Randomized Clinical Trials in Cardiovascular Medicine

By

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Abstract

Cardiovascular (CV) diseases (CVD) have been the leading cause of death globally for decades. Effective prevention, treatment and management programs are needed to attenuate the negative impact of CVDs. Despite the efforts to provide the required evidence for these programs, the majority of recommendations issued by major professional organizations have not been supported by high-quality evidence generated by randomized clinical trials (RCT). RCTs have been considered the gold standard of the clinical research for many decades as they minimize the risk of bias and confounding through randomization. Despite the indisputable role of RCTs in evidence generation, impediments such as high cost, the need for large sample size, long study duration and so on, limit their ability to answer our persistently-growing clinical questions. In this thesis, the aim is to explore some of the important aspects of RCT design from endpoints to the level of pragmatism. We also designed and conducted a pilot RCT on the effects of supplemental oxygen therapy in patients with acute heart failure (AHF) for the first time and synthesized the data of similar RCTs from the acute myocardial infarction (AMI) setting.

The first chapter is the introduction and provides some background about the importance of RCTs, their limitations and the need for optimizing their design and implementation.

The second chapter is a retrospective cohort study using linked administrative data from Alberta to explore the provincial uptake of natriuretic peptides (NP) testing, which are biomarkers used in the diagnosis, prognostication, and management of patients with AHF. The study identified several factors including sex, urban residence, the type of healthcare provider and emergency department's (ED) clinical volume as factors that are influencing the NP testing in clinical practice. Patients with AHF who were tested for NP had a higher rate of hospital admission from the ED and lower 7-day and 90-day repeated ED visit rates compared with those who were not assessed using NP.

Endpoint adjudication is a common practice in many RCTs that consider clinical events as primary or secondary endpoints. The third chapter is a secondary analysis of the Providing Rapid Out of Hospital Acute Cardiovascular Treatment 3 (PROACT-3) trial, investigating the agreement between adjudication committee versus site-based diagnoses for clinical conditions. The study showed substantial agreement between the diagnosis of ED physicians and adjudication committee. Nevertheless, in the subgroup of patients where there was disagreement,

there was significantly worse short-term and long-term mortality. This study provided evidence on where adjudication committee or site diagnoses can be used for outcome ascertainment.

Pragmatism is one way to address the above-mentioned limitations of RCTs. The fourth chapter investigates the level of pragmatism in CV RCTs. We found a moderate increase in the level of pragmatism in CV RCTs published from 2000 to 2015. The increase occurred mainly in the eligibility, setting, flexibility of intervention delivery, and primary endpoint domains of the trial design. Knowing more about current RCTs can help us in the design and implementation of more efficient RCTs with broader application.

In the fifth chapter, we presented the results of the HiLo-HF (High versus Low Oxygen therapy in acute Heart Failure) trial which was a pilot RCT about the effects of supplemental oxygen therapy in patients presenting to the ED with AHF. Titrating to high or low SpO_2 targets did not result in changes in biomarkers, symptoms or clinical outcomes. Further RCTs with larger sample sizes are warranted to determine the efficacy and safety of oxygen therapy in patients with AHF.

In chapter 6, we synthesized the evidence from RCTs to investigate the effects of supplemental oxygen therapy in patients with AMI. In this meta-analysis including 7,998 patients, oxygen therapy did not reduce the risk of in-hospital or 30-day mortality in those with AMI. It also had no effect on the cardiac troponin levels or the infarct size as defined by cardiac MRI.

Trialists are required to make multitude of decisions in the trial design to ensure the validity and generalizability of the trial findings, whilst they rarely have the evidence at their disposal on the optimal practice for every single decision. This work identifies and tests potential areas that can be used to improve the design and implementation of RCTs in CV medicine.

Preface

All of the research shown in this thesis are published in peer reviewed journals as provided below. The second chapter is published in Canadian Journal of Cardiology as "Sepehrvand N, Bakal JA, Lin M, McAlister F, Wesenberg JC, Ezekowitz JA: **Factors associated with natriuretic peptide testing in patients presenting to emergency departments with suspected heart failure**. *The Canadian journal of cardiology* 2016, **32**(8):986.e981-988". Ethics approval for this study was received from the Health Panel of the Health Research Ethics Board at University of Alberta, Project Name "**Study of the uptake of natriuretic peptides (BNP and NT-proBNP) testing in patients with suspected Heart Failure in Alberta**", No. **Pro00049619**, 27th July 2014.

