High-concentration versus titrated oxygen therapy in ST-elevation myocardial infarction: A pilot randomized controlled trial

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Background The optimal approach to oxygen therapy in ST-elevation myocardial infarction (STEMI) is uncertain.

Methods A randomized controlled trial was undertaken in which 136 patients presenting with their first STEMI uncomplicated by cardiogenic shock or marked hypoxia were randomized to receive high-concentration (6 L/min via medium concentration mask) or titrated oxygen (to achieve oxygen saturation 93%-96%) for 6 hours after presentation. The main outcome variables were 30-day mortality and infarct size assessed by troponin T level at 72 hours. Secondary outcomes included a meta-analysis of mortality data from this study and previous randomized controlled trials, and infarct size was assessed by magnetic resonance imaging at 4 to 6 weeks.

Results There were 1 of 68 and 2 of 68 deaths in the high-concentration and titrated oxygen groups, respectively; a meta-analysis including these data with those from the 2 previous studies showed an odds ratio for mortality of high-concentration oxygen compared with room air or titrated oxygen of 2.2 (95% CI 0.8-6.0). There was no significant difference between high-concentration versus titrated oxygen in troponin T (ratio of mean levels 0.74, 95% CI 0.50-1.1, $P = .14$), infarct mass (mean difference –0.8 g, 95% CI –7.6 to 6.1, $P = .82$), or percent infarct mass (mean difference –0.6%, 95% CI –5.6 to 4.5, $P = .83$).

Conclusion This study found no evidence of benefit or harm from high-concentration compared with titrated oxygen in initially uncomplicated STEMI. However, our estimates have wide CIs, and as a result, large randomized controlled trials are required to resolve the clinical uncertainty. (Am Heart J 2012;163:168-75.)

The routine administration of high-concentration oxygen to patients with myocardial infarction has been an indoctrinated treatment concept, which until recently was recommended in major consensus guidelines.[1-3] However, this approach is not supported by the available evidence that suggests that its uncontrolled use has the potential to cause harm.[4-6]

There are several biologically plausible mechanisms whereby high-concentration oxygen may cause worse outcomes in myocardial infarction. Hyperoxia causes a marked reduction in coronary blood flow and myocardial oxygen consumption in subjects with cardiac disease.[7,8] High-concentration oxygen therapy also causes a reduction in cardiac output and increases systemic vascular resistance and blood pressure in patients with a recent myocardial infarction.[9] Oxygen therapy also has the potential to worsen reperfusion injury through oxygen-free radical production.[10]

In this study, we have compared high-concentration versus titrated oxygen therapy in uncomplicated ST-elevation myocardial infarction (STEMI). The clinical outcomes of interest were infarct size and 30-day mortality including a preplanned meta-analysis with the previous studies reporting mortality data.

Methods

Trial

This study was a prospective, randomized, unblinded, controlled trial undertaken at Wellington Hospital in New Zealand and South Manchester University Hospital NHS Trust, Manchester, United Kingdom. It was approved by the Central Regional Ethics Committee, Wellington, and the South Manchester Research Ethics Committee, Manchester, and was funded by

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All participants gave written informed consent. Ethical approval was obtained for the use of a short version of the information sheet and consent form at the time of enrolment, followed by a more detailed information sheet and formal long consent form after patients had received primary therapy for STEMI. This study was referred to as Oxygen Protocols for the Treatment of Myocardial Infarction: Mortality, Infarct Size and Efficacy (OPTIMISE).

Study population

Subjects 18 years or older who presented to hospital within 12 hours after the onset of ischemic symptoms, with ST-segment elevation of >0.1 mV in 2 contiguous limb leads or 0.2 mV in 2 or more precordial leads or new onset left bundle-branch block, were eligible for enrolment. Subjects were randomized within 1 hour of arrival to hospital. Exclusion criteria included previous myocardial infarction, severe chronic obstructive pulmonary disease (COPD) or type II respiratory failure, cardiogenic shock or oxygen saturation <85% at the time of presentation, pregnancy, previous bleomycin treatment, or participation in another clinical trial. Subjects with cardiac arrest or ventricular fibrillation were not specifically excluded from the study but had to have recovered sufficiently to be able to give written informed consent. Subjects who were subsequently diagnosed to have a condition other than STEMI (eg, pericarditis), who had an exclusion criterion recognized after randomization, or in whom no formal long consent was documented were withdrawn and not included in the study analysis.

