Oxygen Therapy in Myocardial Infarction Patients With or Without Diabetes: A Predefined Subgroup Analysis From the DETO2X-AMI Trial

*Thomas Nyström,[1] Stefan K. James,[2,3] Bertil Lindahl,[2,3] Ollie Östlund,[3] David Erlinge,[4] Johan Herlitz,[5] Elmir Omerovic,[6] Linda Mellbin,[7] Joakim Alfredsson,[8] Ole Fröbert,[9] Tomas Jernberg,[10] and Robin Hofmann,[11] for the DETO2X-SWEDEHEART Investigators**

Diabetes Care 2019;42:2032–2041 | https://doi.org/10.2337/dc19-0590

OBJECTIVE

To determine the effects of oxygen therapy in myocardial infarction (MI) patients with and without diabetes.

RESEARCH DESIGN AND METHODS

In the Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction (DETO2X-AMI) trial, 6,629 normoxemic patients with suspected MI were randomized to oxygen at 6 L/min for 6–12 h or ambient air. In this prespecified analysis involving 5,010 patients with confirmed MI, 934 had known diabetes. Oxidative stress may be of particular importance in diabetes, and the primary objective was to study the effect of supplemental oxygen on the composite of all-cause death and rehospitalization with MI or heart failure (HF) at 1 year in patients with and without diabetes.

RESULTS

As expected, event rates were significantly higher in patients with diabetes compared with patients without diabetes (main composite end point: hazard ratio [HR] 1.60 [95% CI 1.32–1.93], $P < 0.01$). In patients with diabetes, the main composite end point occurred in 16.2% (72 of 445) allocated to oxygen as compared with 16.6% (81 of 489) allocated to ambient air (HR 0.93 [95% CI 0.67–1.27], $P = 0.81$). There was no statistically significant difference for the individual components of the composite end point or the rate of cardiovascular death up to 1 year. Likewise, corresponding end points in patients without diabetes were similar between the treatment groups.

CONCLUSIONS

Despite markedly higher event rates in patients with MI and diabetes, oxygen therapy did not significantly affect 1-year all-cause death, cardiovascular death, or rehospitalization with MI or HF, irrespective of underlying diabetes, in line with the results of the entire study.

Myocardial infarction (MI) is defined as myocardial cell death due to prolonged ischemia with a mismatch of substrate and oxygen supply and demand. For decades, guidelines (based on expert opinion) recommended supplemental oxygen as a cornerstone of supportive treatment to all MI patients (1). However, since the

[1]Division of Endocrinology, Department of Clinical Science and Education, Karolinska Institutet, Södersjukhuset, Stockholm, Sweden
[2]Cardiology, Department of Medical Sciences, Uppsala University, Uppsala, Sweden
[3]Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden
[4]Cardiology, Department of Clinical Sciences, Lund University, Lund, Sweden
[5]Department of Health Sciences, University of Borås, Borås, Sweden
[6]Department of Molecular and Clinical Medicine and Sahlgrenska University Hospital Department of Cardiology, University of Gothenburg, Gothenburg, Sweden
[7]Division of Cardiology, Department of Medicine, Solna, Karolinska Institutet, and Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden
[8]Department of Medical and Health Sciences and Department of Cardiology, Linköping University, Linköping, Sweden
[9]Department of Cardiology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
[10]Cardiology, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden
[11]Division of Cardiology, Department of Clinical Science and Education, Karolinska Institutet, Södersjukhuset, Stockholm, Sweden

Corresponding author: Robin Hofmann, robin.hofmann@sll.se

Received 25 March 2019 and accepted 29 June 2019

Clinical trial reg. no. NCT01787110, clinicaltrials.gov

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-0590/-/DC1.

**A complete list of the DETO2X-SWEDEHEART Investigators can be found in the Supplementary Data.*

See accompanying article, p. 2019.

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), updated guidelines no longer recommend routine oxygen therapy in normoxic patients with acute MI (3).

Even though a marked reduction in the incidence of cardiovascular complications and death among patients with diabetes recently was reported (4), the risk of cardiovascular complications in general, and MI in particular, remains very high (5,6). In patients with diabetes, coronary heart disease is a common cause of death, and the risk of MI is two- to fourfold higher than in patients without diabetes (4). Furthermore, patients with diabetes have worse outcomes after MI (7). This risk is further increased if glycemic control is poor (8).

Many conditions specific to the diabetic heart are important in the setting of MI. Patients with diabetes are predisposed to myocardial dysfunction due to previous silent infarction, myocardial fibrosis, endothelial dysfunction, cardiac autonomic neuropathy, and loss of metabolic flexibility (9–11). These predispositions may lead to increased myocardial oxygen demand in patients with diabetes, which may be alleviated by supplemental oxygen. On the other hand, above-normal oxygen levels in the blood can cause coronary vasoconstriction (12), increasing myocardial oxygen consumption, myocardial contractile dysfunction, and oxidative stress (13). Oxidative stress is suggested as one unifying mechanism for the increased risk of vascular complication in diabetes (14).

Consequently, the role of supplemental oxygen in MI patients with diabetes is controversial. The aim of this prespecified subgroup analysis was therefore to investigate the effect of oxygen therapy on all-cause mortality and rehospitalization with MI or heart failure (HF), among patients with and without diabetes and who had confirmed MI and no hypoxemia at baseline.

RESEARCH DESIGN AND METHODS

Study Design

The DETO2X-AMI trial was a nationwide, multicenter, open-label, registry-based randomized clinical trial (15) comparing routine supplemental oxygen therapy to ambient air in patients with suspected MI. The trial was based on the Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) (16) registry for patient recruitment, trial procedures, and follow-up.

The trial design (17), methods, and first results have been described in detail previously (2,18,19). The Regional Ethical Review Board in Gothenburg (DNR 287-12) and the Medical Products Agency of Sweden (EudraCT2013-002882-20) approved the study. The trial sponsor was Karolinska Institutet. Uppsala Clinical Research Center at Uppsala University was responsible for trial administration, data management, and statistical analyses and is running the SWEDEHEART registry.

Patient Population

At first medical contact with the ambulance service, emergency department, coronary care unit, or catheterization laboratory of participating hospitals, patients were evaluated for enrollment. Eligible patients had to be 30 years of age or older and to have symptoms suggestive of MI (chest pain or dyspnea) for $<$6 h, oxygen saturation of $\geq$90% on pulse oximetry, and either changes on electrocardiography (ECG) indicating ischemia (20) or elevated cardiac troponin on admission (above the locally defined decision limit for MI). Only Swedish residents with a unique personal identification number were enrolled to allow complete follow-up through the Swedish National Population Registry. Patients with ongoing oxygen therapy or cardiac arrest prior to enrollment were excluded.

