Randomized comparison of early supplemental oxygen versus ambient air in patients with confirmed myocardial infarction: Sex-related outcomes from DETO2X-AMI

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Background The purpose of this study is to investigate the impact of oxygen therapy on cardiovascular outcomes in relation to sex in patients with confirmed myocardial infarction (MI).

Methods The DETermination of the role of Oxygen in suspected Acute Myocardial Infarction trial randomized 6,629 patients to oxygen at 6 L/min for 6-12 hours or ambient air. In the present subgroup analysis including 5,010 patients (1,388 women and 3,622 men) with confirmed MI, we report the effect of supplemental oxygen on the composite of all-cause death, rehospitalization with MI, or heart failure at long-term follow-up, stratified according to sex.

Results Event rate for the composite endpoint was 18.1% in women allocated to oxygen, compared to 21.4% in women allocated to ambient air (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.65-1.05). In men, the incidence was 13.6% in patients allocated to oxygen compared to 13.3% in patients allocated to ambient air (HR 1.03, 95% CI 0.86-1.23). No significant interaction in relation to sex was found (P= .16). Irrespective of allocated treatment, the composite endpoint occurred more often in women compared to men (19.7 vs 13.4%, HR 1.51; 95% CI, 1.30-1.75). After adjustment for age alone, there was no difference between the sexes (HR 1.06, 95% CI 0.91-1.24), which remained consistent after multivariate adjustment.

Conclusion Oxygen therapy in normoxemic MI patients did not significantly affect all-cause mortality or rehospitalization for MI or heart failure in women or men. The observed worse outcome in women was explained by differences in baseline characteristics, especially age. (Am Heart J 2021;237:13–24.)

Until recently, guidelines—based on expert opinion—recommended supplemental oxygen as a cornerstone of supportive treatment to all MI patients.[1] However, the Determination of the role of Oxygen in suspected Acute Myocardial Infarction (DETO2X-AMI) trial demonstrated that oxygen therapy was not associated with reduced mortality,[2] and updated guidelines no longer support routine oxygen therapy in normoxemic patients with acute MI.[3-5]

There are substantial differences in demographics and baseline characteristics between women and men with MI. For example, women with MI are older, with more

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comorbid conditions, but less obstructive coronary disease.[6-9] Consequently, the incidence of MI with nonobstructive coronary arteries (MINOCA) is disproportionally higher in women compared to men.[10,11] Lower prevalence of an obstructive disease among women with MI has, at least in part, been explained by differences in pathophysiology, with, for example, spontaneous coronary artery dissection,[12] takotsubo cardiomyopathy,[13,14] and microvascular dysfunction being more common in women.[15]

In addition, sex differences in the production of reactive oxygen species (ROS) have been reported.[16]

Taken together, sex differences in baseline characteristics and pathophysiology indicate a possible difference in the effect of oxygen therapy in the setting of an acute MI between women and men.

As the primary trial report presented outcomes in the broad population of patients with suspected MI,[2] the focus of this subgroup analysis was to investigate the effect of supplemental oxygen on all-cause mortality, rehospitalization with MI, or heart failure (HF), in women compared with men, with confirmed MI. A secondary aim was to compare cardiovascular outcomes in women vs men irrespective of oxygen therapy.

Methods

Study design

The DETO2X-AMI trial was a nationwide, multicenter, open-label, registry-based randomized clinical trial[17] evaluating routine oxygen therapy and ambient air in patients with suspected MI.[2] The Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART)[18] registry was used for randomization, trial procedures, and follow-up.

The study design,[19] methods, and primary results have been described in detail previously.[2,20,21] The ethical review authority (Gothenburg DNR 287-12) and the medical products agency of Sweden (EudraCT 2013-002882-20) approved the trial.

The authors designed and conducted the trial, wrote the manuscript, and vouch for the data, all analyses, and the fidelity of this report to the trial protocol and statistical analysis plan available in the supplemental appendix. The funding agencies had no access to the study data and no role in trial design, implementation, or reporting.

Patient population

Assessment for enrollment was carried out at first medical contact with the ambulance service, emergency department, coronary care unit, or catheterization laboratory of participating hospitals. Patients were eligible if they were ≥30 years of age with typical symptoms suggestive of MI (defined as chest pain or dyspnea) for <6 hours, oxygen saturation of ≥90% on pulse oximetry, and electrocardiography changes indicating ischemia[22] or raised cardiac troponin levels on admission (above the locally defined decision limit for MI). Only Swedish residents with a unique personal identification number were enrolled allowing almost complete follow-up from the Swedish National Population Registry.[23]

Patients were excluded if they had ongoing oxygen therapy or cardiac arrest prior to enrollment.

The main study population included patients with suspected MI (N = 6,629) with all-cause death within 1 year as the primary outcome. Subgroup findings was presented in the main publication (online supplement) with no interaction according to sex (women: HR 0.97, 95% CI 0.69-1.37; men: HR 0.97, 95% CI 0.74-1.28; P= .99, for interaction).[2]

Furthermore, we have presented data on the composite of all-cause death or hospitalization for HF by sex within 1 year with similar findings (women: HR 0.85, 95% CI 0.64-1.12; men: HR 1.09, 95% CI 0.88-1.36; P= .16, for interaction).[21]

As we have recently reported, there are profound differences in background characteristics and cardiovascular outcomes in patients admitted with a strong suspicion of MI but discharged without an MI diagnosis.[24] To achieve a more homogenous population with a well-defined pathophysiological risk-benefit controversy between women and men, we focused in the current report on sex-related aspects in patients with confirmed MI (N = 5,010) which provides superior data completeness, including in most cases coronary angiography and intervention.