Treatment of STEMI

Primary percutaneous coronary intervention (PPCI) was the only treatment strategy for patients enrolled in Manchester. Those enrolled in Wellington were treated with PPCI during the hours from 8 AM to 4 PM and with thrombolysis at other times. However, subjects with contraindications to thrombolysis were treated with PPCI.

Design

Subjects were randomized to receive high-concentration or titrated oxygen therapy for 6 hours, commencing after presentation to the emergency department. The high-concentration regime consisted of 6 L/min of oxygen delivered via a medium concentration mask. If saturations fell to <92%, then higher oxygen concentrations were delivered. The titrated regime consisted of oxygen delivered via nasal prongs or a medium concentration mask: the flow-rate was adjusted to achieve an oxygen saturation of 93% to 96%. Oxygen saturation was monitored continuously, and flow rate in the titrated patients was adjusted according to half-hourly observations. If the oxygen saturations were ≥93% while breathing room air in subjects randomized to titrated oxygen, no supplemental oxygen was administered.

Magnetic resonance imaging protocols

Imaging was performed on 1.5-T magnetic resonance imaging (MRI) scanners (Philips Achieva and Philips Intera, Philips Medical Systems, Best, The Netherlands, and Siemens Magnetom Avanto, Siemens Medical Solutions USA Inc, Malvern, PA). Sequences were acquired prospectively during breath-hold using a 5-element cardiac phased array coil, gated to the vectorcardiogram. Comprehensive MRI scans were performed as previously described.[11] Delayed enhancement (DE) short-axis images covering the whole left ventricle were acquired at end-diastole 15 minutes after bolus injection (0.2 mmol/kg body-weight) of gadopentetate dimeglumine (Magnevist; Bayer HealthCare Pharmaceuticals, Berlin, Germany) using an inversion-recovery gradient echo sequence (repetition time 3.7, echo time 1.8, flip angle 20°; typical spatial resolution was 1.5 × 2 × 8 mm). The inversion time delay was optimized in order to obtain the maximal contrast between viable and infarcted myocardium.

Image analysis

Off-line image analysis was performed on an independent workstation with dedicated software (Qmass 7.2; Medis, Leiden, The Netherlands). Left ventricular (LV) end-diastolic and end-systolic volumes were obtained by manually tracing the epicardial and endocardial borders on the cine images together with tracking of the mitral valve annular plane. Left ventricular mass was assessed by manually tracing the epicardial and endocardial borders on the DE images. Papillary muscles were included as part of the ventricular mass. Infarct size was determined by previously validated threshold analysis.[12] The analysis was performed by a cardiologist accredited in cardiac magnetic resonance imaging (VS), blinded to the treatment arms and biomarker data.

Outcome variables

The main outcome variables were 30-day mortality and infarct size as measured by the troponin T level 66 to 78 hours after randomization (Roche E170 analyzer, fourth-generation assay with functional sensitivity 0.03 ng/mL, Roche Diagnostics, Indianapolis, IN). Because of the recognition that this study was likely to be underpowered for the main outcome variables, a related preplanned secondary outcome variable was the relative risk of mortality, determined by meta-analysis of data from this and the only other randomized controlled trial of high-concentration oxygen in myocardial infarction,[13] identified by systematic review.[5] Subsequently, another randomized controlled trial of high-concentration oxygen in myocardial infarction[14] was identified in a Cochrane review[6] and included in the planned meta-analysis.

Secondary outcome measures were infarct mass (absolute and as a percent of LV DE mass) and LV ejection fraction (LVEF), documented by cardiac MRI at 4 to 6 weeks, and N-terminal pro-brain natriuretic peptide (NT-proBNP) 24 hours after randomization (Roche NT-proBNP reagent kit with an analytical range of 5 to 35,000 pg/mL).

Major adverse cardiac events were death, reinfarction, or target vessel revascularization at 30 days.

Statistical analysis

Independent *t* tests compared the mean values of the continuous variables. Troponin and BNP levels both had highly skewed distributions, and analysis was carried out on the natural logarithm of these variables. Exponentiation of the result is equivalent to calculating the ratio of means of these 2 variables.