The overall study population encompassed patients with suspected MI (n = 6,629), and the primary outcome all-cause death by diabetes status was already presented in the main publication (Supplementary Data); we found no interaction according to diabetes status (2). As one-fourth of the enrolled patients received other discharge diagnoses than acute MI, we focused in the current report on the pathophysiological risk-benefit controversy in the more defined population with confirmed MI (n = 5,010) with or without diabetes, which implies superior data completeness, including in most cases coronary angiography and intervention. Thus, for the present analysis, only patients with discharge diagnosis MI (both non–ST-segment elevation MI [NSTEMI] and ST-segment elevation MI [STEMI]) were included; all others were excluded. Thereafter, the study population was divided depending on randomized therapy (oxygen vs. ambient air) and diabetes status at admission, as recorded in SWEDEHEART (diabetes vs. no diabetes).

Study Procedures

After providing initial oral consent, patients who fulfilled all inclusion criteria and had no exclusion criteria were randomly assigned, in a 1:1 ratio, to either oxygen therapy at 6 L/min for 6–12 h delivered by open face mask or ambient air. Randomization was done by an online randomization module according to a computer-generated list within the SWEDEHEART database. The study treatment was initiated directly on site immediately after randomization.

The oral agreement to participate had to be confirmed by signature within 24 h. All patients were treated according to standard of care. Oxygen saturation was documented at the beginning and end of the randomized treatment period. If deemed clinically indicated by the caring physician, in particular in cases of hypoxemia (defined as oxygen saturation $<$90%) of any cause, patients received supplemental oxygen outside the protocol, which was reported separately.

End Points and Follow-up

The primary end point of the main trial was all-cause mortality in the intention-to-treat population with suspected MI (2). In this predefined subgroup analysis, the main end point was time from randomization to the composite of all-cause death or hospitalization with MI or HF, censored at 365 days, in the confirmed MI population with and without diabetes. Secondary end points included the individual components of the composite end point, as well as cardiovascular death, assessed at 365 days, in the MI populations with and without diabetes and testing for interactions between the groups.

Mortality data were obtained from the Swedish population registry, which includes the vital status of all Swedish residents with 99.5% completeness within a month (21). Data on rehospitalization with MI were obtained from the SWEDEHEART registry and defined according to ICD codes I21 and I22. Data on hospitalization for HF were obtained

from the Swedish National Patient Registry, including all ICD codes from all admissions in Sweden with high retention (22), and defined as ICD code I50. Data on cardiovascular death, defined as ICD codes I00–I99 or unclassified, were obtained from the Swedish National Cause-of-Death Registry.

Data on diabetes status were obtained from SWEDEHEART. Diabetes status at admission is one of the key background variables in an MI registration in SWEDEHEART. The information obtained includes data from patients and electronic health records, both for dietary-controlled and medically managed diabetes. The variable is mandatory, so completeness is very high. In our data set, the agreement with the National Patient Registry was >99%.

The end of follow-up was 30 December 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 locking of the database. Only authorized SWEDEHEART registry personnel had access to the randomization list. 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 (2,17). The present subgroup analysis was prespecified in the original statistical analysis plan, but no separate power calculation was performed. Thus, the results should be considered exploratory.

The results were analyzed according to the intention-to-treat principle. Time to event within 365 days is presented in Kaplan-Meier curves. Hazard ratios (HRs) between treatment groups were calculated using a Cox proportional hazards model, adjusted for age in years (as a linear covariate on the log-hazard scale) and sex, separately for diabetes and for no diabetes. Interaction of diabetes and treatment was assessed by adding diabetes and diabetes-treatment interaction to the analysis model. Estimates of treatment differences are presented with two-tailed 95% CIs and associated *P* values, for each subgroup, and the interaction *P* value from the interaction model. Analyses of diabetes versus no diabetes were performed using proportional hazards models, presented crude (model 1), adjusted for age and sex (model 2), and adjusted for age, sex, hypertension, smoking, BMI, and renal function (estimated glomerular filtration rate) (model 3), as the HR for diabetes versus no diabetes with 95% CIs and *P* values. The proportional hazards assumption was evaluated by visual inspection of Kaplan-Meier curves, by comparison of HRs with analyses censored at 30 and 365 days (crude and adjusted), and by inserting a time-treatment interaction term in the analysis model, and we found no evidence against proportionality. Data on the highest measured level of high-sensitive troponin T (hs-troponin T) concentration during hospitalization were analyzed using an unadjusted log-linear model with randomized treatment as a factor, for each subgroup separately, and interaction analyses including diabetes status and treatment-diabetes interaction in the model. Results are presented as the geometric mean ratios from the subgroup-specific analyses with 95% CI and *P* values and the interaction *P* value. The difference for diabetes versus no diabetes was analyzed with a log-linear model, with diabetes status as the only factor.

All analyses were conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC). A two-tailed *P* value of <0.05 was considered statistically significant.

RESULTS

Study Population

Of the 6,629 patients enrolled in the main trial, 5,010 (76%) had a discharge diagnosis of MI (2,952 [59%] with STEMI and 2,058 [41%] with NSTEMI) and were included in this analysis. At admission, 934 patients (19%) had diabetes (Supplementary Fig. 1).

In short, baseline characteristics and clinical presentation were similar between the treatment groups (oxygen vs. ambient air). However, when comparing patients with diabetes with patients without diabetes, patients with diabetes were older and had a higher BMI, higher rates of hypertension and previous cardiovascular disease, and more medications at baseline (antiplatelet therapy, β-blockers, statins, calcium blockers, ACE blockers, or angiotensin II blockers), but active smoking was less frequent. Clinically, patients with diabetes more frequently had elevated blood pressure, a higher heart rate, and pulmonary rales on admission (Table 1).

In total, 71% arrived by ambulance to the hospital; 31% (38% with diabetes vs. 29% without diabetes) were admitted to the emergency department and 40% (33% with diabetes vs. 41% without diabetes) directly to the coronary care unit or catheterization laboratory.

Overall, 4,807 (96%) patients were enrolled due to chest pain and 73 (1.5%) due to shortness of breath as the qualifying symptom (Table 1).

Procedural Data

At the time of randomization, the median oxygen saturation was 97.0% (interquartile range [IQR] 95.0–98.0) in all groups. Of all randomized patients with confirmed MI (*n* = 5,010), 2,485 were allocated to oxygen, which was initiated immediately after randomization, and 2,525 were allocated to ambient air. Of the 934 patients with diabetes, 445 were allocated to oxygen and 489 allocated to ambient air.

In patients with diabetes, in-hospital medication, trial and percutaneous coronary intervention (PCI) procedures, and complications were similar between the treatment groups (oxygen/ambient air), except for the rate of hypoxemia, which developed less frequently in the oxygen group (2.7% vs. 10.0%, $P < 0.001$), and the median oxygen saturation at the end of the treatment period (99.0% vs. 96.0%, $P < 0.001$). Similar results were found in patients without diabetes. Hypoxemia developed less frequently in the oxygen group (2.2% vs. 8.9%, $P < 0.001$), and the oxygen saturation at the end of treatment period was significantly higher (99.0% vs. 97.0%, $P < 0.001$) (Table 2).