Study procedures

Eligible patients were, after initial oral informed consent, randomly assigned in an unrestricted 1:1 ratio to either oxygen therapy at 6 L/min for 6-12 hours delivered by open face mask or ambient air. Randomization was performed online with a randomization module incorporated in SWEDEHEART, directly followed by the initiation of allocated therapy. Within 24 hours oral consent was confirmed in writing. All patients were treated according to the standard of care. Oxygen saturation was documented at the beginning and the end of the randomized treatment period. Patients received supplemental oxygen outside the protocol limits at the discretion of the caring physician, most commonly in cases where hypoxemia (defined as oxygen saturation <90%) developed, which was reported separately.

Outcomes and follow-up

The primary outcome of the main trial was all-cause mortality within 1 year in the intention-to-treat population with suspected MI.[2] In this predefined subgroup analysis, the main objective was to study the effect of supplemental oxygen on the composite of all-cause

death or rehospitalization with MI or HF during long-term follow-up (median [range] 760 [366-1357] days).

As secondary objectives, individual components of the composite outcome including cardiovascular death were reported at 30 days and 1 year, as well as the highest recorded level of high-sensitivity cardiac troponin T (hs-cTnT) as a proxy for infarct size.

Mortality data were obtained from the Swedish National Population Registry, which includes the vital status of all Swedish residents.[23] Data on rehospitalization with MI were obtained from the SWEDEHEART registry and defined according to international classification of disease (ICD) version 10 codes I21 and I22. Data on rehospitalization for HF were obtained from the national Swedish patient registry,[25] including all ICD codes from all admissions in Sweden, and defined as ICD code I50.

Data on cardiovascular death, defined as ICD codes I00 through I99 or unclassified, were obtained from the Swedish national cause-of-death registry.

The end of follow-up was December 30, 2016, 365 days after randomization of the last patient. No central adjudication or study-specific patient follow-up was performed.

The study team and steering committee were blinded to treatment comparisons until unlocking the database. Accumulated data without treatment group information were available for monitoring of study progress throughout the trial.

Statistical analysis

The sample size calculations for the overall trial have been described in detail previously.[2,19] The subgroup analysis according to sex in the intention-to-treat (ITT) population with suspected MI (N = 6,629) was prespecified and presented in the supplementary appendix to the main publication.[2] Here, we present novel endpoint clinical outcome data (all-cause death, rehospitalization with MI, rehospitalization for HF, cardiovascular death) from the more homogenous subgroup with confirmed MI (N = 5,010) stratified by sex. Since we had access to rehospitalizations for HF,[21] that were unavailable for the primary publication, the composite of all-cause death or rehospitalization with MI or HF was chosen post-hoc as the main outcome for this analysis to include clinically relevant outcomes and increase statistical power. To further increase the power to detect an interactive effect, we decided to include all follow-up time for all patients in the statistical analyses.

The results were analyzed according to the intention-to-treat principle. Time to the event is presented in Kaplan–Meier curves, and the number and percentage of patients with the event are presented by sex and therapy. The effect of treatment by sex was evaluated using a Cox proportional hazard model including treatment, sex, and treatment-sex interaction, and age as a linear covariate on the log-hazard scale. The results are presented as estimates of treatment differences with two-tailed 95% CIs for each subgroup, and the interaction *P* value. Components of the primary composite are analyzed and presented in the same way as the primary outcome, with death handled as censoring.

Outcomes in women vs men were analyzed using Cox proportional hazards models, adjusted for age, and adjusted for age, hypertension, diabetes, previous MI, PCI, HF, and infarct type. Results are presented as a hazard ratio of women vs men with 95% CIs and *P* values. The proportional hazards assumption was evaluated by visual inspection of Kaplan–Meier curves and comparison of hazard ratios with analyses censored at 30 and 365 days (crude and adjusted).

The highest recorded level of high-sensitivity cardiac Troponin (hs-cTn) T concentration during hospitalization was analyzed using an unadjusted log-linear model with randomized treatment as a factor, and interaction analyses including sex and sex-treatment interaction in the model. Results are presented as medians (IQR), the geometric mean ratios from the subgroup-specific analyses with 95% CI and *P* values, and the interaction *P* value, and displayed using empirical cumulative distribution function plots.

A two-tailed *P* value of $<.05$ was considered statistically significant.

All analyses were conducted with SAS v.9.4 (SAS Institute Inc., Cary, NC).

Results

Study population

Of the 6,629 patients with suspected MI who were enrolled in the main trial, 5,010 (76%) received a primary discharge diagnosis of MI (2,952 [59%] ST-segment elevation myocardial infarction [STEMI], 2,058 [41%] Non-STEMI [NSTEMI]) and were included in this analysis; 2,485 were allocated to supplemental oxygen and 2,525 were allocated to ambient air. Stratified by sex, 1,388 (28%) were women of whom 711 (51%) were allocated to oxygen as compared with 3,622 (72%) men of whom 1,774 (49%) were assigned to oxygen (study flow chart, Figure 1 and Supplementary Figure A1).

In general, women were older, suffered more often from hypertension, and had a more intensive antihypertensive therapy (β-blockers, angiotensin converting enzyme [ACE] inhibitors or angiotensin receptor blocker [ARB], calcium channel blockers, and diuretics), and were more often active smokers with diagnosed chronic obstructive pulmonary disease. Men, however, had more often a previous diagnosis of HF, a higher body mass index, and more often previous cardiovascular disease (MI, cardiac surgery). Other risk factors such as diabetes, previous stroke, and peripheral arterial disease were similarly distributed. At presentation, women were more often admitted due to dyspnea and had more often reduced renal function, and anemia (Table I).

