DETermination of the role of OXygen in suspected Acute Myocardial Infarction trial

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Background The use of supplemental oxygen in the setting of suspected acute myocardial infarction (AMI) is recommended in international treatment guidelines and established in prehospital and hospital clinical routine throughout the world. However, to date there is no conclusive evidence from adequately designed and powered trials supporting this practice. Existing data are conflicting and fail to clarify the role of supplemental oxygen in AMI.

Methods A total of 6,600 normoxemic (oxygen saturation [SpO2] ≥90%) patients with suspected AMI will be randomly assigned to either supplemental oxygen 6 L/min delivered by Oxymask (MedCore Sweden AB, Kista, Sweden) for 6 to 12 hours in the treatment group or room air in the control group. Patient inclusion and randomization will take place at first medical contact, either before hospital admission or at the emergency department. The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies registry will be used for online randomization, allowing inclusion of a broad population of all-comers. Follow-up will be carried out in nationwide health registries and Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies. The primary objective is to evaluate whether oxygen reduces 1-year all-cause mortality. Secondary end points include 30-day mortality, major adverse cardiac events, and health economy. Prespecified subgroups include patients with confirmed AMI and certain risk groups. In a 3-month pilot study, the study concept was found to be safe and feasible.

Conclusion The need to clarify the uncertainty of the role of supplemental oxygen therapy in the setting of suspected AMI is urgent. The DETO2X-AMI trial is designed and powered to address this important issue and may have a direct impact on future recommendations. (Am Heart J 2014;167:322-8.)

Background and rationale

Supplemental oxygen has been used in the setting of suspected acute myocardial infarction (AMI) in prehospital and hospital clinical routine throughout the world for over a century[1] and is still included in international treatment guidelines.[2,3] This practice is based on the belief that the administration of supplemental oxygen leads to increased oxygen delivery to the ischemic myocardium and thereby reduces infarct size and subsequent risk of complications such as heart failure and malignant arrhythmias.

Scientifically, only experimental laboratory data and small studies in human beings have supported this practice. In 2 studies on anesthetized dogs, 40% to 100% oxygen after coronary artery occlusion reduced myocardial infarct size and improved left ventricular ejection fraction as compared with room air.[4,5] In a small study in human beings, 17 patients with anterior AMI received 100% oxygen, and a reduction in ST-segment elevation was seen on precordial electrocardiographic (ECG) mapping.[6]

Encouraged by the assumption that a higher arterial oxygen tension reduces infarct size, other techniques have been tested. In a multicenter trial, 112 patients with ST-elevation myocardial infarction (STEMI) were randomized to either hyperbaric oxygen or usual supplemental oxygen during thrombolysis for anterior STEMI.[7] No

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significant benefit was found with this technique. Another randomized multicenter trial used an even more advanced approach. A total of 269 STEMI patients were randomly allocated to either intracoronary hyperoxemic reperfusion after percutaneous coronary intervention (PCI) of the target vessel or normoxemic reperfusion.[8] At 30 days, there was no significant difference between the groups concerning infarct size, ST-segment resolution, or wall motion score index. Later, a post hoc analysis on a subgroup of patients with anterior infarctions and early reperfusion proposed a benefit of hyperoxemic reperfusion on cardiac function.[9]

Since the late 1960s, several studies have suggested possible harmful effects of supplemental oxygen by causing a decrease in cardiac output, coronary blood flow, left ventricular perfusion, coronary and systemic oxygen delivery, and an increase in coronary vascular resistance.[10-15] A thorough review of existing data in 2010[16] summarized the mechanisms of hyperoxemic coronary vasoconstriction and the potentially negative effects of oxygen. Apart from direct effects on the regulation of vessel tension by hyperoxemia, the generation of reactive oxygen species and subsequent decrease in the bioavailability of nitric oxide seem to be of importance in the pathophysiology of vasoconstriction.[17-19] Furthermore, reactive oxygen species lead to leukocyte chemotaxis and inflammation as well as directly induce electrophysiologic changes by increasing oxidative stress, which can heighten the risk of lethal arrhythmias.[20] Clinically, vasoconstriction mediated by oxygen therapy may result in underestimation of vessel size during PCI, increasing the risk of subsequent stent thrombosis.[21]

