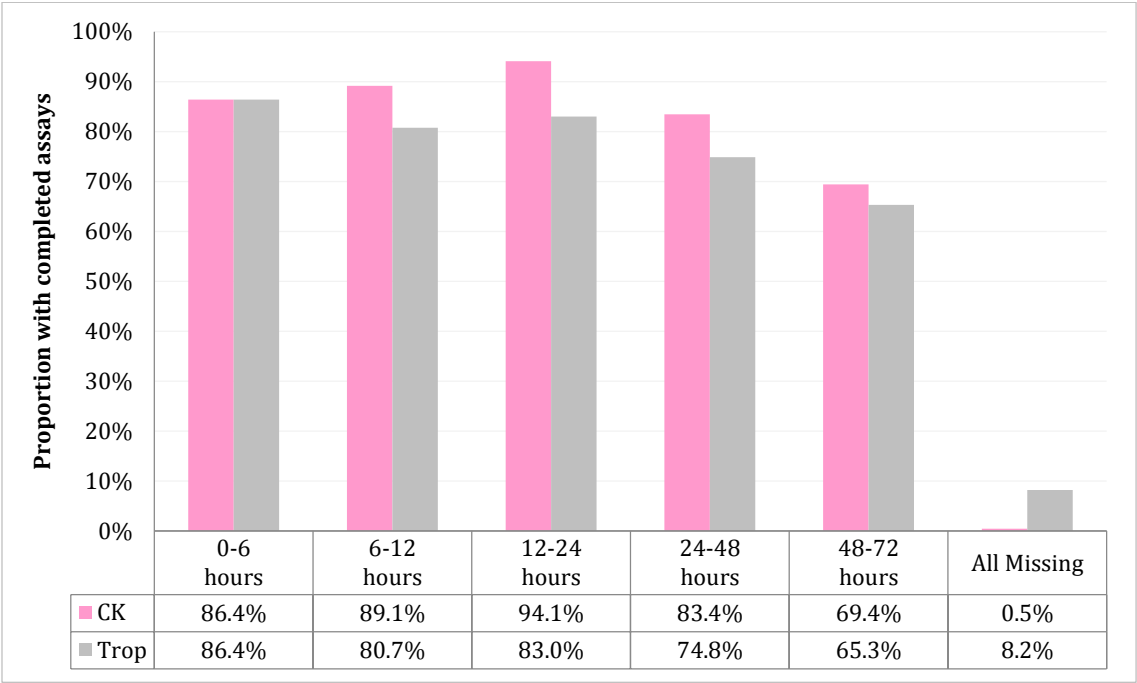
|  | Oxygen Arm<br>N=218 | No Oxygen Arm<br>N=223 | P-Value |
|--|---------------------|------------------------|---------|
| Aspirin  | 172 (83.9)          | 181 (85.8)             | 0.59    |
| Clopidogrel  | 84 (41.0)           | 82 (38.9)              | 0.66    |
| Prasugrel  | 39 (19.0)           | 45 (21.3)              | 0.56    |
| Ticagrelor   | 41 (20.0)           | 44 (20.9)              | 0.83    |
| Aspirin + (Clopidogrel OR Prasugrel OR Ticagrelor) | 151 (73.7)          | 159 (75.4)             | 0.69    |
| Beta-blocker                                       | 161 (78.5)          | 171 (81.0)             | 0.52    |
| Statin   | 182 (88.8)          | 182 (86.3)             | 0.44    |
| ACE/ARB  | 166 (81.0)          | 169 (80.1)             | 0.82    |
| Ca-channel blocker                                 | 10 (4.9)            | 9 (4.3)                | 0.77    |
| Aldosterone antagonist                             | 1 (0.5)             | 2 (0.9)                | 0.58    |
| Diuretic   | 23 (11.2)           | 14 (6.6)               | 0.10    |
| Anticoagulation                                    | 9 (4.4)             | 5 (2.4)                | 0.25    |

**Table S10. Baseline characteristics and findings in 139 patients with confirmed STEMI undergoing cardiac magnetic resonance imaging (CMRI) at six months follow-up.**