The third chapter is published at the Clinical Trials journal as "Sepehrvand N, Zheng Y, Armstrong PW, Welsh R, Goodman SG, Tymchak W, Khadour F, Chan M, Weiss D, Ezekowitz JA: **Alignment of site versus adjudication committee-based diagnosis with patient outcomes: Insights from the Providing Rapid Out of Hospital Acute Cardiovascular Treatment 3 trial**. *Clinical trials (London, England)* 2016, **13**(2):140-148".

The fourth chapter is published at the Journal of American Medical Association Cardiology (JAMA Cardiology) as "Sepehrvand N, Alemayehu W, Das D, Gupta AK, Gouda P, Ghimire A, Du AX, Hatami S, Babadagli HE, Verma S *et al*: **Trends in the explanatory or pragmatic nature of cardiovascular clinical trials over 2 decades**. *JAMA cardiology* 2019" with the doi of 10.1001/jamacardio.2019.3604.

The fifth chapter is published in European Society of Cardiology Heart Failure (ESC-HF) journal as "Sepehrvand N, Alemayehu W, Rowe BH, McAlister FA, van Diepen S, Stickland M, Ezekowitz JA: **High vs. low oxygen therapy in patients with acute heart failure: HiLo-HF pilot trial**. *ESC heart failure* 2019, **6**(4):667-677". Ethics approval for this study was received from the Biomedical Panel of the Health Research Ethics Board at University of Alberta, Project Names "HILO-HF-2 Trial: High versus Low SpO_2 oxygen therapy in patients with acute Heart Failure", No. **Pro00069142**, 6th December 2016 and "HILO-HF Registry: High versus Low SpO_2 oxygen therapy in patients with acute Heart Failure", No. **Pro00066607**, 20th July 2016.

The sixth chapter is published in the Heart journal as "Sepehrvand N, James SK, Stub D, Khoshnood A, Ezekowitz JA, Hofmann R: **Effects of supplemental oxygen therapy in patients with suspected acute myocardial infarction: a meta-analysis of randomised clinical trials**. *Heart (British Cardiac Society)* 2018, **104**(20):1691-1698".

The seventh chapter is the general discussion, summarizing the findings of this thesis and highlighting the areas that can be used to improve the design and implementation of RCTs in CV medicine.

Dedications

I dedicate this work to the love of my life, Sanaz Hatami, to my parents, Saeid Sepehrvand and Seyedeh Tayebe Motie-Langroudi and to all the mentors who shaped my life and brought me here

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List of Abbreviations

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACCP	American College of Chest Physicians
ACE	Angiotensin-converting enzyme
ACEi	Angiotensin converting enzyme inhibitors
ACS	Acute Coronary Syndrome
AF	Atrial fibrillation
AHA	American Heart Association
AHF	Acute heart failure
AMI	Acute myocardial infarction
ANCOVA	Analysis of Covariance
ARB	Angiotensin II receptor blockers
ASA	Acetyl salicylic acid
AST	Aspartate aminotransferase
AUC	Area under the curve
AVOID	Air Versus Oxygen In myocarDial infarction
BL	Baseline
BMS	Bare metal stents
BNP	Brain-type Natriuretic peptide
BP	Blood pressure
CABG	Coronary artery bypass grafting

CAD	Coronary Artery Disease;
CaO_2	Arterial oxygen content
CCB	Calcium channel blockers
CCS	Canadian Cardiovascular Society
CEC	Central endpoint committee
CI	Confidence interval
CIHI	Canadian Institute of Health Information
CK	Creatine kinase
CKD	Chronic kidney disease
CK-MB	Creatine Kinase-MB
CMG	Case mix groups
CMR	Cardiac MRI
CO	Cardiac output
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
COURAGE	Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation
CPAP	Continuous positive airway pressure
CRF-2	Corticotropin releasing factor type-2
CSANZ	Cardiac Society of Australia and New Zealand;
CV	Cardiovascular
CVA	Cerebrovascular accidents
CVD	Cardiovascular diseases
DAD	Discharge Abstract Database

DES	Drug-eluting stents
DETO$_2$X-AMI	DETermination of the role of OXygen in suspected Acute Myocardial Infarction
DM	Diebetes Mellitus
DO$_2$	Tissue oxygen delivery
EBM	Evidence-based medicine
ED	Emergency department
eGFR	Estimated Glomerular Filtration Rate
EHJ	European Heart Journal
EHR	Electronic health record
EMeRG	Emergency Medicine Research Group
EMS	Emergency Medical Services
ESC	European Society of Cardiology
ET	Endothelin
FDA	Food and Drug Agency
FiO$_2$	Fraction of inspired oxygen
FMH	Foothills Medical Hospital
GRACE	Global Registry of Acute Coronary Events
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
GUIDE-IT	Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure
h	Hours
HF	Heart Failure
HFSA	Heart Failure Society of America;