Table I. Baseline characteristics, clinical presentation, and final diagnoses in patients with confirmed MI, stratified by sex and treatment*

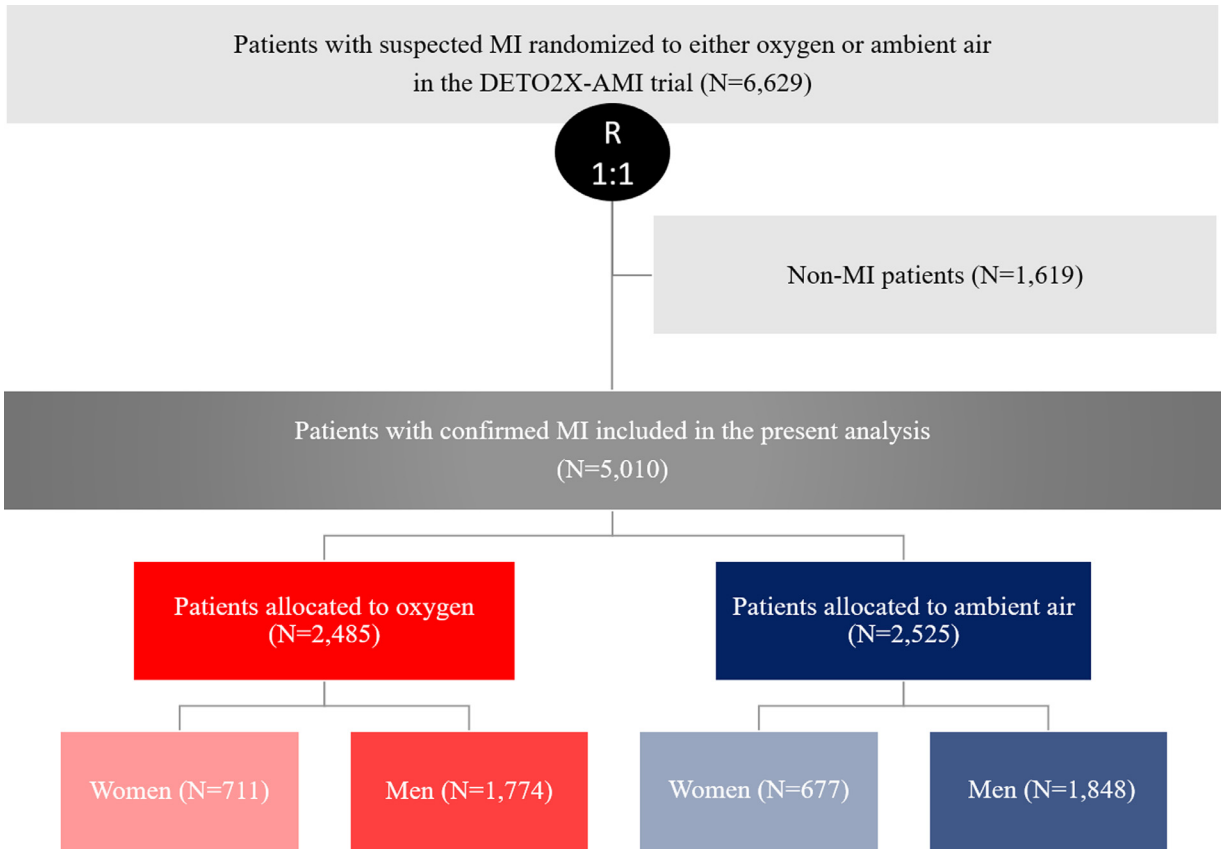
Characteristics Number (%)	All 5,010 (100)		Women 1,388 (27.7)		Men 3,622 (72.3)	
	Women	Men	Oxygen	Ambient air	Oxygen	Ambient air
Number	1,388	3,622	711	677	1,774	1,848
Demographics Number (%)						
Age—years, median† (IQR)	72 (64.0-80.0)	67 (58.0-74.0)	72 (64.0-81.0)	72 (65.0-80.0)	67 (58.0-74.0)	67 (58.0-74.0)
Risk factors and medical history—no (%)						
Body-mass index†,‡	26.8 (±5.0)	27.3 (±4.0)	26.8 (±5.1)	26.8 (±4.9)	27.3 (±4.0)	27.3 (±4.0)
Current smoking†	349 (25.1)	850 (23.5)	167 (23.5)	182 (26.9)	419 (23.6)	431 (23.3)
Hypertension†	761 (54.8)	1,597 (44.1)	385 (54.1)	376 (55.5)	784 (44.2)	813 (44.0)
Diabetes	267 (19.2)	665 (18.4)	129 (18.1)	138 (20.4)	316 (17.8)	349 (18.9)
COPD†	78 (5.6)	113 (3.1)	40 (5.6)	38 (5.6)	59 (3.3)	54 (2.9)
MI†	211 (15.2)	688 (19.0)	105 (14.8)	106 (15.7)	342 (19.3)	346 (18.7)
PCI†	135 (9.7)	559 (15.4)	63 (8.9)	72 (10.6)	273 (15.4)	286 (15.5)
CABG†	44 (3.2)	218 (6.0)	23 (3.2)	21 (3.1)	113 (6.4)	105 (5.7)
HF (EF $\leq$ 50%)†	67 (4.8)	195 (5.4)	29 (4.1)	38 (5.6)	94 (5.3)	101 (5.5)
Stroke	67 (4.8)	168 (4.6)	32 (4.5)	35 (5.2)	94 (5.3)	74 (4.0)
PAD	59 (4.3)	152 (4.2)	28 (3.9)	31 (4.6)	84 (4.7)	68 (3.7)
Cause of admission						
Chest pain†	1,301 (93.7)	3,506 (96.8)	665 (93.5)	636 (93.9)	1,722 (97.1)	1,784 (96.5)
Dyspnea†	32 (2.3)	41 (1.1)	13 (1.8)	19 (2.8)	15 (0.8)	26 (1.4)
Medication on admission—number (%)						
Aspirin	362 (26.1)	907 (25.0)	184 (25.9)	178 (26.3)	428 (24.1)	479 (25.9)
P2Y12 receptor Inhibitor†	66 (4.8)	139 (3.8)	38 (5.3)	36 (5.3)	75 (4.2)	80 (4.3)
β-blocker†	448 (32.3)	968 (26.7)	225 (31.6)	223 (32.9)	470 (26.5)	498 (26.9)
Statin	315 (22.7)	893 (24.7)	160 (22.5)	155 (22.9)	431 (24.3)	462 (25.0)
ACE or ARB†	514 (37.0)	1221 (33.7)	253 (35.6)	261 (38.6)	597 (33.7)	624 (33.8)
Presentation and laboratory measures						
Systolic blood pressure—mmHg	149.9 (±29.6)	149.3 (±27.4)	150.1 (±29.9)	149.6 (±29.3)	150.4 (±27.3)	148.2 (±27.4)
Heart rate†—beats/min	79.5 (±18.1)	76.7 (±18.3)	80.1 (±17.8)	78.8 (±18.4)	76.8 (±18.5)	76.5 (±18.2)
Rales	59 (4.3)	102 (2.8)	34 (4.8)	25 (3.7)	47 (2.6)	55 (3.0)
eGFR CKD-EPI*†	73.9 (±21.9)	80.8 (±19.7)	74.3 (±21.5)	73.5 (±22.3)	81.0 (±19.7)	80.6 (±19.7)
Hb† (g/L)	131.21 (±15.96)	143.58 (±15.44)	131.06 (±15.77)	131.36 (±16.17)	143.70 (±15.46)	143.45 (±15.43)
Hs-cTnT (ng/L)—median (IQR)	881 (220-3,174)	1,000 (233-2,670)	829 (254-3,050)	946 (223-2,622)	1,000 (235-3,099)	1,000 (231-2,650)
MI characteristics number (%)						
STEMI†	835 (60.2)	2,117 (58.4)	427 (60.1)	408 (60.3)	1,004 (56.6)	1,113 (60.2)
MI type 1†	1,314 (94.7)	3,522 (97.2)	675 (94.9)	639 (94.4)	1,721 (97.0)	1,801 (97.5)
MI type 2†	56 (4.0)	55 (1.5)	29 (4.1)	27 (4.0)	33 (1.9)	22 (1.2)