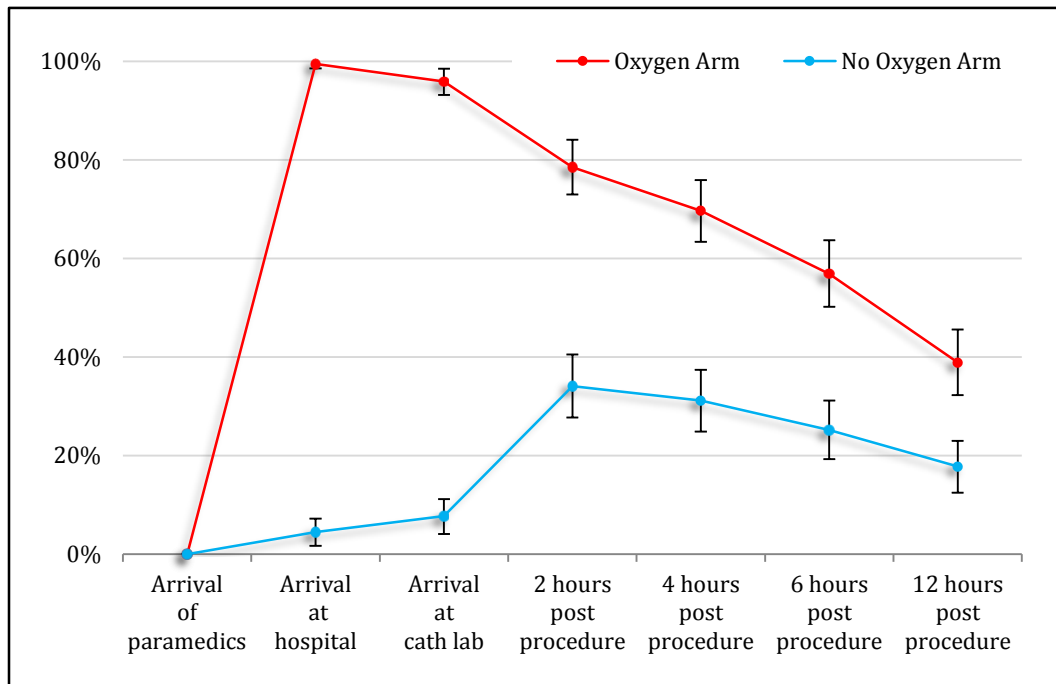
| Characteristic/measure                                | Oxygen Arm<br>N=65   | No Oxygen Arm<br>N=74 | P-Value |
|---|----------------------|-----------------------|---------|
| Age in years, mean (SD)                               | 60.0 (10.7)          | 59.0 (9.9)            | 0.60    |
| Males, n (%)  | 55 (84.6)            | 62 (83.8)             | 0.89    |
| Body mass index, median (IQR)                         | 26.8 (25.2, 30.8)    | 27.7 (24.8, 31.0)     | 0.90    |
| Previous IHD, n (%)                                   | 12 (18.5)            | 12 (16.2)             | 0.73    |
| LAD culprit artery, n (%)                             | 27 (26.5)            | 55 (39.6)             | 0.43    |
| Pre-procedural TIMI flow 0/1, n (%)                   | 58 (89.2)            | 65 (87.8)             | 0.80    |
| Post-procedural TIMI flow 0/1, n (%)                  | 0                    | 1 (1.4)               | 0.35    |
| Symptom-to-intervention time in minutes, median (IQR) | 147.0 (119.0, 221.5) | 162.0 (129.0, 213.5)  | 0.32    |
| Recurrent MI, n (%)                                   | 4 (6.2)              | 1 (1.4)               | 0.13    |
| LV end diastolic volume, mean (SD)                    | 180.4 (43.9)         | 178.1 (44.1)          | 0.75    |
| LV end systolic volume, median (IQR)                  | 84.3 (59.8, 108.1)   | 77.7 (56.9, 100.5)    | 0.34    |
| LV stroke volume, mean (SD)                           | 96.1 (21.8)          | 95.3 (20.8)           | 0.81    |
| LV ejection fraction, mean (SD)                       | 54.4 (9.5)           | 54.9 (10.0)           | 0.76    |
| Pre-procedural TIMI flow 0/1                          | 53.9 (9.7)           | 54.3 (9.8)            | 0.83    |
| Pre-procedural TIMI flow 2/3                          | 58.9 (6.9)           | 59.7 (10.9)           | 0.86    |
| LAD culprit artery                                    | 52.7 (9.3)           | 52.8 (10.9)           | 0.96    |