When comparing patients with and without diabetes, we found that the duration from symptom onset and diagnostic ECG to randomization was significantly longer among patients with diabetes ($P < 0.001$) (Table 1). The median oxygen saturation at the end of the treatment period was 99.0% (IQR 97.0–100.0) in the oxygen group irrespective of diabetes status; however, in patients assigned to ambient air, patients with diabetes had a median oxygen saturation of 96.0% (IQR 95.0–98.0) as

Table 1—Baseline characteristics, clinical presentation, and MI type at discharge in the DETO2X-AMI diabetes substudy

	Diabetes (n = 934 [18.6%])		No diabetes (n = 4,076 [81.4%])		Total (n = 5,010 [100%])	
Characteristic	Oxygen (n = 445 [17.9%])	Ambient air (n = 489 [19.4%])	Oxygen (n = 2,040 [82.1%])	Ambient air (n = 2,036 [80.6%])	Diabetes (n = 934 [18.6%])	No diabetes (n = 4,076 [81.4%])
Demographics						
Age (years), median (IQR)†	70.0 (62.0–78.0)	70.0 (62.0–77.0)	68.0 (59.0–76.0)	68.0 (59.0–76.0)	70.0 (62.0–77.0)	68.0 (59.0–76.0)
Male sex, n (%)	316 (71.0)	350 (71.6)	1,458 (71.5)	1,498 (73.6)	666 (71.3)	2,956 (72.5)
Risk factors						
BMI†**	27.1 ± 4.4	29.1 ± 4.6	26.8 ± 4.1	26.7 ± 4.1	29.0 ± 4.8	26.7 ± 4.1
Current smoking, n (%)†	704 (21.3)	102 (20.9)	508 (24.9)	511 (25.1)	180 (19.3)	1,019 (25.0)
Previous CV disease, n (%)						
Hypertension†	1,575 (47.6)	335 (68.5)	867 (42.5)	854 (41.9)	637 (68.2)	1,721 (42.2)
MI†	151 (33.9)	159 (32.5)	295 (14.5)	290 (14.2)	310 (33.2)	585 (14.4)
PCI†	107 (24.0)	137 (28.0)	229 (11.2)	221 (10.9)	244 (26.1)	450 (11.0)
CABG†	57 (12.8)	41 (8.4)	79 (3.9)	85 (4.2)	98 (10.5)	164 (4.0)
HF (EF ≤50%)†	56 (12.6)	56 (11.5)	118 (5.8)	145 (7.1)	112 (12.0)	263 (6.5)
Stroke†	50 (11.2)	36 (7.4)	76 (3.7)	73 (3.6)	86 (9.2)	149 (3.7)
PAD†	42 (9.4)	33 (6.7)	70 (3.4)	66 (3.2)	75 (8)	136 (3.3)
Causes of admission, n (%)						
Chest pain	428 (96.2)	459 (93.9)	1,959 (96.0)	1,961 (96.3)	887 (95.0)	3,920 (96.2)
Dyspnea	6 (1.3)	15 (3.1)	22 (1.1)	30 (1.5)	21 (2.2)	52 (1.3)
Medication on admission, n (%)						
Aspirin†	192 (43.1)	213 (43.6)	420 (20.6)	444 (21.8)	405 (43.4)	864 (21.2)
P2Y12 receptor inhibitors†	46 (10.3)	42 (8.6)	67 (3.3)	66 (3.2)	88 (9.4)	133 (3.3)
β-Blockers†	214 (48.1)	234 (47.9)	481 (23.6)	487 (23.9)	448 (48.8)	968 (23.7)
Statins†	223 (50.1)	247 (50.5)	368 (18.0)	370 (18.2)	470 (50.3)	738 (18.1)
ACE or AT II blockers†	253 (56.9)	295 (60.3)	597 (29.3)	590 (29.0)	548 (58.7)	1,187 (29.1)
Calcium blockers†	137 (30.8)	153 (31.3)	315 (15.4)	311 (15.3)	290 (31.0)	626 (15.4)
Diuretics†	122 (27.4)	115 (23.5)	232 (11.4)	229 (11.2)	237 (25.4)	461 (11.3)
Presentation						
Time from symptom onset to randomization, minutes, median (IQR)†	284.0 (160–500)	255.0 (142–468)	220.0 (120–405)	227.0 (120–420)	265.0 (149–483)	222.0 (120–410)
Time from diagnostic ECG to randomization, minutes, median (IQR)†	65.0 (29–128)	67.0 (32–137)	55.0 (25–101)	54.0 (27–105)	66.0 (30–130)	55.0 (26–103)
Ambulance to emergency department, n (%)†	169 (38.0)	187 (37.6)	602 (29.5)	578 (28.4)	353 (37.8)	1,180 (28.9)
Ambulance to coronary care unit or catheterization laboratory, n (%)†	144 (32.4)	162 (33.1)	837 (41.0)	840 (41.3)	306 (32.8)	1,677 (41.1)
Systolic blood pressure (mmHg)†	151.5 ± 25.7	151.6 ± 27.3	150.1 ± 28.5	147.9 ± 28.0	151.6 ± 26.5	149.0 ± 28.3
Heart rate (bpm)†	82.7 ± 19.3	82.1 ± 18.9	76.6 ± 17.9	76.0 ± 17.9	82.4 ± 19.1	76.3 ± 17.9
Rales, n (%)†	17 (3.8)	27 (5.6)	64 (3.1)	53 (2.6)	44 (4.7)	117 (2.9)
Oxygen saturation (%), median (IQR)	97 (95–98)	97 (95–98)	97 (95–98)	97 (95–98)	97 (95–98)	97 (95–98)
Discharge MI type, n (%)						
NSTEMI†	223 (50.1)	241 (49.3)	831 (40.7)	763 (37.5)	464 (49.7)	1,594 (39.1)
STEMI†	222 (49.9)	248 (50.7)	1,209 (59.3)	1,273 (62.5)	470 (50.3)	2,482 (60.9)

Data are means ± SD unless otherwise indicated. There were no significant differences in baseline characteristics between oxygen group and the ambient air group except as otherwise noted. AT II, angiotensin II; bpm, beats per minute; CABG, coronary-arterial bypass graft; CV, cardiovascular; EF, ejection fraction; PAD, peripheral artery disease. †$P < 0.05$ for the comparison between the group with diabetes and the group without diabetes. **BMI = weight in kilograms divided by the square of the height in meters.

compared with 97.0% (IQR 95.0–98.0) in patients without diabetes (P = 0.013). More angiography and PCI procedures were performed in patients without diabetes ($P < 0.001$), and even the rate of acute coronary-arterial bypass graft was higher. The group with diabetes frequently received more treatment for acute HF (i.v. diuretics and nitroglycerin) ($P < 0.005$), but the rates of in-hospital complications (reinfarction, new-onset atrial fibrillation, atrioventricular block grade II or III, cardiogenic shock, cardiac arrest, and death) were similar between groups (Table 2).