A Cochrane report[22] in 2010 reviewed the evidence available from randomized controlled trials (RCTs) and identified 3 studies meeting the inclusion criteria: Rawles and Kenmure[23] from 1976, Wilson and Channer[24] from 1995, and Ukholkina et al[25] from 2005, adding up to a total of 387 patients in the meta-analysis. No significant difference was found between oxygen therapy and room air concerning mortality or analgesic effect, although there was a nonsignificant trend toward more deaths in the oxygen group.

Despite a lack of evidence, almost 90% of patients presenting with acute coronary syndrome today are still provided with oxygen, regardless the levels of SpO2.[26] Oxygen is also administrated for its presumed analgesic effect to reduce chest pain. However, the recent OXYPAIN study randomized >300 patients treated with PCI to oxygen or air but did not find any difference in analgesic effect.[27]

In summary, the existing data are conflicting and fail to clarify the role of supplemental oxygen in patients with AMI. Available studies are outdated and of poor quality or largely underpowered to show clinically relevant effects. The need to clarify this important issue in a large randomized trial is urgent. However, to perform such a study is problematic for several reasons. Most importantly, it is expensive and difficult to organize because of the lack of funding and infrastructure from the industry. Furthermore, acceptance from the medical community to challenge a "common knowledge" has been questioned,[28] and the study has therefore been difficult to undertake. However, the issue is nowadays frequently discussed in various articles, blogs, and reviews, which could indicate a changing attitude.[28-34]

Since 2012, 2 RCTs have been started investigating oxygen therapy in STEMI patients; the Australian AVOID study[35] is aiming to include 490 patients looking at infarct size by cardiac biomarkers as primary end point, whereas the Swedish SOCCER trial assesses myocardial salvage index by cardiac magnetic resonance imaging in 100 patients.[36]

The DETO2X-AMI study has been designed, with appropriate power, to evaluate whether supplemental oxygen therapy influences mortality in patients with suspected AMI.

Methods

Registry-based randomized clinical trial—a new trial concept

The DETO2X-AMI trial is a multicenter, prospective, controlled, registry-based randomized clinical trial (RRCT). This trial concept was introduced in the TASTE trial,[37] which has now been successfully completed.[38] The basis for this concept is the fact that in Sweden, almost all patients with acute ischemic heart disease are registered in the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry, which includes the National Registry of Acute Coronary Care, National Registry of Angiography and Angioplasty, Swedish Heart Surgery Registry, and National Registry of Secondary Prevention.[39]

The registry is web-based with all data registered online directly by the caregiver and transferred in an encrypted format to a central server. During registration, the whole process of care is kept together in 1 record even if the patient is transferred between different units and hospitals. The technical platform, OpenQreg (General Public License version 3.0, Open Source Initiative, Palo Alto, CA), is published as open source software that can receive data via the Internet or from other databases and electronic patient journals. The platform is in direct contact with the Swedish National Population Registry for immediate access to personal data and deaths. For patients admitted to hospital because of symptoms suggestive of acute coronary syndrome, information is collected prospectively for 106 variables and include patient demographics, admission logistics, risk factors, medical history, medical treatment before admission, ECG changes, biochemical markers, other clinical features and investigations, medical treatment in hospital, interventions, hospital outcome, discharge diagnoses, and discharge medications.

The SWEDEHEART provides manuals, education, and technical advice, including a telephone help desk for all users of the registry. The system has error-checking routines for range and consistency with immediate feedback to the caregiver. Definitions are easily available when data are entered. To ensure the correctness of the data entered, monitors visit the hospitals on a regular basis. The agreement between key variables in the registry and medical records has repeatedly been 95% to 96%.