HiLo-HF	HIgh versus Low Oxygen therapy in acute Heart Failure
HLP	Hyperlipidemia
HR	Heart rate
HR	Hazard ratio
HTN	Hypertension
ICD	International Classification of Diseases
ICU	Intensive care unit
IHD	Ischemic heart disease
IMPROVE-CHF	Improved Management of Patients with Congestive Heart Failure
IQR	Interquartile range
IRI	Ischemia/reperfusion injury
JACC	Journal of the American College of Cardiology
JAMA	Journal of the American Medical Association
JVD	Jugular vein distention
JVP	Jugular vein pressure
K_{ATP}	Adenosine triphosphate–dependent potassium channels
KM	Kaplan-Meier
LAD	Left anterior descending artery
LCX	Left circumflex artery
LMCA	Left main coronary artery
L/min	Litres/min
LOS	Length of Stay
LVEF	Left ventricular ejection fraction

MACE	Major adverse cardiovascular events
MeSH	Medical subject heading
MI	Myocardial infarction
mmHg	Millimetres of mercury
MMP	Matrix metalloproteinase
MONA	Morphine, oxygen, nitrate, and aspirin
MRA	Mineralocorticoid receptor antagonists
N	Number
N/A	Not available
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
NIMV	Non-invasive mechanical ventilation
NIV	Non-invasive ventilation
NACRS	National Ambulatory Care Reporting System
NEJM	New England Journal of Medicine
NHFA	National Heart Foundation of Australia
NO	Nitric oxide
NOAC	Novel oral anticoagulant
NP	Natriuretic peptides
NR	Not reported
NSTEMI	non-ST segment elevation myocardial infarction
NT-proBNP	N-terminal proBNP
NYD	Not yet diagnosed

NYHA	New York Heart Association
O_2	oxygen
OR	Odds ratio
$PaCO_2$	partial arterial carbon dioxide pressure
PaO_2	partial arterial oxygen pressure
PCI	percutaneous coronary intervention
PEF	peak expiratory flow
PGA	patient global assessment
PGI_2	prostacyclin
PICO	population, intervention, control (comparison), and outcome
PRECIS-2	PRagmatic Explanatory Continuum Index Summary-2
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROACT-3	Providing Rapid Out of Hospital Acute Cardiovascular Treatment 3
PROBE	prospective, open-label, blinded-endpoint
Pts	patients
Q_1	25th percentile
Q_3	75th percentile
RAH	Royal Alexandra Hospital
RCA	right coronary artery
RCT	randomized clinical trial
RIW	Resource Intensity Weight
ROS	reactive oxygen species
RR	respiratory rate

SD	Standard deviation
sGC	soluble Guanylate Cyclase
SpO_2	Peripheral oxygen saturation level
STEMI	ST-segment elevation myocardial infarction
SVD	Single vessel disease
SWEDEHEART	Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies
T0	Time zero
TNF	Tumor necrosis factor
UA	Unstable angina
UAH	University of Alberta Hospital
ULI	Unique lifetime identifier
VAS	Visual analogue scale
WHF	Worsening heart failure
Yr	Years

Chapter 1 : Introduction

1.1 Cardiovascular disease

Cardiovascular (CV) disease (CVD) is the term used to refer to a multitude of diseases that affect the heart and/or blood vessels, including coronary artery disease and heart failure (HF). Following the epidemiological shift in the pattern of diseases during the past century from the communicable to non-communicable and chronic diseases, CVD has been the leading cause of morbidity and mortality globally for decades. In 2017, 17.79 million deaths worldwide was attributed to CVD, representing roughly one-third (31.8%) of the total reported deaths in the world.[1,2]

Nevertheless, there has been a decline in the CVD death in the developed world.[3-8] The high-income countries have shown a greater decline in age-specific death rates as compared to middle- or low- income countries during the last decade,[9,10] and currently three-quarter of the CVD-related deaths occur in the developing world. Mitigating population health risk factors and progress in screening, diagnosis, and treatment of these diseases (emergency responses, hospital and post-hospital care), are some of the factors that contributed to the reduction of CVD mortality in the industrial world.[5]

This decline in the CVD death has led to another epidemiological transition towards cancer-related deaths.[11,12] This decline in the number of CV deaths implies that the number of patients living with CVD will grow each year. The proportion of Canadians living with heart disease increased by 67% from 2000-2001 to 2012-2013.[13] Approximately half (121.5 million, 48%) of all adults in the United States are living with some type of CVD.[14]

1.2 Level of evidence and certainty

The recent improvement in cardiovascular disease outcomes is in part a result of a tremendous amount of effort directed towards providing answers and evidence for clinical questions. Evidence-based medicine (EBM) was developed to teach clinicians and healthcare professionals the art of utilizing high quality and reliable evidence for their day-to-day decisions. Physicians who try to practice EBM have experienced and realized the lack of high-quality studies in many research areas.