As expected, patients with diabetes had higher plasma glucose levels at admission compared with patients without diabetes (10.7 vs. 6.7 mmol/L), reflected also in deteriorated long-term glycemic control assessed by HbA_{1c} in a subgroup of patients (IFCC: 59.0 vs. 38.0 mmol/mol; NGSP: 7.5% vs. 5.6%) ($P < 0.001$).

Clinical End Points

Patients With Diabetes

The incidence of the composite of all-cause death, rehospitalization with MI, or

Table 2—In-hospital procedural data, medication, procedures, and complications

	Diabetes (n = 934 [18.6%])		No diabetes (n = 4,076 [81.4%])		Total (n = 5,010 [100%])	
Variable	Oxygen (n = 445 [17.9%])	Ambient air (n = 489 [19.4%])	Oxygen (n = 2,040 [82.1%])	Ambient air (n = 2,036 [80.6%])	Diabetes (n = 934 [18.6%])	No diabetes (n = 4,076 [81.4%])
Duration of oxygen therapy (h), median (IQR)	11.62 (6.0–12.0)	—	11.72 (6.0–12.0)	—	—	—
Hypoxemia, *n* (%)	12 (2.7)	49 (10.0)	45 (2.2)	182 (8.9)	61 (6.5)	227 (5.6)
Oxygen saturation at end of treatment period (%), median (IQR)†	99.0 (97–100)	96.0 (95–98)	99.0 (97–100)	97.0 (95–98)	97.0 (96–99)	98.0 (96–99)
Laboratory measures						
hs-troponin T (ng/L), median (IQR)†	664.0 (170–2,387)	758.0 (140–2,541)	1,000.0 (276–2,981)	1,013.0 (249–3,030)	724.0 (154–2,450)	1,000.0 (261–2,990)
Plasma glucose (mmol/L), median (IQR)†**	10.4 (8.1–13.9)	10.9 (8.3–14.2)	6.8 (5.9–8.1)	6.7 (5.9–8.0)	10.7 (8.2–14.1)	6.7 (5.9–8.0)
HbA_{1c}†***						
IFCC (mmol/mol), median (IQR)	57.1 (49.0–73.0)	60.0 (49.0–74.0)	38.0 (35.0–41.0)	38.0 (36.0–41.5)	59.0 (49.0–73.0)	38.0 (35.0–41.0)
NGSP (%), median (IQR)	7.4 (6.6–8.8)	7.6 (6.6–8.9)	5.6 (5.4–5.9)	5.6 (5.4–5.9)	7.5 (6.6–8.8)	5.6 (5.4–5.9)
Estimated glomerular filtration rate CKD-EPI†	74.3 ± 19.5	74.5 ± 24.0	80.2 ± 19.5	79.6 ± 19.6	74.4 ± 23.8	79.0 ± 19.6
Hb (g/L)†	137.14 ± 17.20	136.45 ± 17.67	140.78 ± 16.34	141.06 ± 16.12	136.78 ± 17.44	140.92 ± 16.23
CRP (mg/L), median (IQR)†	5.00 (2.0–9.0)	4.00 (2.0–9.2)	3.4 (1.1–8.0)	4.00 (1.4–8.0)	4.75 (2.0–9.0)	3.80 (1.3–8.0)
Procedures, *n* (%)						
Coronary angiography†	413 (92.8)	455 (93.0)	1,939 (95.0)	1,958 (96.2)	868 (92.9)	3,897 (95.6)
Single-vessel disease†	141 (31.7)	165 (33.7)	942 (46.2)	947 (46.5)	306 (32.8)	1,889 (46.3)
Multivessel disease†	251 (56.4)	270 (55.2)	892 (43.7)	915 (44.9)	521 (55.8)	1,807 (44.3)
PCI†	349 (78.4)	395 (80.8)	1,731 (84.9)	1,753 (86.1)	744 (79.7)	3,484 (85.5)
CABG	26 (5.8)	27 (5.5)	84 (4.1)	95 (4.7)	53 (5.7)	179 (4.4)
Hospital stay (days), median (min–max)†	4.0 (0–22)	3.0 (0–95)	3.0 (0–68)	3.0 (0–71)	4.0 (0–95)	3.0 (0–71)
Medication, *n* (%)						
I.v. diuretics†	59 (13.3)	68 (13.9)	194 (9.5)	194 (9.5)	127 (13.6)	388 (9.5)
I.v. inotropes	14 (3.1)	10 (2.0)	30 (1.5)	54 (2.7)	24 (2.6)	84 (2.1)
I.v. nitroglycerin†	47 (10.6)	50 (10.2)	163 (8.0)	148 (7.3)	97 (10.4)	311 (7.6)
Aspirin†	402 (90.3)	452 (92.4)	1,912 (93.7)	1,929 (94.7)	854 (91.4)	3,841 (94.2)
P2Y12 blockers†	391 (87.9)	439 (89.8)	1,868 (91.6)	1,848 (90.8)	830 (88.9)	3,713 (91.1)
β-Blockers†	409 (91.9)	453 (92.6)	1,803 (88.4)	1,829 (89.8)	862 (92.3)	3,632 (89.1)
Statin	415 (93.3)	454 (92.8)	1,917 (94.0)	1,906 (93.6)	869 (93.0)	3,823 (93.8)
ACE inhibitors or ARBs†	395 (88.8)	437 (89.4)	1,738 (85.2)	1,680 (82.5)	832 (89.1)	3,418 (83.9)
Calcium blockers†	118 (26.5)	130 (26.6)	219 (10.7)	232 (11.4)	248 (26.6)	451 (11.1)
Diuretics†	134 (30.1)	143 (29.2)	282 (13.8)	280 (13.8)	277 (29.7)	562 (13.8)
Anticoagulation†	61 (13.7)	61 (12.5)	179 (8.8)	174 (8.5)	122 (13.1)	353 (8.7)
Complications, *n* (%)						
Reinfarction	2 (0.4)	1 (0.2)	13 (0.6)	12 (0.6)	3 (0.3)	25 (0.6)
New-onset atrial fibrillation	10 (2.2)	15 (3.1)	72 (3.5)	69 (3.4)	25 (2.7)	141 (3.5)
Atrioventricular block II or III	10 (2.2)	12 (2.5)	33 (1.6)	39 (1.9)	22 (2.4)	72 (1.8)
Cardiogenic shock	6 (1.3)	1 (0.2)	23 (1.1)	34 (1.7)	7 (0.7)	57 (1.4)
Cardiac arrest	14 (3.1)	7 (1.4)	58 (2.8)	51 (2.5)	21 (2.2)	109 (2.7)
Death	13 (2.9)	7 (1.4)	36 (1.8)	33 (1.6)	20 (2.1)	69 (1.7)

Data are means ± SD unless otherwise indicated. ARB, angiotensin receptor blocker; CABG, coronary-arterial bypass graft; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Hb, hemoglobin. **Plasma glucose on admission, or first available measurement. Available data in 88.3% of patients with diabetes, 86.3% of patients without diabetes. ***HbA_{1c} was only available in 28.4% of patients with diabetes and 22.7% without diabetes. †$P < 0.05$ for the comparison between the group with diabetes and the group without diabetes.

rehospitalization for HF at 1 year was 16.2% (72 of 445) in patients allocated to oxygen compared with 16.6% (81 of 489) in patients allocated to ambient air (HR 0.95 [95% CI 0.69–1.30], P = 0.74) (Fig. 1*A* and Table 3).