For the dichotomous outcome variables, the relative risk and appropriate CI was calculated together with χ^2 tests for the contingency tables. After initial analyses indicated an imbalance of infarct location by oxygen group, post hoc analyses were undertaken in which the differences in infarct size and LV function between the oxygen groups were adjusted for infarct location, time to reperfusion intervention, and time oxygen was administered before randomization.

Meta-analysis was by Peto 1-step odds ratio, carried out according to the formulae given by Bradburn et al.[15] Publication bias was explored by formal statistical tests and a funnel plot. Heterogeneity of study estimates was tested by standard methods. SAS 9.1 (SAS Institute Inc., Cary, NC) was used.

Power calculations

The level of troponin T that constitutes a clinically important difference is not known. A sample size of 64 in each arm of a 2-arm trial gives 80% power, α of 5%, to detect a difference of half a standard deviation. This can be considered to represent a moderate to large difference. Allowing for a 15% dropout resulted in a planned sample size of 75 in each arm. This sample size was similar to the previous study, which reported a significantly greater peak aminotransferase level with high-concentration oxygen versus room air in the treatment of myocardial infarction in 157 patients.[13]

Results

From November 2007 to August 2009, 209 subjects presenting with a STEMI were assessed for eligibility. Sixty-one were excluded because of previous myocardial infarction (n = 25), late presentation (n = 8), cardiogenic shock (n = 6), or other reasons (n = 22). One hundred forty-eight subjects were randomized with 12 subsequently withdrawn because of no formal long consent documented (n = 5), an alternative diagnosis (n = 5; 2 cases with pericarditis and 3 cases with normal coronary arteries), and exclusion criteria recognized after randomization (n = 2; with 2 cases of cardiogenic shock). Because there was no outcome data for these 12 withdrawn subjects, 136 randomized subjects were included in the study analysis (Figure 1).

The baseline characteristics of the subjects are detailed in Table I. The mean age was 61 years, and 74% were male. Most (80/136, or 59%) were on no cardiac medications at presentation. Their clinical characteristics are detailed in Table II.

There was similar prehospital (ambulance) use of oxygen in the 2 groups, being administered in 85% of subjects for a mean of 62 minutes. The time from STEMI onset to either thrombolytic therapy or PPCI was similar in the 2 groups. A greater proportion of subjects randomized to the high-concentration group presented with an inferior or posterior infarct (72% vs 54%, P = .02). Subjects with anterior myocardial infarction had significantly higher log troponin T levels (0.79 vs 0.31 ng/mL, difference 0.5, 95% CI 0.07-0.88, P = .02) and MRI infarct mass (20.7 vs 13.4 g, difference 7.3, 95% CI 0.4-14.1, P = .04) than those with inferior or posterior infarcts. The reperfusion strategy used was PPCI in 103 (75.7%) of 136, prehospital thrombolysis in 11 (8.1%) of 136, and in-hospital thrombolysis in 19 (14.0%) of 136, with similar proportions in the 2 treatment groups. In 11 subjects, there was incomplete data for the time to therapy. In 2 subjects, the primary treatment was coronary artery bypass graft surgery, and in 1 subject, no reperfusion treatment was administered.

There were 1 of 68 and 2 of 68 deaths in the high-concentration and titrated oxygen groups, respectively (relative risk 0.5, 95% CI 0.05-5.4, P = .56). There was 1 case of reinfarction in the high-concentration oxygen group. Thus, major adverse cardiac events occurred in 2 subjects in each of the treatment groups.