Clinical practice guidelines incorporate the best evidence and provide explicit and applicable recommendations for decision-making in clinical practice. During the last decades, the number of practice guidelines to assist clinicians with their daily practice has increased; However, but this increase has not always been supported with a simultaneous increase in definitive evidence. In 2009, a study assessed the class and level of evidence of the 7196 recommendations of the 53 American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines from 1984 to 2008, and found the majority of recommendations to be based on a low level of evidence, expert opinions, or standard of care,[15] showcasing the consistent gaps in evidence and highlighting the need for generating new and high-quality evidence to fill that gap.

Another study later in 2019 evaluated ACC/AHA guideline recommendations (2008-2018) in parallel to the current European Society of Cardiology (ESC) clinical guidelines and showed that despite efforts in the last decade to simplify and facilitate RCTs by using innovative methods such as leveraging administrative health data for patient follow-up,[16-19] more public/private funding for RCTs and focusing on patient-centered questions, a similar or even lower percentage of guideline recommendations (8% of ACC/AHA recommendations and 14% of ESC recommendations) are supported by evidence from multiple RCTs or a single, large RCT (Level of evidence A; Figure 1.1).[20] Even among recommendations with a strong class I and III recommendation (what should be done and should not be done, respectively), only 13% had a level of evidence A and 38% were based on expert opinion or clinical experience. This lack of high-quality evidence is not specific to the field of Cardiology, and other studies from other disciplines have shown similar lack of high-quality evidence supporting guideline recommendations.[21,22]

1.2.1 Uncertainties in the Management of Acute Coronary Syndrome

It is essential for many stakeholders to know about what is known or unknown regarding the potential benefits or risks of medications, procedures, devices, or health care services. These include clinicians who attempt to incorporate up-to-date science into their daily practices, patients who want to make well-informed decisions about their own care, medical associations and professional societies that are responsible for developing clinical practice guidelines, and

payers and policymakers who want to deliver the best care to the population in a sustainable way.[23]

SIZE OF TREATMENT EFFECT

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/Test — Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit — is not recommended; is not indicated; should not be performed/ administered/ other; is not useful/ beneficial/ effective COR III: Harm — potentially harmful; causes harm; associated with excess morbid-ity/mortality; should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

Figure 1.1 Guideline recommendations classification scheme used by American College of Cardiology and American Heart Association[24]

Acute Coronary Syndrome (ACS), which includes unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI), remains an important public health issue with a significant burden on any healthcare system. About 2.4 million (8.5%) Canadian adults live with diagnosed ischemic heart disease (IHD).[13] Roughly 70,000 myocardial infarctions occur in Canada each year and 160,000 adult

Canadians receive a diagnosis of IHD.[24] About 18,000 Canadians die from ACS each year, accounting for 17.2 deaths per 1,000 individuals diagnosed with the disease.[25]

During the last 3-4 decades, there has been a significant decline in the mortality from ACS, predominantly because of improvements in the system of care such as shorter time to treatment intervals, increase in reperfusion therapy, and improved anti-platelet, or lipid-lowering therapies. Treatment with beta blockers, angiotensin-converting enzyme (ACE) inhibitors, or angiotensin receptor blockers has improved secondary prevention post ACS.[26,27] Optimizing emergency medical systems to transport patients with suspected ACS, has helped to reduce the time from symptom onset to initiating evidence-based treatment.[28]

Nevertheless, ischemic heart disease is still a major cause of mortality and morbidity worldwide. The rise in the ACS risk factors from obesity [29] to diabetes or hypertension is alarming. So many questions remain unanswered and there is still need for further progress and optimizing the treatment strategies.