| Non-LAD culprit artery                                | 55.8 (9.6)           | 56.2 (9.4)            | 0.85    |
| Symptom to intervention ≤180mins                      | 54.5 (9.9)           | 55.4 (9.3)            | 0.76    |
| Symptom to intervention >180mins                      | 54.2 (9.0)           | 55.0 (11.4)           | 0.80    |
| Infarct size (grams), median (IQR)                    | 20.3 (9.6, 29.6)     | 13.1 (5.2, 23.6)      | 0.04    |
| Pre-procedural TIMI flow 0/1                          | 20.7 (10.0, 31.4)    | 15.2 (6.3, 24.3)      | 0.06    |
| Pre-procedural TIMI flow 2/3                          | 16.2 (4.2, 25.0)     | 7.0 (2.3, 24.2)       | 0.64    |
| LAD culprit artery                                    | 20.7 (10.6, 33.3)    | 20.1 (4.4, 632.3)     | 0.60    |
| Non-LAD culprit artery                                | 15.2 (7.4, 26.3)     | 10.6 (5.2, 18.9)      | 0.05    |
| Symptom to intervention ≤180mins                      | 20.3 (9.9, 29.1)     | 12.9 (6.2, 22.2)      | 0.10    |
| Symptom to intervention >180mins                      | 20.8 (8.2, 30.5)     | 13.1 (3.3, 25.8)      | 0.15    |
| Infarct size (% of LV mass), median (IQR)             | 12.6 (6.7, 19.2)     | 9.0 (4.1, 16.3)       | 0.08    |
| Pre-procedural TIMI flow 0/1                          | 12.7 (6.9, 19.3)     | 9.5 (5.5, 16.3)       | 0.14    |
| Pre-procedural TIMI flow 2/3                          | 9.0 (3.4, 17.0)      | 5.9 (2.1, 14.1)       | 0.32    |
| LAD culprit artery                                    | 13.5 (8.1, 21.0)     | 14.8 (3.3, 20.1)      | 0.64    |
| Non-LAD culprit artery                                | 11.9 (5.8, 17.2)     | 8.1 (4.1, 15.0)       | 0.13    |
| Symptom to intervention ≤180mins                      | 11.9 (6.3, 17.6)     | 9.4 (4.3, 16.2)       | 0.28    |
| Symptom to intervention >180mins                      | 12.8 (7.4, 20.4)     | 7.9 (2.5, 16.5)       | 0.13    |