* Plus-minus values are means ±SD.

† $P < .05$ for the comparison between woman and men.

‡ The body-mass index (the weight in kilograms divided by the square of the height in meters).ACE, angiotensin converting enzyme, ARB, angiotensin renin blocker; CABG, coronary-arterial bypass graft; Hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; MI, myocardial infarction; NSTEMI, Non-ST-elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Figure 1



Enrollment, randomization, and analysis (study flow chart). Eligible patients presenting to the ambulance service, emergency departments, coronary care units, or catheterization laboratories of participating hospitals with suspected myocardial infarction were evaluated for inclusion. Shown are the numbers of patients who were enrolled in the main study, randomly assigned to a study group, and analyzed during the study period. In the present analysis, only patients with confirmed MI were analyzed and stratified by sex. DETO2X-AMI denotes determination of the role of oxygen in acute myocardial infarction. MI, myocardial infarction; R, randomization.

In-hospital procedural data

At the time of randomization, the median oxygen saturation overall was 97.0% (IQR 95.0%-98.0%). The median duration of oxygen therapy was similar in both groups with overall median oxygen saturation at the end of the treatment period of 98.0% (IQR 96.0%-99.0%). Overall, woman developed hypoxemia more often compared with men, 109 (8%) vs 179 (5%), respectively, with a most pronounced difference in the ambient air group were 89 (13%) woman developed hypoxemia as compared with 142 (8%) men, a statistically significant difference. Moreover, the distribution of MI subtypes (STEMI/ NSTEMI) was similar but men were more often diagnosed with multivessel disease and women more often with non-obstructive coronary disease. Women were less frequently treated with guideline-recommended diagnostics (angiography, radial access) and revascularization therapies (PCI/CABG, complete revascularization). Secondary preventive medications (aspirin, P2Y12 inhibitors, statins, ACE/ARB) were less frequently prescribed at discharge. Myocardial injury measured by hs-cTnT was similar between the sexes (Table II, Supplementary Figures S2-S4). Despite somewhat better left ventricular function, women presented more often with signs and symptoms of acute HF, were more often treated with intravenous diuretics and continuous positive airway pressure therapy and experienced more bleeding complications, and cardiogenic shock during the hospitalization period. In addition, in-hospital mortality was higher in women (Table II).