As an example, oxygen therapy has been used for over a century in the management of patients with suspected acute myocardial infarction (AMI). It has been part of the mnemonic MONA (morphine, oxygen, nitrate, and aspirin) that was taught for decades to healthcare professionals for the acute care of patients with suspected AMI. However, recent studies have raised concerns about the efficacy and safety of supplemental oxygen in patients with normal blood oxygen saturation levels. Figure 1.1 summarizes some potential mechanisms of effect for supplemental oxygen therapy in patients with cardiac diseases. The two main purported pathways for the detrimental effects associated with hyperoxia are the overproduction of reactive oxygen species and its related oxidative stress and the hyperoxia-induced vasoconstriction which could lead to a decreased coronary blood flow and cardiac dysfunction.[30] Up until recently, the clinicians did not know how to treat their patients in terms of oxygen management. In 2017, the DETO2X-AMI (DETermination of the role of OXygen in suspected Acute Myocardial Infarction) trial, enrolling 6,629 patients into a registry-based RCT shed some light on this important matter.[31] According to their results, supplemental O_2 therapy delivered at 6 L/min for 6-12 hours through an open face mask was not associated with reduced or increased mortality or re-hospitalization within one year after randomization. In chapter 8, we synthesized the evidence from randomized clinical trials to investigate the effects of supplemental oxygen therapy in patients with suspected or confirmed AMI.[32]

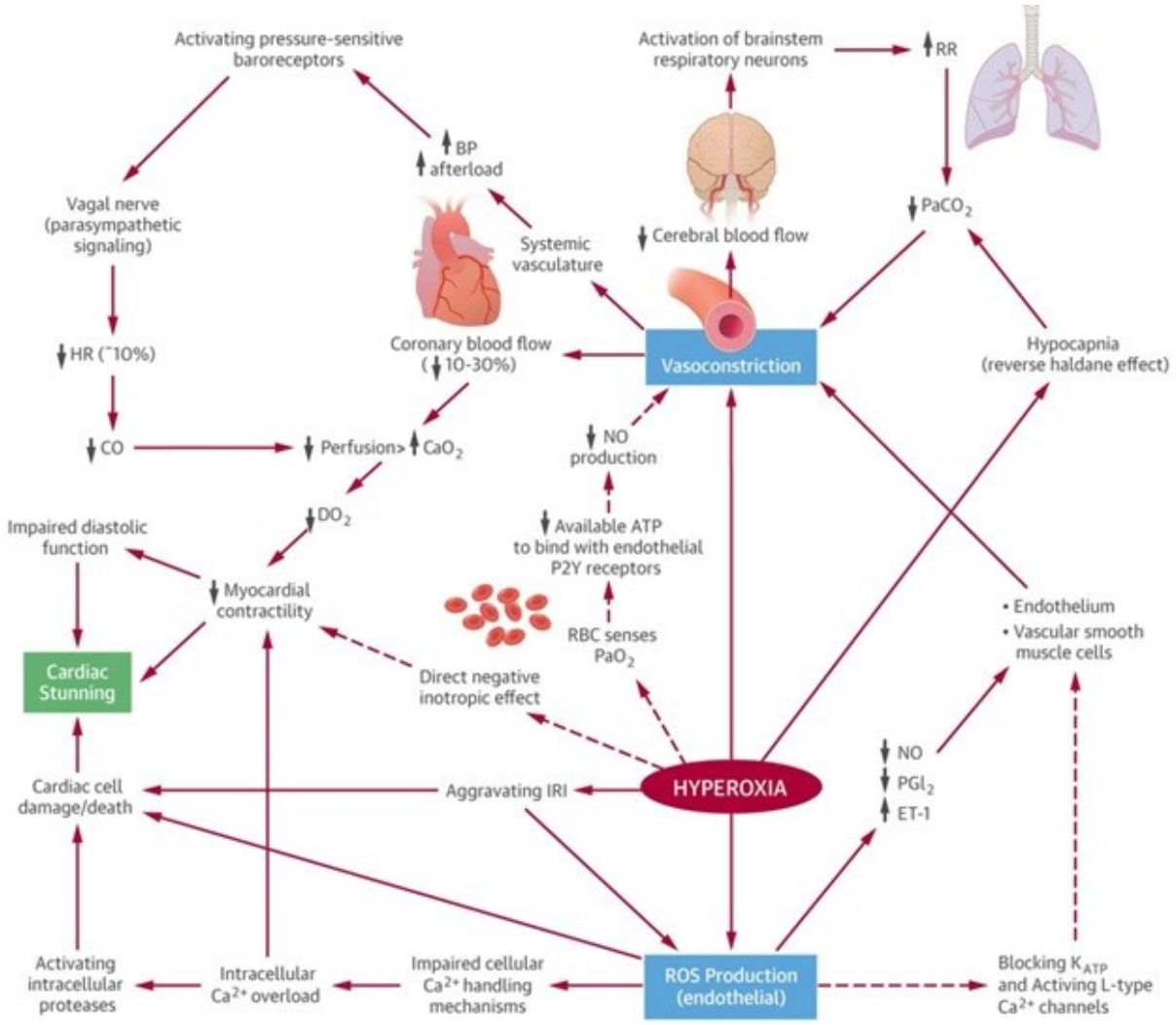


Figure 1.2 Schematic illustration of the potential mechanism of effect of hyperoxygenation on patients with cardiac disease[31]