LV denotes left ventricular, IHD ischemic heart disease, TIMI thrombolysis in myocardial infarction, LAD left anterior descending, IQR interquartile range, SD standard deviation, MI myocardial infarction.

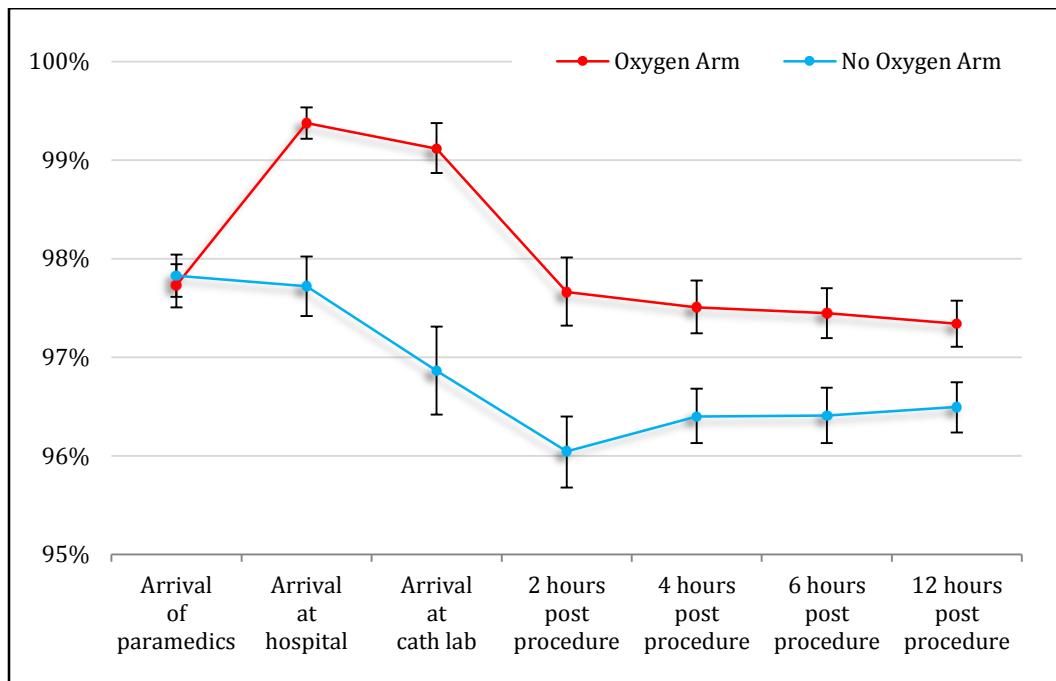
Figure S1: Proportion of patients with completed biomarker assays for each time-point.



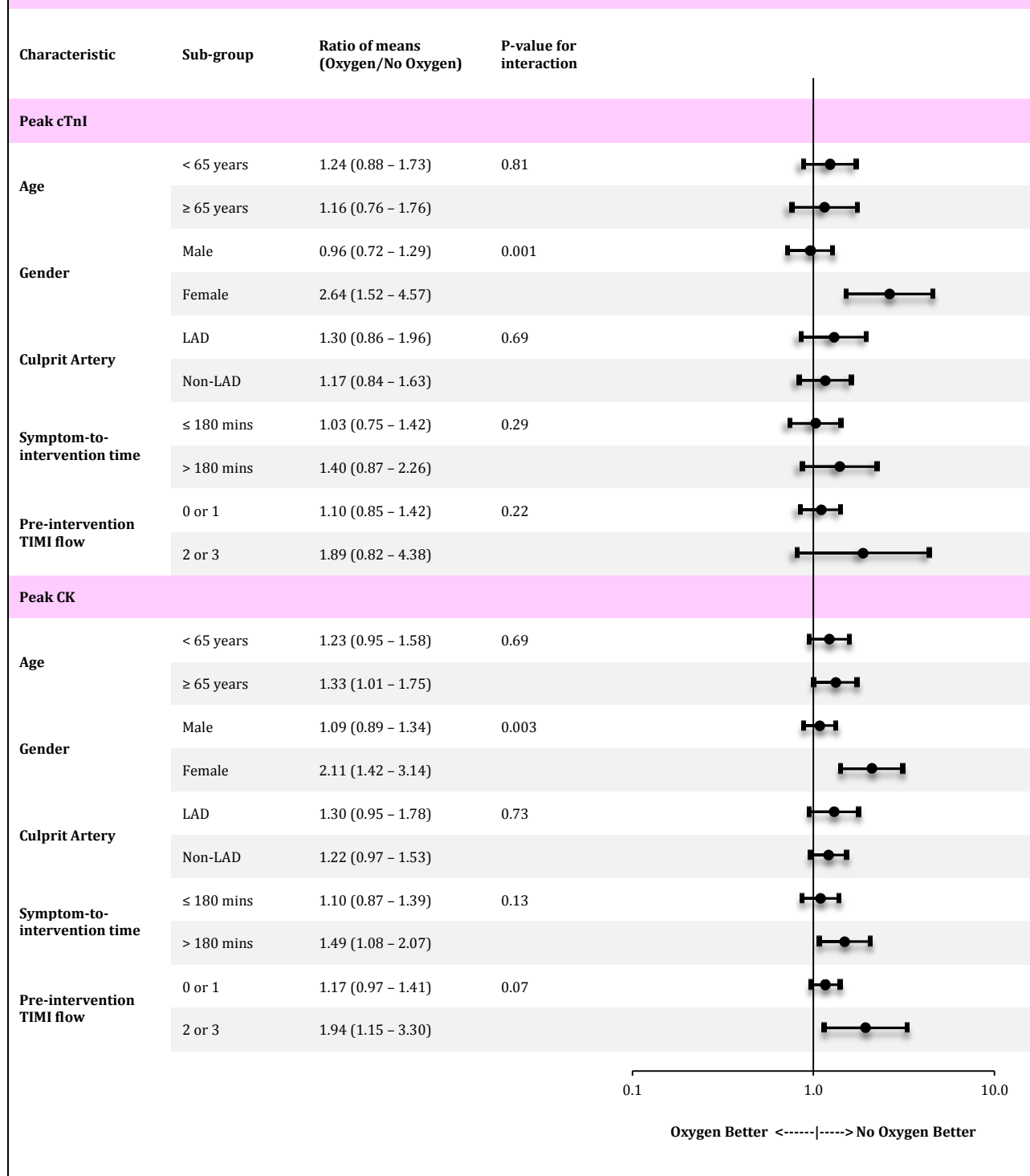
**Figure S2. Proportion of patients receiving supplemental oxygen across study time points and treatment groups in patients with confirmed STEMI.**