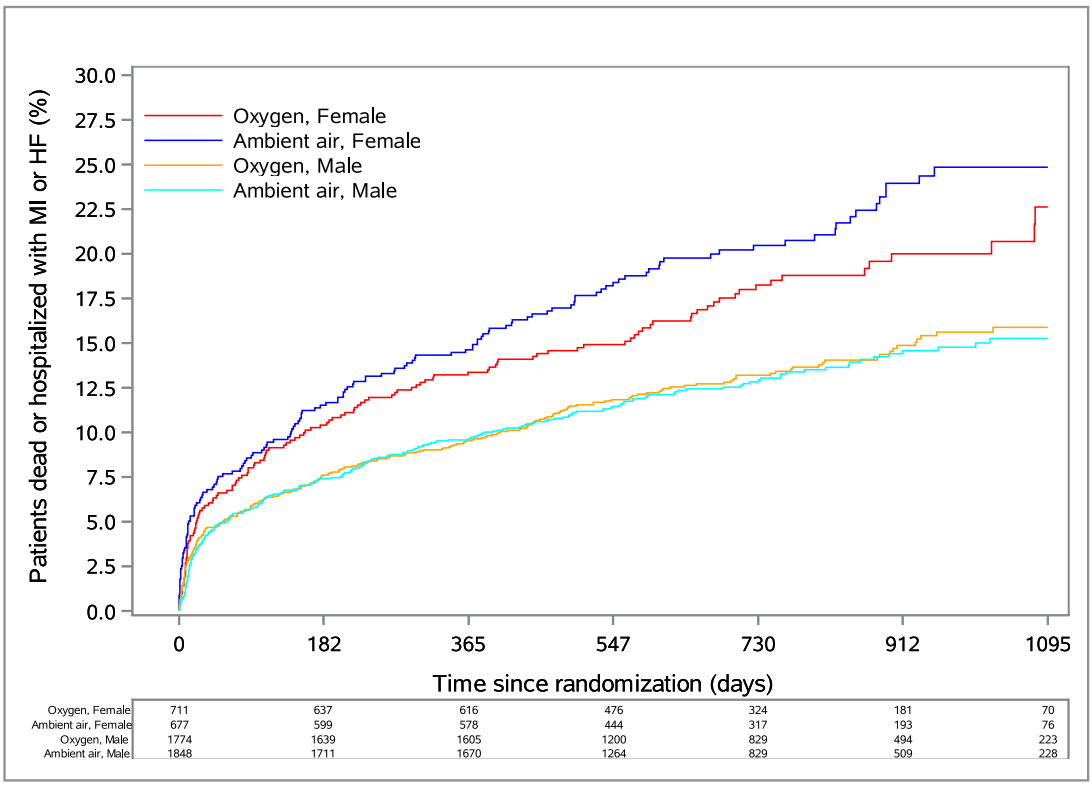
Table II. In-hospital procedural data, medication, procedures, and complications in patients with confirmed MI stratified by sex and treatment*

Characteristic Number (%)	All5,010 (100)		Women1,388 (27.7)		Men3,622 (72.3)	
	Women	Men	Oxygen	Ambient air	Oxygen	Ambient air
Oxygen saturation at inclusion, %, median (IQR)	97.0 (95.00-98.00)	97.0 (95.00-98.00)	97.0 (95.00-98.00)	97.0 (95.00-98.00)	97.0 (95.00-98.00)	97.0 (95.00-98.00)
Duration of oxygen therapy hours, median (IQR)	11.4 (6.0-12.0)	11.8 (6.0-12.0)	11.0 (6.0-12.0)	11.5 (6.0-12.0)	11.8 (6.0-12.0)	11.7 (6.0-12.0)
Hypoxemia during study†	109 (7.9)	179 (4.9)	20 (2.8)	89 (13.1)	37 (2.1)	142 (7.7)
Oxygen saturation at end of treatment period %, median (IQR)	98.0 (96.0-99.0)	98.0 (96.0-99.0)	99.0 97.0-100.0	97.0 95.0-98.0	99.0 97.0-100.0	97.0 95.0-98.0
Procedures – no. (%)						
Echocardiography No (%)†						
Normal (LVEF ≥50%)	747 (53.8)	1884 (52.0)	371 (52.2)	376 (55.5)	929 (52.4)	955 (51.7)
Midrange (LVEF 40-49%)	251 (18.1)	756 (20.9)	136 (19.1)	115 (17.0)	374 (21.1)	382 (20.7)
Reduced (LVEF < 40%)	185 (13.3)	556 (15.4)	104 (14.6)	81 (12.0)	264 (14.9)	292 (15.8)
Angiography†						
Normal or atheromatosis	126 (9.9)	111 (3.2)	64 (9.9)	62 (9.8)	60 (3.5)	51 (2.9)
1-2 vessel disease	931 (67.0)	2,526 (69.7)	479 (67.4)	452 (66.8)	1,208 (68.1)	1,318 (71.3)
3 vessel disease and/or LM	225 (16.2)	846 (23.4)	105 (14.8)	115 (17.0)	432 (24.4)	412 (22.3)
PCI†	1083 (78.0)	3145 (86.8)	548 (77.1)	535 (79.0)	1532 (86.4)	1613 (87.3)
CABG†	26 (1.9)	122 (3.4)	10 (1.4)	16 (2.4)	53 (3.0)	69 (3.7)
In-hospital complications—number (%)						
Reinfarction	8 (0.6)	20 (0.6)	3 (0.4)	5 (0.7)	12 (0.7)	8 (0.4)
Bleeding†						
Fatal	6 (0.4)	3 (0.1)	2 (0.3)	4 (0.6)	1 (0.1)	2 (0.1)
Cerebral	1 (0.1)			1 (0.1)		
Requiring surgery/transfusion	22 (1.6)	11 (0.3)	10 (1.4)	12 (1.8)	5 (0.3)	6 (0.3)
New-onset atrial fibrillation†	57 (4.1)	109 (3.0)	31 (4.4)	26 (3.8)	51 (2.9)	58 (3.1)
AV-block II-III	25 (1.8)	69 (1.9)	10 (1.4)	15 (2.2)	33 (1.9)	36 (1.9)
Cardiogenic shock†	26 (1.9)	38 (1.0)	11 (1.5)	15 (2.2)	18 (1.0)	20 (1.)
Cardiac arrest	36 (2.6)	94 (2.6)	18 (2.5)	18 (2.7)	54 (3.0)	40 (2.2)
Death†	39 (2.8)	50 (1.4)	19 (2.7)	20 (3.0)	30 (1.7)	20 (1.1)
Medication at discharge—number (%)						
Aspirin†	1273 (91.7)	3422 (94.5)	648 (91.1)	625 (92.3)	1666 (93.9)	1756 (95.0)
P2Y12 inhibitor†						
Clopidogrel	258 (18.6)	519 (14.3)	134 (18.8)	124 (18.3)	266 (15.0)	253 (13.7)
Prasugrel	14 (1.0)	20 (0.6)	5 (0.7)	9 (1.3)	12 (0.7)	8 (0.4)
Ticagrelor	952 (68.6)	2778 (76.7)	495 (69.6)	457 (67.5)	1345 (75.8)	1433 (77.5)
β-blocker†	1228 (88.5)	3266 (90.2)	628 (88.3)	600 (88.6)	1584 (89.3)	1682 (91.0)
Statins†	1234 (88.9)	3458 (95.5)	641 (90.2)	593 (87.6)	1691 (95.3)	1767 (95.6)
ACE or ARB†	1141 (82.2)	3109 (85.8)	589 (82.8)	552 (81.5)	1544 (87.0)	1565 (84.7)
Calcium blocker†	216 (15.6)	483 (13.3)	111 (15.6)	105 (15.5)	226 (12.7)	257 (13.9)
Diuretic†	294 (21.2)	545 (15.0)	161 (22.6)	133 (19.6)	255 (14.4)	290 (15.7)