Solid lines represent the availability of strong evidence supporting the proposed process. **Dotted lines** represent the availability of some but not strong supporting evidence. BP = blood pressure; CaO_2 = arterial oxygen content; CO = cardiac output; DO_2 = tissue oxygen delivery; ET = endothelin; HR = heart rate; IRI = ischemia/reperfusion injury; K_{ATP} = adenosine triphosphate–dependent potassium channels; NO = nitric oxide; $PaCO_2$ = partial arterial carbon dioxide pressure; PaO_2 = partial arterial oxygen pressure; PGI_2 = prostacyclin; ROS = reactive oxygen species; RR = respiratory rate.

1.2.2 Uncertainties in the Management of Heart Failure

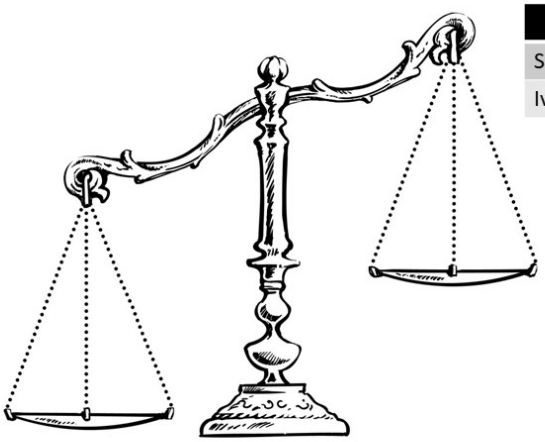
Heart failure (HF) is a multifactorial condition in which decreased function of the heart muscles impairs the ability of the heart to pump blood to the vital organs and extremities. The prevalence of chronic HF in the North American adult population is 1.5 to 2.5% and is increasing.[33,34] The majority of patients present to the hospital directly or via the emergency department (ED) with 'acute' HF.[34] In Alberta alone, in 2017/18, there were 6,494 discharges and 79,232 inpatient days attributable to a primary diagnosis of HF, with a 30-day readmission rate of 26%, a 9.1% in-hospital mortality rate, 14.2% post-discharge 30-day mortality rate and $108 million spent on hospital-based HF care (data from Alberta Health Services).

Acute HF (AHF) represents a condition where chronic HF deteriorates. Treatment of AHF is focused on improving symptoms and reducing morbidity and mortality. Although evidence has emerged from recent AHF trials and cohorts, many clinical questions remain unanswered. For example, the diuretics have been the cornerstone of the treatment of patients who present to hospital with AHF for decades. However, their optimal dose or route of administration was not clear up until recently. The DOSE trial improved our understanding about diuretic dosing and method of administration in a modestly sized (n=308) National Institute of Health (NIH)-funded randomized clinical trial (RCT) and has informed clinicians on how to use this long-standing therapy and led to guideline recommendations.[35] Similarly, non-invasive mechanical ventilation (NIMV) was used widely and thought to be a potential therapy but when tested in a larger RCT, there was no additional mortality benefit of this strategy.[36] A recent trial of 1,069 patients failed to show any benefit in mortality, rates of intubation, length of stay, or other clinically relevant outcomes, when NIMV was tested in a rigorous manner against routine non-pressurized oxygen therapy with saturations targeted to >92%. These trials, in addition to the ongoing trials using pharmacologic agents in Phase 2 or 3 testing, demonstrate how little we know about the cornerstones of AHF treatment and our need to ensure testing of all aspects in the care of patients with AHF.

Clinicians treating patients with AHF have few proven therapies at their disposal and thus, diuretics and oxygen are often used, despite the lack of high-quality evidence supporting either intervention. While most clinicians are concerned about hypoxia in the acute setting, early clinical work demonstrated the negative consequences of hyperoxygenation in patients with HF. Reviewing the HF trials over the past three decades, there were only two agents (i.e.