The rate of death from any cause was 7.2% vs. 7.2% in the two groups (oxygen/ambient air), respectively (HR 0.97 [95%

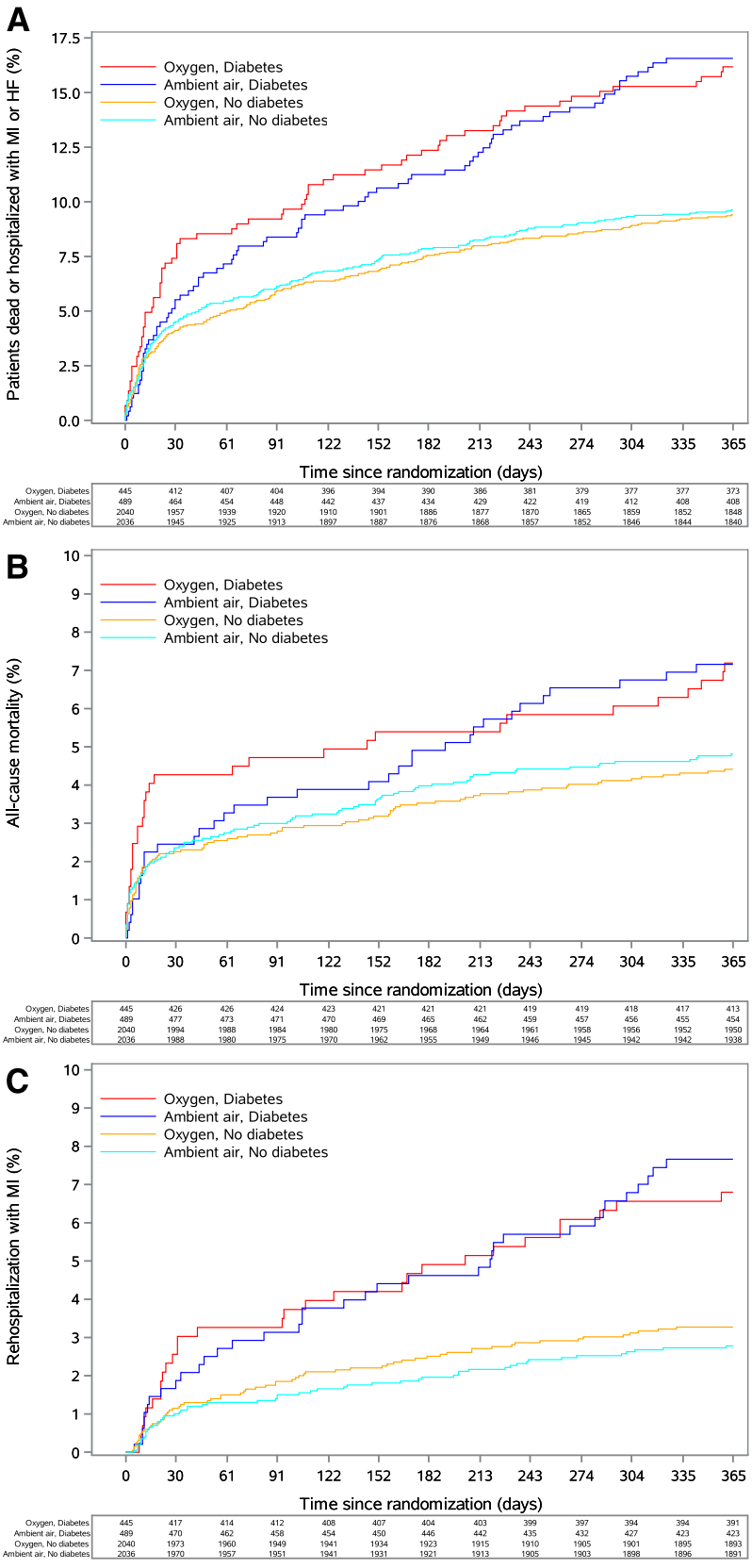

Figure 1—Kaplan-Meier curves are shown for the cumulative probability of the composite end point of all-cause death, rehospitalization with MI, or rehospitalization for HF (*A*) and the individual end points of all-cause mortality (*B*), rehospitalization with MI (*C*), and rehospitalization for HF (*D*), up to 365 days after randomization for patients with or without diabetes assigned to oxygen or ambient air.

CI 0.60–1.56], P = 0.89); the rate of rehospitalization with MI was 6.5% vs. 7.4%, respectively (HR 0.85 [95% CI 0.52–1.39], P = 0.53); the rate of rehospitalization for HF was 4.9% vs. 4.1%, respectively (HR 1.19 [95% CI 0.65–2.18], P = 0.58); and the rate of cardiovascular death was 6.1% vs. 4.1%, respectively (HR 1.44 [95% CI 0.80–2.56], P = 0.22) (Fig. 1*B–D* and Table 3). Data on the highest measured level of cardiac hs-troponin T showed no significant difference between the treatment groups (Table 3).

Patients Without Diabetes

The incidence of the composite of all-cause death, rehospitalization with MI, or rehospitalization for HF at 1 year was 9.4% (192 of 2,040) in the patients allocated to oxygen compared with 9.6% (196 of 2,036) in patients allocated to ambient air (HR 0.96 [95% CI 0.79–1.18], P = 0.71) (Fig. 1*A* and Table 3).

The rate of death from any cause was 4.4% vs. 4.8% in the two groups (oxygen/ambient air), respectively (HR 0.90 [95% CI 0.67–1.19], P = 0.46); the rate of rehospitalization with MI was 3.2% vs. 2.7% (HR 1.18 [95% CI 0.82–1.69], P = 0.37); the rate of rehospitalization for HF was 2.7% vs. 3.2% (HR 0.84 [95% CI 0.59–1.21], P = 0.36); and the rate of cardiovascular death was 3.4% vs. 3.7% (HR 0.91 [95% CI 0.65–1.26], P = 0.56) (Fig. 1*B–D* and Table 3). Data on the highest measured level of cardiac hs-troponin T showed no significant difference between the treatment groups (Table 3).

Within 365 days, no significant interaction between the treatment groups and diabetes status on the respective end points was found. Numerically, patients with diabetes in the oxygen group suffered more often from in-hospital cardiac arrest, and all-cause death and rehospitalization with MI within 30 days, similarly, but without statistically significant difference (Table 3).