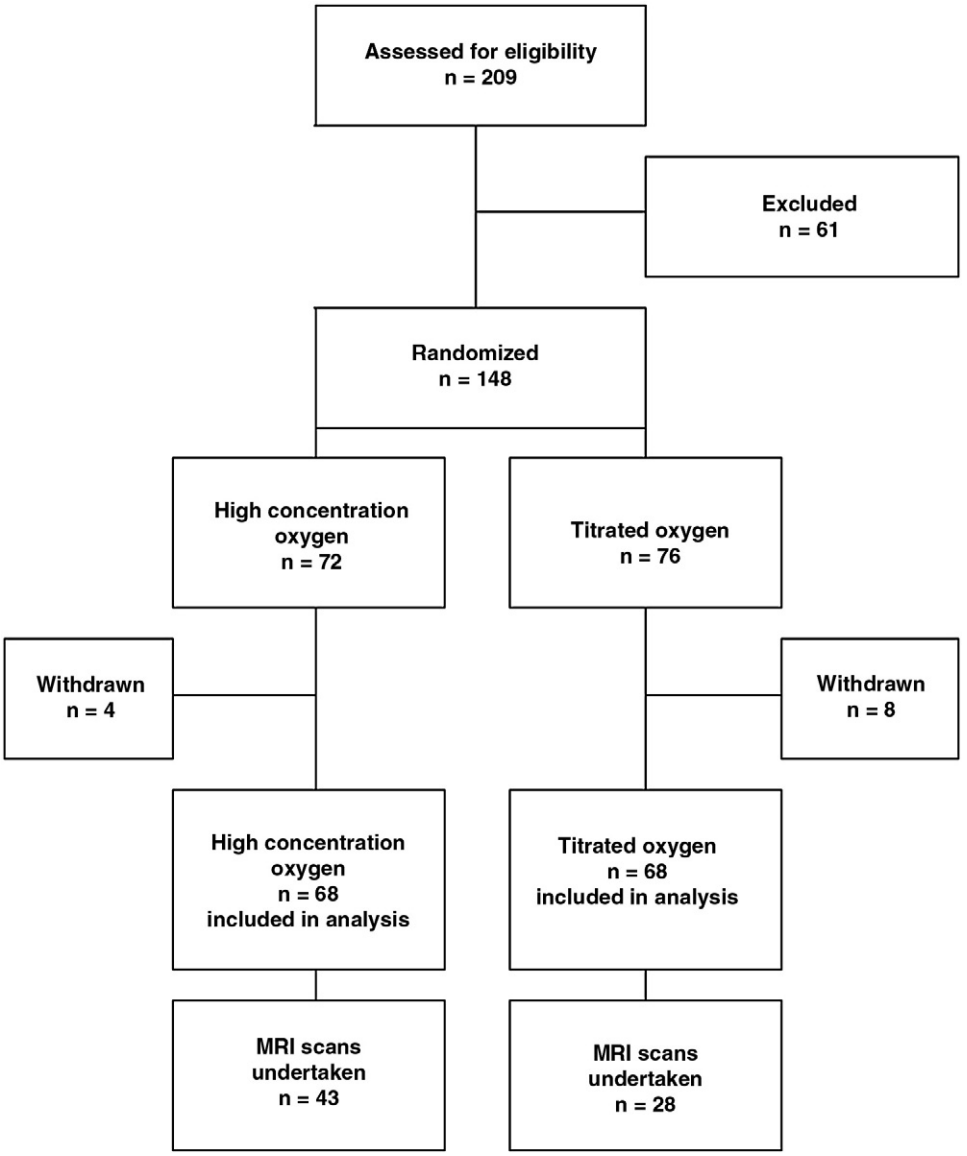
There was no significant difference in troponin T level between the 2 groups with a ratio of mean levels favoring the high-flow group based on the logarithm-transformed data of 0.74 (95% CI 0.50-1.1, P = .14) (Table III). There was no difference in BNP level between treatment groups with a ratio of mean levels favoring the high-flow group based on the logarithm-transformed data of 0.82 (95% CI 0.50-1.37, P = .45) (Table IV). Magnetic resonance imaging scans were performed in 71 subjects, and none had evidence of a myocardial infarction in 2 arterial territories or noninfarct distribution scarring. There was no significant difference in the mean infarct mass or percent infarct mass between the high-concentration and titrated groups (−0.8 g, 95% CI −7.6 to 6.1, P = .82 and −0.6%, 95% CI −5.6 to 4.5, P = .83, respectively) (Table III). The LVEF was measured with MRI in 70 subjects because 1 scan had insufficient image quality for this calculation. The LVEF was not significantly different between the high-concentration and titrated groups, with a mean difference of −0.08% (95% CI −5.4 to 5.2, P = .98). In a post hoc analysis, adjustment for infarct location (anterior vs inferior or posterior), time to reperfusion intervention, and time oxygen that was administered before randomization did not significantly affect the difference between high-concentration and titrated oxygen treatments for the secondary outcome measures of infarct size or cardiac function (Table IV).