In the DETO2X-AMI trial, randomization will be performed by means of a separate and easily accessible online randomization module in which inclusion criteria need to be affirmed and exclusion criteria denied before the patient is allocated to 1 of the treatments. Randomized patients will be automatically registered in the SWEDEHEART registry, and all relevant data will be obtained directly from the registry; no other documentation is needed. Mortality data outside hospital will be obtained by merging with the Swedish Population Registry, which includes information of the vital status of all Swedish citizens. Other clinical end points are collected by merging with the National Patient Registry, which includes diagnoses on all patients hospitalized in Sweden. Thanks to the unique 10-digit personal identification number of all Swedish citizens, complete follow-up is ensured.

Study sites

The DETO2X-AMI trial started in April 2013 at major university hospitals. During the first months of run-in, approximately 400 patients have been included at 10 hospitals. Further 16 hospitals will start including patients in September and October 2013. It is expected that a majority of the 71 hospitals in the country with acute cardiac care facilities enrolling in the SWEDEHEART registry will participate. The inclusion is planned to be finished in 2015. As both STEMI and non–ST-elevation myocardial infarction (NSTEMI) patients are eligible for inclusion, also hospitals without primary PCI facilities can take part in offering access to a broad population.

Hypothesis—primary and secondary end points

The study hypothesis is that the use of supplemental oxygen in normooxic patients with suspected AMI lowers mortality as compared with room air. A 2-tailed design is used to examine proclaimed effects of oxygen making it possible to detect both clinically relevant benefit and harm.

Primary end point is 1-year all-cause mortality in all patients with suspected AMI. Secondary end points are as follows: (1) 30-day mortality; (2) major adverse cardiac events (MACE) within 30 days and 1 year, including all-cause mortality, reinfarction, hospitalization because of heart failure; and (3) health economy. Predefined subgroups are patients with diagnosed AMI, with STEMI and NSTEMI, with chronic obstructive pulmonary disease, chronic kidney disease, and diabetes mellitus. In substudies, echocardiography and cardiac magnetic resonance imaging will be used to assess cardiac function and infarct size. Coronary microvascular function will be assessed using the index of microcirculatory resistance during primary PCI in STEMI patients.[40-43] In another STEMI subgroup, advanced biomarkers will be analyzed evaluating myocardial damage, oxidative stress, inflammation, and apoptosis. A possible analgesic effect will be examined in a substudy using visual-analog scale.

Inclusion/exclusion criteria

Patients with age ≥30 years with normal SpO2 (≥90% on pulse oximeter) presenting to the Emergency Medical Service (EMS) system or the emergency department (ED) with classic symptoms suggestive of acute coronary syndrome within the last 6 hours and significant ECG changes (characterized by ST-segment elevation ≥0.2 mV in leads V1-V4 or ≥0.1 mV in other leads, ST-segment depression ≥0.1 mV in any lead, negative ischemic T wave in leads V2-V6, pathologic Q wave in ≥2 adjacent leads, or left bundle branch block) or elevated cardiac biomarkers in ED (above local decision limit for AMI) are evaluated for inclusion (Figure).

Patients will be excluded if they do not consent, have continuous oxygen therapy, or have suffered cardiac arrest before inclusion. If supplemental oxygen therapy is started before evaluation for inclusion for <20 minutes, a new evaluation can take place after discontinuation of oxygen delivery and 10 minutes of washout. If deemed clinically necessary, patients randomized to air may receive oxygen, but crossover between randomized groups is discouraged. Unintentional crossover will be minimized with the use of stickers and patient bracelets indicating to which group the patient has been randomized.

Informed consent, randomization, and ethics

If a patient is deemed eligible, oral informed consent is obtained by EMS staff or ED personnel before 1:1 randomization to oxygen or room air. The patient will receive study information on paper directly after being admitted to a ward and asked to confirm informed consent by signature. Patients who withdraw their study consent will receive whatever alternative appears to be clinically relevant and excluded from any study specific activities. However, they will remain in the national registries according to routine and be available for evaluation of the primary end point because mortality is publicly available. Patients who decline participation in the national registry will be withdrawn from the registry database but remain in the study database.