Patients with diabetes had significantly higher event rates concerning the main composite end point as compared with patients without known diabetes at admission (HR model 1: 1.77 [95% CI 1.47–2.13], $P < 0.001$; HR model 2: 1.60 [95% CI 1.32–1.93], $P < 0.001$; HR model 3: 1.53 [95% CI 1.24–1.88], $P < 0.001$). Similar results were found for

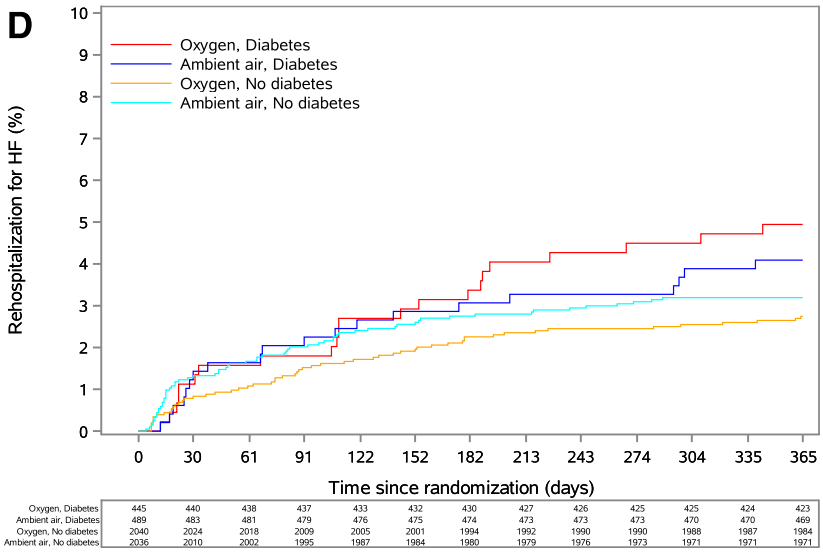

Figure 1—(Continued.)

the secondary end points all-cause death (HR model 1: 1.57 [95% CI 1.19–2.07], P = 0.002; HR model 2: 1.43 [95% CI 1.08–1.89], P = 0.01; HR model 3: 1.48 [95% CI 1.08–2.02], P = 0.02) and rehospitalization for MI (HR model 1: 2.43 [95% CI 1.80–3.29], $P < 0.001$; HR model 2: 2.24 [95% CI 1.66–3.03], $P < 0.001$; HR model 3: 2.01 [95% CI 1.42–2.84], $P < 0.001$). However, when addressing the secondary end points rehospitalization with HF (HR model 1: 1.52 [95% CI 1.07–2.16], P = 0.02; HR model 2: 1.39 [95% CI 0.98–1.98], P = 0.06; HR model 3: 1.21 [95% CI 0.82–1.80], P = 0.33) and cardiovascular death (HR model 1: 1.43 [95% CI 1.03–1.98], P = 0.03; HR model 2: 1.30 [95% CI 0.94–1.81], P = 0.12; HR model 3: 1.27 [95% CI 0.87–1.85], P = 0.21), the association was only significant in the crude analysis. After adjusting for age and sex, or other cofactors, the association was no longer significant.

CONCLUSIONS

In this prespecified subgroup analysis of the DETO2X trial, a registry-based randomized clinical trial of supplemental oxygen or ambient air in MI patients with or without diabetes, we found no significant treatment effect on the rate of the composite end point of all-cause death and rehospitalization with MI or HF. Nor was there any difference for the individual components of the composite end point between the randomized groups. However, during 1-year follow-up, we observed a 60% increased relative risk of the composite end point in patients with diabetes, compared with patients without diabetes, irrespective of treatment group.

Effect of Supplemental Oxygen in Patients With or Without Diabetes

Historically, supplemental oxygen has been used routinely in the treatment of patients with MI based on the rationale that oxygen therapy increases oxygen delivery to the ischemic myocardium and thereby reduces infarct size and subsequent complications (23).

This practice may seem especially appealing in patients with diabetes when considering certain conditions specific to the diabetic heart, such as previous silent infarction, cardiac autonomic neuropathy, hypertension resulting in cardiac fibrosis, endothelial dysfunction leading to impaired coronary perfusion at the microvascular level, and metabolic perturbations caused by high adrenergic-mediated levels of free fatty acids (9,10,24). These maladaptations characterize diabetic cardiomyopathy and may lead to myocardial dysfunction on different levels, including myocardial oxygen uptake and consumption. However, in the current study, supplemental oxygen in MI patients with diabetes was not beneficial compared with ambient air. Numerically, patients with diabetes in the oxygen group suffered more often from in-hospital cardiac arrest, and all-cause death and rehospitalization with MI within 30 days, but statistically the neutral findings were consistent in the short-term regarding the rate of in-hospital complications as well as myocardial injury assessed by cardiac hs-troponin T and overall regarding all-cause or cardiovascular mortality and rehospitalization with MI or HF.

These results may be especially important pertaining to potential harm caused by supplemental oxygen in patients with diabetes. Acute MI leads to metabolic stress, and the concept of providing maximal metabolic support to injured myocardial cells in patients with diabetes and MI is of great interest (9,25). Metabolic flexibility, the ability of the heart to adapt to environmental changes by switching substrate from fatty acids to carbohydrates, is impaired in diabetes, which further deteriorates normal cardiac metabolism and enhances hyperglycemia (11). The latter causes excessive formation of reactive oxygen species and enhances the inflammatory response to MI (14), which may be further enhanced by oxygen therapy (26). Several theories have been put forward to explain the association between hyperglycemia and the excess risk of cardiovascular disease in diabetes. One central mechanism raised by Brownlee (14) suggests cellular oxidative stress as the clinical correlation linking diabetes with accelerated atherosclerosis, cardiomyopathy, and increased post-MI fatality. In an experimental setting, oxidative stress may even be induced by oxygen supplementation and be harmful for the heart (27). Previous studies have demonstrated an increased production of reactive oxygen species in patients with diabetes, further exaggerated by supplemental oxygen, which may cause uncoupling of key enzymes important for the vasculature and the heart (28). It was also recently questioned whether supplemental oxygen in normoxic patients potentially leads to a worse outcome in a stressed situation, such as acute MI (12). However, our study did not demonstrate any detrimental effects from supplemental oxygen, compared with ambient air, in patients with diabetes and acute MI. Nevertheless, it is important to bear in mind that reported event rates were small and underpowered to identify a statistical difference with certainty. Future studies with much larger sample sizes are required to clarify this issue.