The meta-analysis, including mortality from this and the 2 previous studies reporting mortality data from randomized controlled trials of high concentration versus room air, identified a fixed-effects odds ratio of death associated with high-concentration oxygen therapy of 2.2 (95% CI 0.8-6.0) and a random effects odds ratio of 2.1 (95% CI 0.7-6.5), with an I^2 statistic of 14.6 (95% CI 0.0-91.1) (Table V) (Figure 2). There was no evidence of publication bias on Funnel plot or formal tests.

Discussion

This study found no evidence of benefit or harm from high-concentration compared with titrated oxygen therapy in patients with STEMI not complicated by

Figure 1



Flow of subjects in the study.

cardiogenic shock or marked hypoxia at initial presentation. However, our estimates had wide CIs, and even when the data were combined with the only other 2 published studies that reported comparable data,[13,14] it was not possible to rule out an increased or reduced risk of mortality with high-concentration compared with titrated oxygen therapy.

Several methodological issues are relevant to the interpretation of our findings. We excluded subjects with a history of previous myocardial infarction because this might have affected MRI estimates of infarct size, those with cardiogenic shock or marked hypoxia, and those with severe COPD in whom high-concentration oxygen therapy might result in hypercapnia. This approach resulted in a low-risk trial population, limiting the generalizability of the findings to those with an initially uncomplicated first myocardial infarction, and consequently reduced the power to determine differences in mortality.

Randomization occurred at hospital presentation, and most subjects had already received high-concentration oxygen administered by ambulance staff for an average of 60 minutes. If the effect of high-concentration oxygen is crucial in determining outcomes in myocardial infarction, this prehospital therapy will have reduced the power of the study to detect differences. Ideally, future studies should randomize at the time of ambulance attendance.

Table I. Baseline characteristics of subjects

	High-concentration oxygen (n = 68)	Titrated oxygen (n = 68)
Age (y), mean (SD)	60 (12.8)	62.1 (12.5)
Male sex, n (%)	53 (77.9)	48 (70.6)
Body mass index ($kg \cdot m^{-2}$), mean (SD)	27.7 (5.4)	27.4 (5.0)
Hypertension, n (%)	23 (33.8)	28 (41.2)
Diabetes, n (%)	7 (10.3)	8 (11.8)
Current smokers, n (%)	32 (47.1)	21 (30.9)
Hyperlipidemia, n (%)	19 (27.9)	25 (36.8)
Previous CABG, n (%)	1 (1.5)	0 (0)
Previous PCI, n (%)	2 (2.9)	5 (7.4)
Medications, n (%)		
Aspirin	11 (16.2)	11 (16.2)
β-Blocker	7 (10.3)	7 (10.3)
Statin	17 (25)	14 (20.6)
ACE inhibitor or ARB	13 (19.1)	18 (26.5)

CABG, Coronary artery bypass graft surgery; *PCI*, percutaneous coronary intervention; *ACE inhibitor*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker.

Table II. Clinical characteristics including management of subjects

	High-concentration oxygen (n = 68)	Titrated oxygen (n = 68)
Infarct territory, n (%)		
Anterior	18 (26.5)	31 (45.6)
Lateral	1 (1.5)	0 (0)
Inferior/posterior	49 (72.0)	37 (54.1)
Prehospital oxygen administered, n (%)	59 (86.8)	57 (83.8)
Duration of prehospital oxygen therapy (min), mean (sd)	64.7 (59.3)	59.6 (36.7)
Prehospital thrombolysis, n (%)	7 (10.3)	4 (5.9)
Time to thrombolytic (min),* mean (SD)	124 (45)	96 (31)
In-hospital thrombolysis, n (%)	11 (16.2)	8 (11.8)
Time to thrombolytic (min),* mean (SD)	241 (135)	163 (43)
PPCI, n (%)	48 (70.6)	55 (80.9)
Ischemic time† (min), mean (SD)	236 (126)	241 (158)
Baseline logarithm troponin T, mean (SD)	−2.95 (2.68)	−2.99 (2.68)

* Time to thrombolytic indicates MI onset to initiation of thrombolysis.
† Ischemic time indicates MI onset to first balloon dilatation or direct stenting.