**Figure S3. Geometric mean (95% CI) for peripheral blood oxygen saturation (SpO<sub>2</sub>) across time points in patients with confirmed STEMI.**



**Figure S4: Ratio of geometric means (95% CI) for peak cTnI and peak CK release in patients with confirmed STEMI.**



TIMI denotes thrombolysis in myocardial infarction, LAD left anterior descending,

# ST분절 상승 심근경색증 환자의 통상적인 치료 중 하나인 산소요법은 오히려 해로울 수 있다: AVOID 연구

신 준 한 교수 아주대학교병원 순환기내과

## 초록

### 배경

산소요법은 ST분절 상승 심근경색증(ST-segment elevation myocardial infarction, STEMI) 환자의 통상적인 치료 중 하나이지만, 기존의 일부 연구에서는 산소요법이 관상동맥의 수축을 유발하고 산화스트레스를 증강시켜서 심근손상을 악화시킬 가능성이 있다고 보고하였다.

### 방법 및 결과

본 연구는 다기관, 전향적, 무작위 치료군-대조군 연구로 응급 구조사가 출동한 현장에서 촬영한 심전도검사로 STEMI 진단을 받은 환자를 대상으로, 한 군은 안면마스크로 8L/min의 산소를 투여하였고, 다른 군은 산소를 투여하지 않았다. 총 638명의 환자 중 분석이 가능한 환자는 총 441명이었다. 일차종료점은 심근 효소인 troponin I와 CK(creatine kinase)로 평가한 경색의 크기로 하였다. 이차종료점은 경색의 재발, 부정맥, 6개월째에 심장 MRI(magnetic resonance imaging)로 측정된 경색의 크기로 하였다.

산소투여군과 비투여군 간에 평균 최고 troponin I 농도는 차이가 없었다(57.4 vs. 48.0 µg/L; ratio, 1.20; 95% CI, 0.92-1.56;

$P=0.18$ ). 그러나 평균 최고 CK는 산소투여군에서 유의하게 높았다(1,948 vs. 1,543 U/L; means ratio, 1.27; 95% CI, 1.04-1.52;  $P=0.01$ ). 심근경색증의 재발률(5.5 vs. 0.9 %;  $P=0.006$ )과 부정맥의 발생(40.4 vs. 31.4 %;  $P=0.05$ )은 산소투여군에서 유의하게 높았다. 6개월째 경색의 크기 역시 산소투여군에서 의미 있게 컸다(20.3 vs. 13.1 g;  $P=0.04$ , 139명).

### 결론

저산소증이 없는 STEMI 환자에게 통상적인 산소요법을 사용하는 것은 조기 심근손상을 증가시키고 6개월째 경색의 크기를 증가시킨다.