Table 3—End points according to treatment group and randomization status at 365 days and 30 days after randomization

	Diabetes (n = 934 [18.6%])				No diabetes (n = 4,076 [81.4%])				Total (n = 5,010 [100%])		
End point	Oxygen (n = 445 [17.9%])	Ambient air (n = 489 [19.4%])	HR (95% CI), P value		Oxygen (n = 2,040 [82.1%])	Ambient air (n = 2,036 [80.6%])	HR (95% CI), P value	Interaction oxygen vs. ambient air	Diabetes (n = 934 [18.6%])	No diabetes (n = 4,076 [81.4%])	HR (95% CI), P value
365 days, n (%)											
Composite of all-cause death and rehospitalization with MI or HF	72 (16.2)	81 (16.6)	0.95 (0.69–1.30), P = 0.74		192 (9.4)	196 (9.6)	0.96 (0.79–1.18), P = 0.71	0.81	153 (16.4)	388 (9.5)	1.53 (1.24–1.88), P < 0.01
All-cause death	32 (7.2)	35 (7.2)	0.97 (0.60–1.56), P = 0.89		90 (4.4)	98 (4.8)	0.90 (0.67–1.19), P = 0.46	0.85	67 (7.2)	188 (4.6)	1.48 (1.08–2.02), P = 0.01
Rehospitalization with MI	29 (6.5)	36 (7.4)	0.85 (0.52–1.39), P = 0.53		65 (3.2)	55 (2.7)	1.18 (0.82–1.69), P = 0.37	0.28	65 (7.0)	120 (2.9)	2.01 (1.42–2.84), P < 0.01
Rehospitalization for HF	22 (4.9)	20 (4.1)	1.19 (0.65–2.18), P = 0.58		56 (2.7)	65 (3.2)	0.84 (0.59–1.21), P = 0.36	0.40	42 (4.5)	121 (3.0)	1.21 (0.82–1.80), P = 0.33
Cardiovascular death	27 (6.1)	20 (4.1)	1.44 (0.80–2.56), P = 0.22		70 (3.4)	75 (3.7)	0.91 (0.65–1.26), P = 0.56	0.21	47 (5.0)	145 (3.6)	1.27 (0.87–1.85), P = 0.21
30 days, n (%)											
Composite of all-cause death and rehospitalization with MI or HF	33 (7.4)	27 (5.5)	1.33 (0.80–2.21), P = 0.27		84 (4.1)	92 (4.5)	0.89 (0.66–1.20), P = 0.44	0.23	60 (6.4)	176 (4.3)	1.31 (0.95–1.82), P = 0.10
All-cause death	19 (4.3)	12 (2.5)	1.69 (0.82–3.48), P = 0.16		46 (2.3)	48 (2.4)	0.93 (0.62–1.39), P = 0.72	0.18	31 (3.3)	94 (2.3)	1.38 (0.87–2.19), P = 0.17
Rehospitalization with MI	11 (2.5)	9 (1.8)	1.33 (0.55–3.21), P = 0.53		23 (1.1)	20 (1.0)	1.15 (0.63–2.10), P = 0.65	0.81	20 (2.1)	43 (1.1)	1.74 (0.97–3.10), P = 0.06
Rehospitalization for HF	5 (1.1)	7 (1.4)	0.79 (0.25–2.49), P = 0.69		17 (0.8)	27 (1.3)	0.62 (0.34–1.14), P = 0.12	0.80	12 (1.3)	44 (1.1)	0.87 (0.44–1.75), P = 0.70
Cardiovascular death	17 (3.8)	11 (2.2)	1.65 (0.77–3.53), P = 0.19		43 (2.1)	46 (2.3)	0.90 (0.60–1.37), P = 0.64	0.20	28 (3.0)	89 (2.2)	1.32 (0.81–2.15), P = 0.26

Comparison Between Patients With or Without Diabetes Irrespective of Treatment Group

About 20% of the enrolled subjects in the main DETO2X-AMI trial had diagnosed diabetes at admission (2). This proportion is in line with figures reported in other large randomized controlled trials in the field and confirms the high incidence and prevalence of cardiovascular disease in people with diabetes (29,30). During the last two decades, a significant decline in cardiovascular complications in patients with and without diabetes has been observed (4). Despite this, a wealth of observational studies still demonstrate a much higher risk of cardiovascular complications in patients with diabetes (5,6). Similarly, in the current study, patients with diabetes were at 60% relative higher risk of death or rehospitalization with MI or HF compared with patients without diabetes. For the single estimates and after adjustments, there was a 40% relative increased risk of all-cause death, followed by a twofold increased risk of recurrent MI, in patients with diabetes compared with patients without diabetes.

Various aspects may be of importance to explain these findings. In the current study, patients with diabetes were more often diagnosed with vascular comorbidities prior to MI, which may be a major contributing factor. Moreover, time from symptom onset and diagnostic ECG to suspected MI diagnosis (in the trial time point of randomization) was significantly longer in patients with diabetes. In this context, we found significantly more often clinical signs of HF leading to more frequent use of i.v. diuretics and nitroglycerin. Additionally, patients with diabetes arrived more often by ambulance but presented less frequently with STEMI. Consequently, they were less often directly referred for acute PCI, a factor clearly associated with worse prognosis (31).

The angiopathic process is aggravated in patients with diabetes and more often diffusely distributed in the coronary arteries (32), which was confirmed in our trial where patients with diabetes more commonly had multivessel coronary artery disease. One mechanistic explanation for this may be due to the exposure of hyperglycemia (14), inducing oxidative stress

(14), inflammation, and endothelial dysfunction (9). Chronic hyperglycemia is an important modifiable risk factor for long-term complications in diabetes (33,34). However, controversy remains: some studies have demonstrated beneficial action on cardiovascular risk by lowering blood glucose (33,35), whereas others could not confirm these results (36,37).

Strengths and Limitations

General and conceptual limitations to the main study have been described in detail previously (2). The results and conclusions of the current study are drawn from a prespecified subgroup analysis without formal power calculation and should be considered hypothesis generating. Several limitations merit consideration. It is well known that patients with diabetes are more prone to silent MI, which we were unable to account for, both at baseline and during follow-up. As neither plasma glucose nor HbA_{1c} are mandatory variables in SWEDEHEART, the data provided are unfortunately incomplete, which greatly reduces information on glycemic control in the study population. Moreover, we had no information on diabetes duration, type of diabetes, or detailed information on antihyperglycemic medication, which is of great importance regarding new drugs and cardiovascular complications (38). For our secondary objective, this may be of minor importance since our aim was to compare patients with or without diabetes. For our primary end point, this may have been of greater significance because diabetes duration, glycemic control, and types of diabetes are all risk factors for our outcome of interest. Additionally, in previous studies, up to 30% of MI patients may have undiagnosed diabetes at presentation (39), which reduces the discriminatory power of our analysis. Consequently, the true underlying difference between patients with and without diabetes is even greater than observed in our trial.

Conclusion

Consistent with the main trial, we were not able to demonstrate a beneficial effect of routine oxygen therapy in normoxemic MI patients with respect to all-cause death, cardiovascular death, or rehospitalization with MI or HF at 1 year, irrespective of underlying diabetes. Thus, it seems reasonable and safe to withhold routine supplemental oxygen even in patients with MI and diabetes, which goes well in line with current guidelines (3). Noteworthy, even though the incidence of cardiovascular outcomes generally has declined substantially over the last decades, we still observed markedly increased event rates in patients with diabetes.