We had considered that this approach would not be feasible, although Australian colleagues have recently shown the utility of cluster randomization by ambulance in the first randomized controlled trial of high-concentration versus titrated oxygen therapy in acute exacerbations of COPD.[16]

The randomized oxygen regimen was administered for 6 hours in accordance with guideline recommendations at the time of protocol development.[1] Treatment could not be blinded because dose adjustments were required in the titrated group. Although this should not have resulted in significant bias because the end points were objective and the MRI measurements were made blind to the randomized treatment, an influence on subsequent care from the knowledge of randomized treatment cannot be excluded.

Validated biochemical and radiologic measures of infarct size, LV function, and prognosis were made. A single measurement of troponin T at 72 hours correlates with infarct size measured by MRI[17] and thallium[18] scans. Troponin T and BNP levels are positively correlated with LV function after myocardial infarction,[17,19] as well as subsequent mortality, thereby providing an indirect measure of prognosis.[19,20] Randomization was not stratified by infarct location, which represented a limitation of our study, because of the imbalance between the treatment groups, with a greater proportion of anterior infarcts in the titrated oxygen group. This was relevant because anterior infarcts had higher troponin T levels and MRI infarct mass than inferior or posterior infarcts.

Our study used cardiac MRI scans at 4 to 6 weeks after myocardial infarction to provide a direct measure of both infarct size and LV function. Cardiac MRI can be considered the criterion standard for quantification of ventricular function and determination of infarct size.[21] However, a limitation of this approach is that many subjects had a contraindication to scanning or did not consent to the procedure, with the result that this assessment was undertaken in only just over half of the subjects, thereby reducing the power to detect differences between the 2 treatment arms. Furthermore, an imbalance in the proportion of subjects who had MRI scanning in each treatment group may have resulted in bias. Our experience suggests that, in future definitive large randomized controlled trials, measures of troponin T and BNP taken during hospital admission would be preferable to MRI scanning for the assessment of infarct size. However, even this approach was problematic in our pilot study because of difficulties with follow-up after transfer back to peripheral hospitals after PPCI at the tertiary hospital.

As anticipated, there was insufficient power to determine statistically significant differences in mortality between the 2 regimes. Inclusion of our mortality data with those from the previous studies in a meta-analysis also lacked statistical power to determine a difference because in the 3 studies, there were only 16 deaths in 431 subjects, with a statistically nonsignificant relative risk of mortality of 2.2 (95% CI 0.8-6.0). Based on a predicted death rate of 4% in patients presenting with STEMI and not in cardiogenic shock,[22] a future randomized controlled trial would require a total of 7,600 subjects to have 90% power at an α of 5% to determine a 1.5-fold

Table III. The effect of high-concentration and titrated oxygen therapy on biochemical and radiologic measures of infarct size and LV function

	High-concentration oxygen	Titrated oxygen	Difference (95% CI)	*P*
Troponin T (ng/mL), mean (SD)* (n)†	2.2 (1.8) 62	2.9 (2.8) 58	−0.7 (−1.5 to 0.2)	.12
Logarithm troponin T (ng/mL), mean (SD) (n)†	0.36 (1.15) 62	0.65 (1.03) 58	−0.3 (−0.7 to 0.10)	.14
BNP (pmol/L),* (n)†	1083 (1334) 61	1783 (4469) 59	−700 (−1885 to 483)	.24
Logarithm BNP (pmol/L), mean (SD) (n)†	6.2 (1.4) 61	6.4 (1.4) 59	−0.19 (−0.70 to 0.31)	.45
MRI infarct mass (g), mean (SD) (n)†	15.6 (15.6) 43	16.3 (11.7) 28	−0.8 (−7.6 to 6.1)	.82
MRI infarct (%), mean (SD) (n)†	12.5 (10.9) 42	13.1 (9.7) 28	−0.6 (−5.6 to 4.5)	.83
MRI LVEF (%) (mean, SD) (n)†	55.9 (11.0) 42	56.0 (10.6) 28	−0.1 (−5.4 to 5.2)	.98

* Data skewed, summary data at *t* test shown for completeness, normal analysis assumptions met for logarithm-transformed data.
† Number of subjects in whom this measure was available.