Sacubitril/Valsartan and Ivabradine) that hold promise, whilst there has been a long list of agents used in trials that generated inconclusive results (Figure 1.2). The situation is even worse for patients with HF and preserved ejection fraction, with no evidence-based therapies shown to improve survival in that group of HF patients. Clearly, an improved understanding of all pharmacologic approaches to HF treatment is also needed and will be complementary to any new drug developed in this area.

Negative trials
renin antagonists
TNF antagonists
ET-1 receptor antagonists
Immune modulation therapy
MMP inhibitors
Statins
vitamin D
neprilysin inhibitors
glucagon-like peptide-1 agonists
CRF-2 receptor agonists
cardiac myosin activator
sGC stimulator
vasopressin receptor antagonists
calcium sensitizers
Adenosine receptor antagonists



Positive trials
Sacubitril/Valsartan
Ivabradine

Figure 1.3. Some examples of successful and unsuccessful therapies tested recently in HF

CRF-2: Corticotropin releasing factor type-2; ET-1: endothelin 1; MMP: matrix metalloproteinase; sGC: soluble Guanylate Cyclase; TNF: tumor necrosis factor;

1.3 Hierarchy of evidence

The hierarchy of evidence is ranked based on the susceptibility to bias and possibility of systematic errors (Figure 1.3). From that perspective, well-designed randomized clinical trials sit at the top of the pyramid, as they have the lowest risk of bias and confounding. The randomization allocates patients into study arms randomly and even if there is a risk for confounders, it distributes confounders randomly among the study groups.

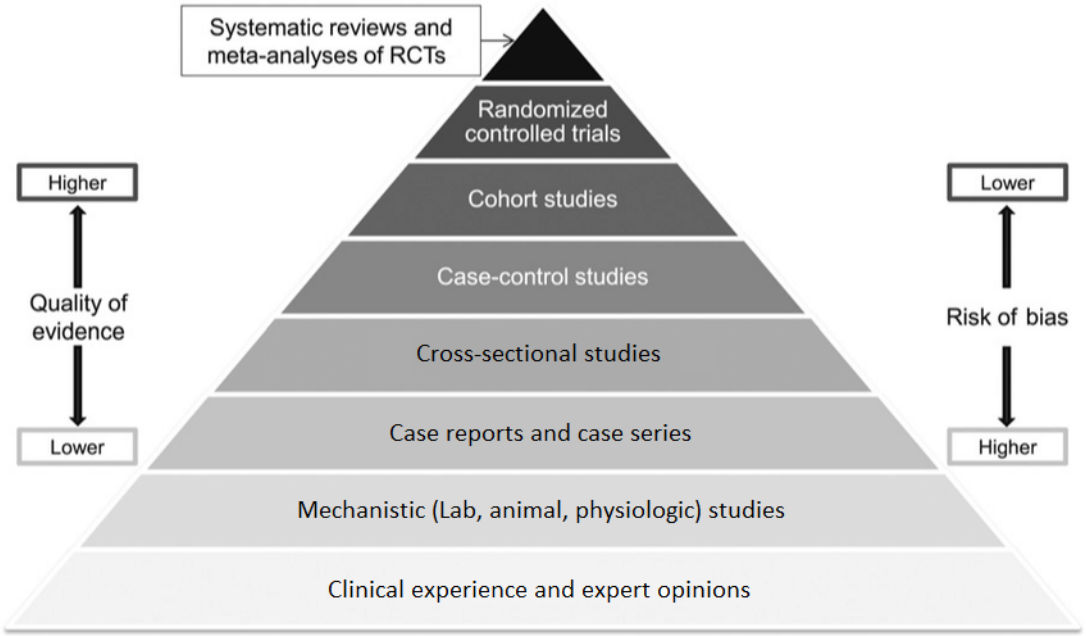


Figure 1.4. Level of evidence pyramid for treatment studies

Similar emphasis to randomized clinical trials is noticeable in other widely used grading schemes, most recently the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.[37-39]

1.4 Randomized Clinical Trials: From inception to today

The rapid creation and dissemination of new medicinal products in the late 19th and early 20th century created an urgent need to assess the efficacy/effectiveness and safety of these therapies. Moreover, the creation and application of methods of clinical investigation that were more reliable than the methods previously relied upon including expert opinion, case-controls studies, physiologic experiments or case reports was needed. An earlier version of the RCTs, known as alternate allocation trials were characterized by treating every other patient or patients seen on every other day with the investigational therapy. This method was able to address the issue of non-controlled deductions in the first half of the twentieth century. However, further reform in the trial design and implementation was needed as alternate-allocation trials were vulnerable to selection bias. The two main changes that made trials the gold standard for medical research were the addition of concealed allocation, randomization and the blinding of researchers and participants to group allocations.[40] Thereafter, the regulatory agencies required pharmaceutical

and device manufacturers to provide evidence of the safety and efficacy of their product through RCTs before they could be considered for potential approval.[41-43]