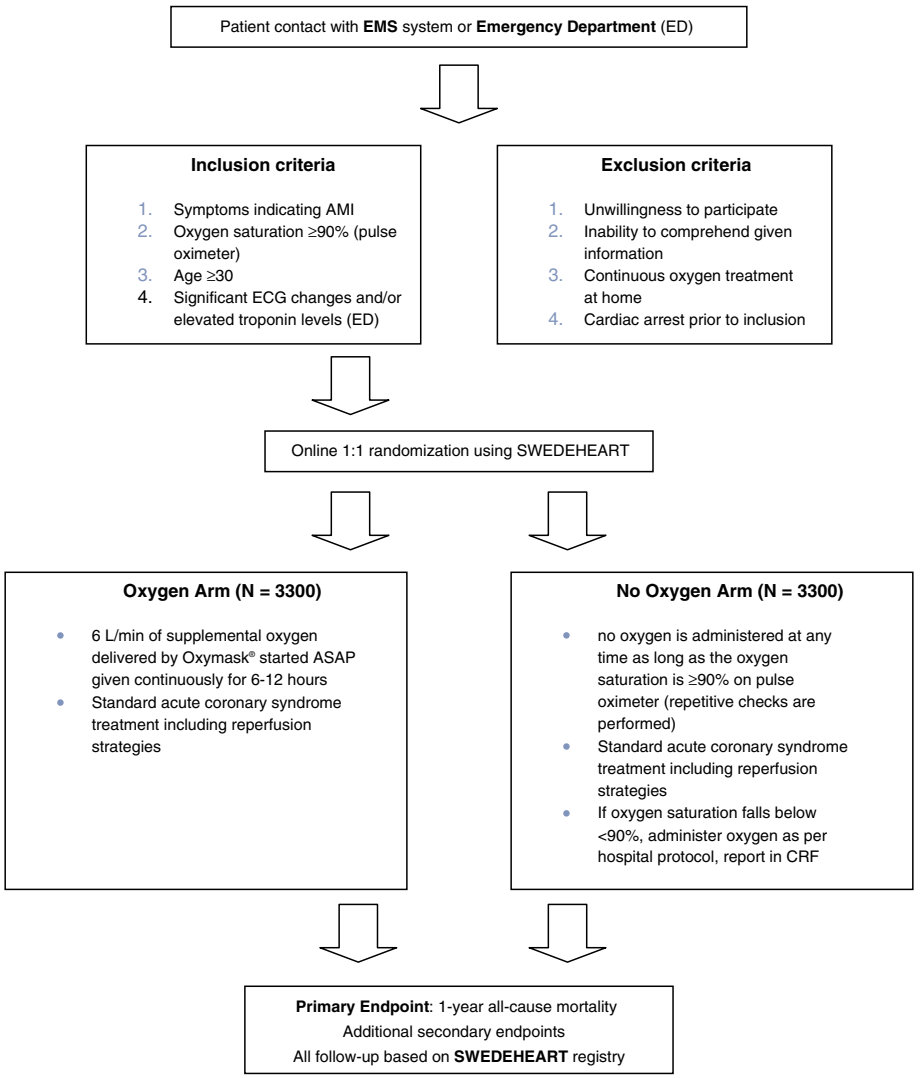
The DETO2X-AMI trial is an open-label trial. Blinding to reduce bias has been discussed but was deemed impossible for several reasons. Because of the lack of pressurized air in Swedish ambulances, and the fact that most companies only use closed Hudson masks, which require a minimum flow of 6 L/min air or oxygen to reduce the risk of carbon dioxide retention, prehospital blinding would put the patients at risk. With 1-year total mortality as the primary outcome, the reduction of the placebo effect by blinding should be of less importance.

The concept of a trial design using national registries as the only basis for follow-up is potentially limited by the lack of formal central adjudication of clinical events. Therefore, we have chosen 1-year all-cause mortality obtained from the Swedish Population Registry as the primary end point of the trial. The implementation of a data and safety monitoring board has been extensively discussed, but due to expected rapid inclusion rate and relatively long follow-up to event time, it was deemed impractical.