* Plus-minus values are means ±SD.

† $P < .05$ for the comparison between women and men.ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary-arterial bypass graft; CPAP, continuous positive airway pressure; eGFR denotes estimated glomerular filtration rate; hs-cTnT, high-sensitivity cardiac troponin T; iv, intravenous; IQR, interquartile range; LVEF, left ventricular ejection fraction; LM, left main; PCI, percutaneous coronary intervention.

Figure 2



Analysis of the relationship between the main composite outcome for the total-follow-up of the trial for patients with confirmed MI stratified by sex and treatment. Kaplan–Meier curves are shown for the cumulative probability of the composite outcome of all-cause death, rehospitalization with MI, or rehospitalization for HF at long-term follow-up (median [range] 760 [366-1357] days) for patients divided by sex and assigned treatment (oxygen vs ambient air). No significant interaction in relation to sex was found (P= .16). HF, heart failure; MI, myocardial infarction.

Clinical outcomes for the complete follow-up adjusted for age-stratified by sex and randomized therapy

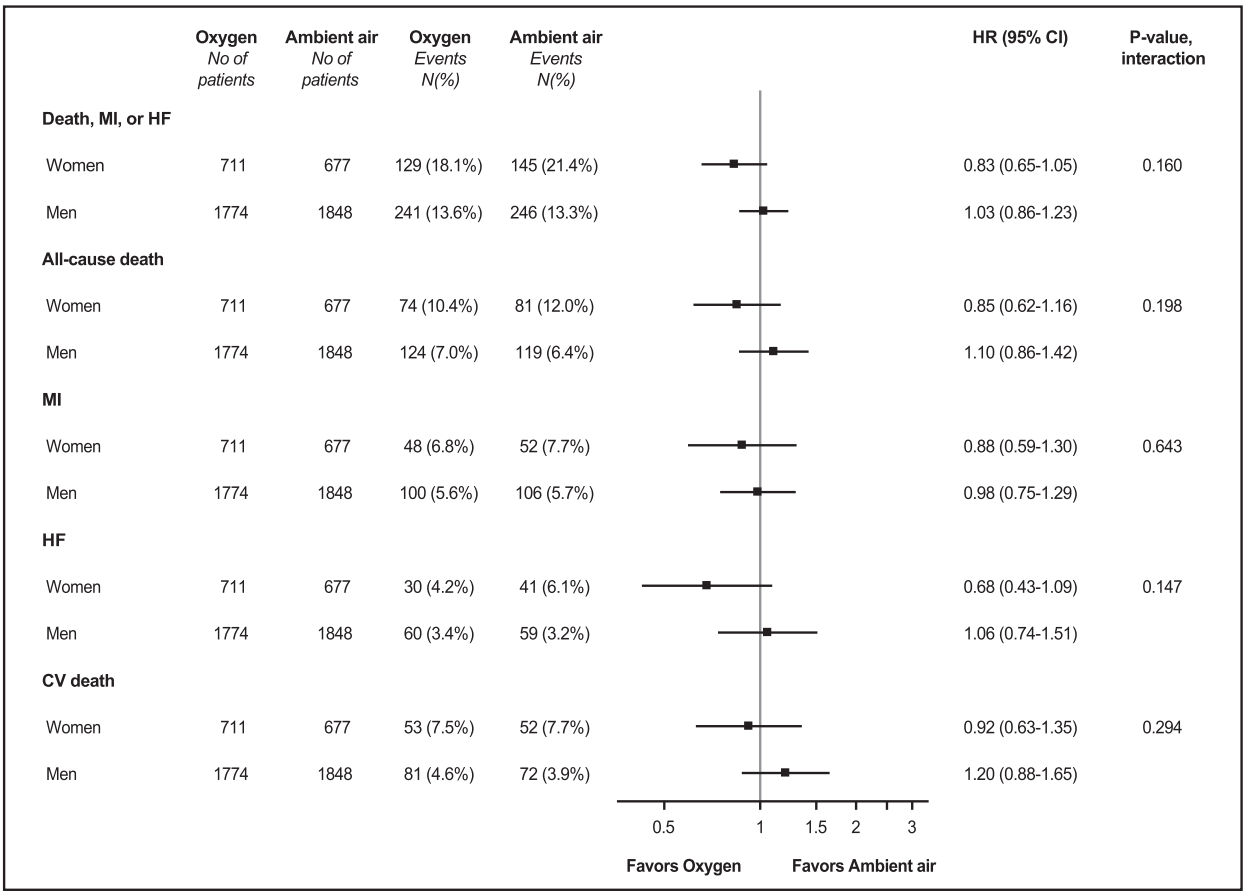
In women, the incidence of the composite of all-cause death or rehospitalization with MI or HF was 18.1% (129 of 711) in patients allocated to oxygen compared to 21.4% (145 of 677) in patients allocated to ambient air (HR 0.83, 95% CI 0.65-1.05). In men, the incidence of the composite outcome was 13.6% (241 of 1774) in patients allocated to oxygen compared to 13.3% (246 of 1848) in patients allocated to ambient air (HR 1.03, 95% CI 0.86-1.23). No significant interaction in relation to sex was found (P= .16) (Figures 2 and 3).