Acknowledgments. The authors thank the staff at all centers participating in the DETO2X collaboration for their professionalism and commitment to this study. The authors are grateful for the assistance from personnel at Uppsala Clinical Research Center, Uppsala University, on all matters of the trial.

Funding. This work was supported by the Swedish Research Council (grant VR20130307) and the Swedish Heart-Lung Foundation (grants HLF20130262 and HLF20160688). O.Ö. and R.H. report grants from the Swedish Research Council and the Swedish Heart-Lung Foundation. R.H. was supported by the Stockholm County Council (clinical postdoctoral appointment).

The funding agencies had no access to the study data and no role in trial design, implementation, or reporting.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. T.N., S.K.J., T.J., and R.H. researched and analyzed data, wrote the first version of the manuscript, reviewed and revised the manuscript, and wrote the final version. B.L., O.Ö., D.E. J.H., E.O., L.M., J.A., and O.F. researched and analyzed data, contributed to the discussion, and reviewed and edited the manuscript. T.N. and R.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. This study was the subject of an oral presentation at the European Society of Cardiology Congress, Paris, France, 31 August to 4 September 2019.

References

1. Loscalzo J. Is oxygen therapy beneficial in acute myocardial infarction? Simple question, complicated mechanism, simple answer. N Engl J Med 2017;377:1286–1287
2. Hofmann R, James SK, Jernberg T, et al.; DETO2X–SWEDEHEART Investigators. Oxygen therapy in suspected acute myocardial infarction. N Engl J Med 2017;377:1240–1249
3. Ibanez B, James S, Agewall S, et al.; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119–177
4. Rawshani A, Rawshani A, Franzén S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med 2017;376:1407–1418
5. Lind M, Svensson AM, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med 2014;371:1972–1982
6. Tancredi M, Rosengren A, Svensson AM, et al. Excess mortality among persons with type 2 diabetes. N Engl J Med 2015;373:1720–1732
7. Norhammar A, Mellbin L, Cosentino F. Diabetes: prevalence, prognosis and management of a potent cardiovascular risk factor. Eur J Prev Cardiol 2017;24(3_Suppl.):52–60
8. Matuleviciene-Anängen V, Rosengren A, Svensson AM, et al. Glycaemic control and excess risk of major coronary events in persons with type 1 diabetes. Heart 2017;103:1687–1695
9. Opie LH. Metabolic management of acute myocardial infarction comes to the fore and extends beyond control of hyperglycemia. Circulation 2008;117:2172–2177
10. Nesto RW, Zarich S. Acute myocardial infarction in diabetes mellitus: lessons learned from ACE inhibition. Circulation 1998;97:12–15
11. Taegtmeyer H, Golfman L, Sharma S, Razeghi P, van Arsdall M. Linking gene expression to function: metabolic flexibility in the normal and diseased heart. Ann N Y Acad Sci 2004;1015:202–213
12. Moradkhan R, Sinoway LI. Revisiting the role of oxygen therapy in cardiac patients. J Am Coll Cardiol 2010;56:1013–1016
13. Zweier JL, Talukder MA. The role of oxidants and free radicals in reperfusion injury. Cardiovasc Res 2006;70:181–190
14. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001;414:813–820
15. Yndigegn T, Hofmann R, Jernberg T, Gale CP. Registry-based randomised clinical trial: efficient evaluation of generic pharmacotherapies in the contemporary era. Heart 2018;104:1562–1567
16. Jernberg T, Attebring MF, Hambraeus K, et al. The Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). Heart 2010;96:1617–1621
17. Hofmann R, James SK, Svensson L, et al. Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction trial. Am Heart J 2014;167:322–328
18. Hofmann R, Witt N, Lagerqvist B, et al.; DETO2X-SWEDEHEART Investigators. Oxygen therapy in ST-elevation myocardial infarction. Eur Heart J 2018;39:2730–2739
19. Jernberg T, Lindahl B, Alfredsson J, et al.; DETO2X-SWEDEHEART Investigators. Long-term effects of oxygen therapy on death or hospitalization for heart failure in patients with suspected acute myocardial infarction. Circulation 2018;138:2754–2762
20. Thygesen K, Alpert JS, Jaffe AS, et al.; Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction; ESC Committee for Practice Guidelines (CPG). Third universal definition of myocardial infarction. Eur Heart J 2012;33:2551–2567
21. Ludvigsson JF, Almqvist C, Bonamy AK, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol 2016;31:125–136

22. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450
23. Shuvy M, Atar D, Gabriel Steg P, et al. Oxygen therapy in acute coronary syndrome: are the benefits worth the risk? Eur Heart J 2013;34:1630–1635
24. Peterson LR, Gropler RJ. Radionuclide imaging of myocardial metabolism. Circ Cardiovasc Imaging 2010;3:211–222
25. Vogelzang M, Zijlstra F. Glucose metabolism and acute myocardial infarction. Eur Heart J 2006;27:1264–1265
26. Rodríguez-González R, Martín-Barrasa JL, Ramos-Nuez Á, et al. Multiple system organ response induced by hyperoxia in a clinically relevant animal model of sepsis. Shock 2014;42:148–153
27. Rodgers JL, Samal E, Mohapatra S, Panguluri SK. Hyperoxia-induced cardiotoxicity and ventricular remodeling in type-II diabetes mice. Heart Vessels 2018;33:561–572
28. Faria A, Persaud SJ. Cardiac oxidative stress in diabetes: mechanisms and therapeutic potential. Pharmacol Ther 2017;172:50–62
29. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990-2010. N Engl J Med 2014;370:1514–1523
30. Norhammar A, Bodegård J, Nyström T, Thuresson M, Eriksson JW, Nathanson D. Incidence, prevalence and mortality of type 2 diabetes requiring glucose-lowering treatment, and associated risks of cardiovascular complications: a nationwide study in Sweden, 2006-2013. Diabetologia 2016;59:1692–1701
31. Scholz KH, Maier SKG, Maier LS, et al. Impact of treatment delay on mortality in ST-segment elevation myocardial infarction (STEMI) patients presenting with and without haemodynamic instability: results from the German prospective, multicentre FITT-STEMI trial. Eur Heart J 2018;39:1065–1074
32. Farkouh ME, Domanski M, Sleeper LA, et al.; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375–2384
33. Nathan DM, Cleary PA, Backlund JY, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653
34. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589
35. Malmberg K, Rydén L, Efendic S, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol 1995;26:57–65
36. Gerstein HC, Miller ME, Genuth S, et al.; ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011;364:818–828
37. Gerstein HC, Bosch J, Dagenais GR, et al.; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–328
38. Sattar N, Petrie MC, Zinman B, Januzzi JL Jr. Novel diabetes drugs and the cardiovascular specialist. J Am Coll Cardiol 2017;69:2646–2656
39. Norhammar A, Tenerz A, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. Lancet 2002;359:2140–2144