Statistical considerations

The main focus of this trial is to gain clinically relevant information on the effect of supplemental oxygen in the setting

Figure



Flowchart of DETO2X-AMI trial.

of suspected AMI. The primary outcome is the time from randomization to all-cause death within 1 year, in all-randomized patients. All outcomes will be analyzed using the intention-to-treat principle, where patients randomized to a certain group will be followed up irrespective of the actual treatment, offering unbiased assessments of treatment efficacy.[44] Supplementary per-protocol analyses and analyses based on patients with diagnosed AMI only will also be performed. Survival probabilities will be displayed and calculated using Kaplan-Meier methodology. Hazard ratios between treatment groups will be calculated using a Cox proportional hazard model, adjusted for age (as a linear covariate on the log-hazard scale) and gender. Patients without events will be censored at 1 year after randomization or the time of withdrawal of informed consent for secondary outcome events. A supplementary analysis using the full follow-up time available for each patient at the time of final analysis will be performed. The same model will be applied to time from randomization to first MACE and the individual MACE subcategories (reinfarction and hospitalization due to heart failure). The same model will be also used for analyses in the per-protocol and the diagnosed AMI populations. Subgroup analyses will be performed by introducing a treatment-subgroup interaction term in the Cox model, excluding any patients not possible to classify. Supplemental analyses of the number of patients with death and with MACE, within 30 days and within 1 year of randomization, will be performed using logistic regression adjusted for age and gender. Estimates of treatment differences will be presented with 2-tailed 95% CI and associated P values. A 2-tailed $P < .05$ is considered statistically significant. Secondary outcomes will be analyzed without adjustment for multiplicity.

Table. Baseline characteristics and final diagnoses in the DETO2X-AMI pilot study

	All (N = 129)	Room air (n = 64)	Oxygen (n = 65)
Demographics			
Age, median (IQR)	68 (58-78)	65 (58-76)	69 (58-78)
Men	87 (67)	47 (73)	40 (62)
Risk factors			
Current smoking	26 (20)	13 (20)	13 (20)
Diabetes mellitus	21 (16)	5 (8)	16 (25)
Hypertension	51 (40)	24 (38)	27 (42)
Previous cardiovascular disease			
Myocardial infarction	26 (20)	15 (23)	11 (17)
Percutaneous coronary intervention	25 (19)	16 (25)	9 (14)
Coronary artery bypass graft	4 (3)	2 (3)	2 (3)
Stroke	3 (2)	2 (3)	1 (2)
Medication on admission			
Aspirin	39 (30)	19 (30)	20 (31)
Clopidogrel	2 (1.6)	1 (1.6)	1 (1.5)
β-blocker	41 (32)	18 (28)	23 (35)
Statin	34 (26)	16 (25)	18 (28)
ACE inhibitor or angiotensin receptor block	37 (29)	16 (25)	21 (32)
Presentation			
Ambulance transportation	82 (64)	42 (66)	40 (62)
Systolic blood pressure	150 (135-170)	150 (136-191)	150 (133-168)
Heart rate	80 (67-93)	80 (67-93)	81 (67-92)
Electrocardiography			
ST elevation	48 (37)	27 (42)	21 (32)
ST depression	28 (22)	13 (20)	15 (23)
T-wave inversion	18 (14)	8 (13)	10 (15)
Normal or other	35 (27)	16 (25)	19 (29)
Final diagnosis			
Myocardial infarction	81 (63)	39 (61)	42 (65)
Unstable or stable angina	17 (13)	11 (17)	6 (9)
Other heart disease	15 (12)	6 (9)	9 (14)
Unknown/other noncardiac cause	16 (12)	8 (13)	8 (12)

Abbreviations: *IQR,* Interquartile range; *ACE,* angiotensin-converting enzyme.