In women, the rate of death from any cause was 10.4% vs 12.0% in the 2 groups (oxygen/ambient air), the rate of rehospitalization with MI was 6.8% vs 7.7%, the rate of rehospitalization for HF was 4.2% vs 6.1%, and the rate of cardiovascular death was 7.5% vs 7.7%, respectively (Figure 3, Supplementary Figure A2). In men, the rate of death from any cause was 7.0% vs 6.4% in the two groups (oxygen/ambient air), the rate of rehospitalization with MI was 5.6% vs 5.7%, the rate of rehospitalization for HF was 3.4% vs 3.2%, and the rate of cardiovascular death was 4.6% vs 3.9%, respectively (Figure 3, Supplementary Figure A2).

Data for the peak level of hs-cTnT showed no significant difference between the treatment groups (Table II, Supplementary Table A1, Supplementary Figures A3-A5).

No significant interactions between the treatment groups and sex was found concerning the composite outcome (P = .16), or the individual components death from any cause (P = .20), rehospitalization with MI (P = .64), rehospitalization for HF (P = .15), or cardiovascular death (P = .29) (Figure 3, Supplementary Figure A2).

Figure 3



Clinical outcomes for the complete follow-up up to 1,357 adjusted for age-stratified by sex and randomized therapy. The effect of treatment by sex was evaluated using a Cox proportional hazard model including treatment, sex, and treatment-sex interaction, and age as a linear covariate on the log-hazard scale. The results are presented as estimates of treatment differences with two-tailed 95% CIs for each subgroup, and the interaction *P* value. CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

Clinical outcomes for the complete follow-up adjusted for age, hypertension, diabetes, previous MI, PCI, HF, and infarct type stratified by sex and randomized therapy

Results remained consistent after multiple adjustments for the composite outcome, individual components, and cardiovascular death stratified by sex. Similarly, no significant interaction was found between the treatment groups and sex (Table III).

Clinical outcomes for women vs men, crude and adjusted

The composite outcome occurred more often in women compared with men at 30 days (HR 1.52, 95% CI 1.16-1.98), at 1 year (HR 1.50, 95% CI 1.26-1.78) and over the complete follow-up period (HR 1.51, 95% CI 1.30-1.75). After adjustment for age alone there was no difference between sexes, in the composite outcome, at any of the specified time-points 30 days (HR 1.03, 95% CI 0.78-1.35), 1 year (HR 1.03, 95% CI 0.86-1.24) or complete follow-up (HR 1.06, 95% CI 0.91-1.24). Further adjustment for comorbid conditions including a history of diabetes, hypertension, HF, previous MI or PCI, and infarct type did not significantly change the results (Supplementary Table A2).

Similar results were obtained when the individual components of the primary outcome were analyzed separately. Death and HF occurred more often in women but there was no difference after adjustment for age (Supplementary Table A2; distribution of study population by age, sex, and outcomes, Supplementary Figure A6).

Table III. Clinical outcomes stratified by sex independent of randomized therapy (crude, adjusted for age, multivariable adjusted), up to 1,357 days after randomization

Outcomes	Women	Men	HR	*P* value
No.	1,388	3,622	(95% CI)	
Composite outcome of all-cause death or rehospitalization with MI or HF				
Crude, n (%)	274 (19.7)	487 (13.4)	1.51 (1.30-1.75)	<.001
Age adjusted			1.06 (0.91-1.24)	.43
Multiple adjusted*			1.08 (0.92-1.27)	.35
All-cause death				
Crude, n (%)	155 (11.2)	243 (6.7)	1.68 (1.38-2.06)	<.001
Age adjusted			0.99 (0.80-1.22)	.93
Multiple adjusted*			0.95 (0.76-1.19)	.68
Rehospitalization with MI				
Crude, n (%)	100 (7.2)	206 (5.7)	1.30 (1.02-1.65)	.03
Age adjusted			1.02 (0.80-1.30)	.89
Multiple adjusted*			1.14 (0.88-1.48)	.32
Rehospitalization for HF				
Crude, n (%)	71 (5.1)	119 (3.2)	1.57 (1.17-2.10)	.003
Age adjusted			1.12 (0.82-1.51)	.47
Multiple adjusted			1.15 (0.83-1.58)	.40
Cardiovascular death				
Crude, n (%)	105 (7.6)	153 (4.2)	1.81 (1.41-2.32)	<.001
Age adjusted			1.02 (0.79-1.31)	.90
Multiple adjusted*			1.01 (0.77-1.33)	.93

*Multiple adjustment included age, hypertension, diabetes, previous MI, previous PCI, previous HF, and infarct type.HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; HF, heart failure.