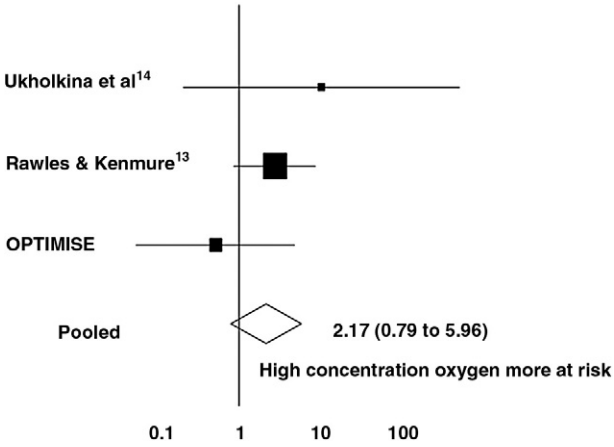
Table IV. High-concentration minus titrated oxygen therapy for biochemical and radiologic measures of infarct size and LV function, adjusted for infarct location, time to reperfusion intervention, and time oxygen administered before randomised treatment

	Unadjusted estimate (95% CI)	*P*	Adjusted estimate (95% CI)	*P*
Logarithm troponin T (ng/mL)	−0.30 (−0.70 to 0.10)	.14	−0.46 (−0.94 to 0.015)	.057
Logarithm BNP (pmol/L)	−0.19 (−0.70 to 0.31)	.45	−0.54 (−1.1 to 0.047)	.07
MRI infarct mass (g)	−0.8 (−7.6 to 6.1)	.82	−4.5 (−10.9 to 1.9)	.16
MRI infarct percent (%)	−0.6 (−5.6 to 4.5)	.83	−3.9 (−9.0 to 1.2)	.13
MRI LVEF (%)	−0.08 (−5.4 to 5.2)	.98	1.9 (−3.4 to 7.1)	.48

Table V. Summary of studies reporting mortality data

	Mortality/total (%)		
Study	High-concentration oxygen	Titrated oxygen or room air	Peto OR (95% CI)
Rawles & Kenmure[13]	9/81 (11.1)	3/77 (3.9)	2.8 (0.9-8.9)
Ukholkina et al[14]	1/58 (1.7)	0/79 (0.0)	10.6 (0.2-561)
OPTIMISE	1/68 (1.5)	2/68 (2.9)	0.5 (0.1-5.0)

Figure 2



The Forest plot shows the point estimates for each trial (in the center of shaded box) and its CI (the ends of the lines). The size of the box is inversely proportional to the individual study variance. The pooled study estimates are represented by the diamond. The odds ratio for risk of mortality is presented on the logarithm scale, and the trials are ranked in order of the size of the odds ratio. The pooled estimate presented is the fixed effect estimate.

difference. This is well within the capacity of the international cardiac research community, experienced in large multicenter trials.

The other main finding of the study was that there was no significant difference in measures of infarct size or LV function between the 2 treatment groups. This interpretation was limited to some extent by the more frequent occurrence of anterior myocardial infarction in the titrated oxygen group, the unanticipated high number of patients who declined to undergo MR imaging, and the missing measures of troponin T and BNP in some subjects who transferred back to peripheral hospitals after PCI. Statistical adjustment for the differences in anterior versus nonanterior infarction moved the point estimates of infarct size toward the possibility of benefit from high-flow oxygen but insufficiently to change our overall

conclusions. As a result, this issue remains unresolved, with the 2 previous studies reporting conflicting results. In the United Kingdom study undertaken in the prereperfusion era, high-concentration oxygen administered for 24 hours after admission for an uncomplicated myocardial infarction resulted in greater cardiac enzyme levels indicative of a larger infarct size when compared with room air.[13] In contrast, the Russian study undertaken in the reperfusion era reported that oxygen therapy administered 30 minutes before and 4 hours after PCI or for 4 hours after PCI reduced infarct size, improved hemodynamics, and decreased the rate of postoperative rhythm disorders compared with room air.[14]

We conclude that there is no substantive evidence of benefit to support the routine administration of oxygen in patients with myocardial infarction, not complicated by cardiogenic shock or marked hypoxia at initial presentation. A strong case exists for multicenter randomized controlled trials, sufficiently powered to determine whether the 2 strategies have a clinically relevant influence on mortality. Pending the results of such studies, we concur with the recent oxygen guidelines recommendation that supplementary oxygen should not be administered routinely to patients with acute chest pain of suspected cardiac origin but limited to patients in whom hypoxia is present, with oxygen saturation monitored and used to guide its administration.[23]

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The authors declare no conflict of interest.

Disclosures

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