To calculate sample size, 2 different sources of data were used; data from Thang et al[45,46] supplying prospective data and analysis from the National Registry of Acute Coronary Care from 2005 to 2010. The 1-year total mortality in patients treated with room air was estimated to 14.4%. A clinically relevant effect of supplemental oxygen was defined as a relative risk reduction of 20%. To be able to reject the null hypothesis with a probability (power) of 0.90, 2,900 patients per group are needed. The type I error probability is 0.05. Loss to follow-up is considered negligible due to virtually complete coverage in the national registries. To control for crossover and failure to complete the protocol, sample size is increased to 3,300 patients per group, resulting in a total of 6,600 patients. The calculation is based on an analysis of proportions at 1 year, and the power for the prespecified adjusted Cox analysis is expected to be as good or better.

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The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Pilot study

To assess power calculation, logistics, safety, and feasibility before starting a nationwide RRCT, a 3-month pilot study was performed at Södersjukhuset, Stockholm. A total of 129 normooxic patients were enrolled by EMS and at the ED. Except for being younger (median [interquartile range] age 68 [58-78]), baseline characteristics were similar to those seen in the overall SWEDEHEART population (Table). A total of 81 (63%) patients were diagnosed with an AMI (53% NSTEMI and 47% STEMI). Of the remaining, 32 (25%) patients were diagnosed with other acute heart diseases such as angina pectoris, myocarditis, heart failure, Takotsubo cardiomyopathy, or valvular disease. Sixteen (12%) patients received "unspecified chest pain" as primary diagnosis. No major logistic or medical problems occurred. Oxygen

delivery for 12 hours was well tolerated. Crossover from room air to oxygen occurred in 2 patients who developed hypoxia due to pulmonary edema. There was no crossover from oxygen to room air. At 30 days, there were 3 (4.6%) deaths in the group receiving room air and no deaths in the group receiving oxygen (P = .12, Fisher exact test).

Thus, the study design of the DETO2X-AMI-trial was found to be sound and feasible, and no major safety issues occurred. Inclusion criteria managed to identify high-risk individuals with acute cardiac disease with a high percentage of AMI among the study population.

Summary and conclusions

In the first RRCT based on the SWEDEHEART platform, the TASTE trial, all patients were included by a dedicated interventional cardiologist at the catheterization laboratory. In the present study, we will extend the concept of RRCT by including a broader population at first medical contact, engaging several different professions, such as other physicians, nurses, and paramedics in the randomization procedure.

The possible advantages and disadvantages of RRCTs have been discussed in detail recently.[37,38,47,48] In brief, an RRCT is not only much less expensive to perform but also includes more unselected patients making the results more applicable to the general population than those from a regular RCT with narrow inclusion criteria and multiple exclusion criteria. Another advantage to using a national registry as a trial platform is the ability to follow up patients for life by merging with other health registries. A limitation relates to nonadjudicated secondary outcome events. Therefore, total mortality was chosen as the primary objective. At present, RRCTs should be considered as complements to regular RCTs suitable for simple but clinically important issues regarding treatment already used in clinical routine for which there is lack of incentives for industry sponsorship due to low potential for revenue.[47] In the absence of full adjudication of events, a valid hard end point with a high degree of completeness should be used as the primary end point. Thus, the issue of routine use of supplemental oxygen in patients with suspected AMI can therefore be considered ideal to be addressed in an RRCT.

The DETO2X-AMI trial focuses on a clinically important question relevant in the current everyday practice. At the time of presentation to the EMS system or the ED, it is impossible to conclusively diagnose AMI, which makes patients with suspected AMI the relevant target group. The DETO2X-AMI pilot study indicates that two-thirds of the included patients will develop an AMI. Consequently, both STEMI and NSTEMI patients will be represented for evaluation in contrast to other studies examining STEMI only.[35,49]

After completion in 2015, the DETO2X-AMI trial will have the potential to answer the question whether supplemental oxygen treatment lowers mortality in patients with suspected AMI and SpO2 ≥90% and provides substantial evidence for the acute care of these patients.

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Disclosures

Conflicts of interest: None to declare.

The trial will be conducted in accordance with the Declaration of Helsinki and has been approved by the Regional Ethical Review Board of Gothenburg, Sweden (DETO2X-AMI 2012/287-12).

A prospective, multicenter, controlled, registry-based randomized clinical trial based on the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies registry.

Study design, rationale, and pilot study.

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