Discussion

In this analysis of a prespecified subgroup from the registry-based randomized DETO2X trial, comparing supplemental oxygen with ambient air in patients with MI, we found no difference in treatment effect between women and men in the composite outcome of all-cause mortality or rehospitalization with MI or HF. The results were consistent including the individual components of the composite outcome and cardiovascular mortality, also during short and median-term follow-up.

In the whole study population, irrespective of randomized treatment, women had a worse outcome compared to men. A finding that was explained by differences in baseline characteristics, especially age.

In agreement with previous studies,[6–9] women included in the DETO2X-AMI trial were older and more often had a history of hypertension and chronic kidney disease, while men more frequently had a history of MI, chronic obstructive pulmonary disease, or revascularization. Contrasting earlier reports, there was no difference in the rate of diabetes and men were more likely to have a history of HF. Moreover, in agreement with previous reports, women in this study had less obstructive coronary artery disease compared to men.[8] Previous studies have shown a higher incidence of cardiogenic shock in women with MI.[7,26-28] Although we could not confirm previously reported differences in Killip class or cardiogenic shock on arrival, more women than men experienced cardiogenic shock during the hospital stay and more women in the ambient air group developed hypoxemia. Major differences in characteristics between women and men with MI may indicate differences in pathophysiology and thereby possible differences in the effect of treatments. Despite these observed sex differences in characteristics, cardiogenic shock, and development of hypoxemia during the hospital stay, there was no difference in the effect of routine oxygen treatment between women and men regarding the composite outcome or any of the individual components including cardiovascular death. Over long-term follow-up, numerically more women than men allocated to ambient air vs oxygen were hospitalized with HF, but it did not reach statistical significance and there was no interaction in treatment effect according to sex.

Differences in microvascular dysfunction and ROS production between women and men have been reported.[16] This may be of special interest regarding oxygen therapy since previous studies have shown vessel constriction and increased peripheral resistance associated with oxygen therapy, and above-normal oxygen levels in the blood can cause coronary vasoconstriction and increase the production of ROS.[29-31] ROS production and microvascular dysfunction was not specifically addressed in this study, but if these factors were at play in this study population, it did not translate into a difference in treatment effect of oxygen therapy or infarct size estimated by cardiac troponin levels.

Irrespective of randomization group, the composite outcome occurred significantly more often in women than in men. The observed difference in unadjusted out-

come was mainly driven by higher mortality and rehospitalization for HF in women. However, after adjustment for age alone, the difference in the composite outcome was substantially attenuated and no longer significant. Also, after adjustment for age, there was no difference between women and men in any of the individual outcomes. Further adjustment for differences in comorbidities did not change the result, neither in the composite outcome nor in the individual components of the composite outcome. Most, but not all, previous studies have reported worse outcomes in women with MI compared with men. As in the present analysis, such differences have most often been explained by differences in age and comorbid conditions.[6,7,32-35]

General and conceptual limitations to the main study have been described in detail previously.[2] The results and conclusions of the present study are drawn from analyses of a prespecified subgroup and should be considered hypothesis-generating. The study sample is large, and the data quality very good concerning baseline characteristics and outcomes derived from compulsory national registries. Notwithstanding, some limitations merit consideration. First, even if the study population is large, this is a subgroup analysis and therefore, due to lack of statistical power, minor differences in the effect of oxygen treatment may have been undetected. Second, clinical and procedural endpoint data were obtained from SWEDEHEART and the Swedish National Population Registry and were not centrally adjudicated. However, all-cause mortality does not require adjudication, and register data are available with 99.5% completeness within a month.[23] Any degree of uncertainty in other non-adjudicated secondary outcome variables should be equally distributed over the two randomized arms. External validations of diagnoses in the patient registry have been published, with the very good concordance with individual patients' medical records.[18,25] Third, regarding our secondary aim, the comparison between women and men is, for obvious reasons, not randomized and unknown confounding cannot be excluded. However, adjustment for age alone completely abolished the observed difference in unadjusted comparisons.

Conclusions

Despite significant differences in baseline characteristics, including the prevalence of obstructive coronary artery disease, indicating possible differences in pathophysiological mechanisms between women and men with MI, there was no difference in the effect of routine oxygen treatment on all-cause mortality or rehospitalization with MI or HF.

The observed worse outcome in women was explained by differences in baseline characteristics, especially age.

Role of the Funder/Sponsor

The Swedish Research Council and the Swedish Heart-Lung Foundation had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Author Contributions

Drs Alfredsson and Hofmann had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Alfredsson, Östlund, Hofmann. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Alfredsson, Hofmann. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Alfredsson, Östlund, Hofmann. Obtained funding: Herlitz, Hofmann. Administrative, technical, or material support: Östlund, Hofmann. Supervision: Alfredsson, James, Östlund, Hofmann.

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Conflict of interest

No relationship with industry or conflict of interest relevant for this trial were reported.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.03.001.

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