1.5 Trial design decisions

The same PICO approach that is routinely used for formulating questions in evidence-based medicine can be considered as the cornerstone of designing a trial. The mnemonic respectively stands for population, intervention, control (comparison), and outcome. Some EBM experts add a "D" to the PICO question in order to focus on the best possible design to answer the question (PICO-D). There are many important measures that should be considered during the trial design (e.g., concealed allocation, identical treatment of groups except for the intervention, randomization, blinding of participant, study personnel and outcome assessors, etc.). Selecting the appropriate primary endpoint is one of the important steps. In the following sections and in chapters 2 and 3, we will cover some of the topics related to the outcome of interest. This schematic figure outlines some fundamental aspects of the trials and how the topics discussed in this thesis are related to those aspects (Figure 1.4).

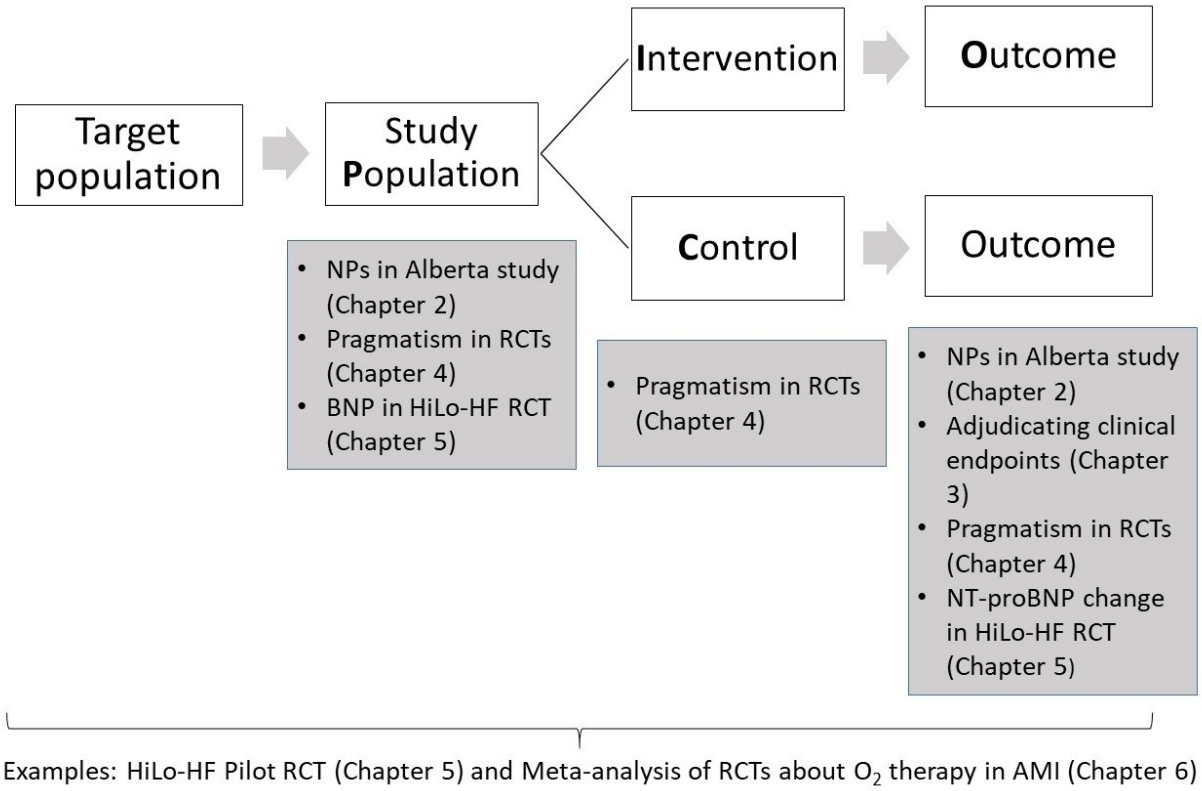


Figure 1.5. PICO in formulating the design for RCTs

BNP: Brain-type Natriuretic peptide; HiLo-HF: High versus Low oxygen therapy in acute Heart Failure; NP: natriuretic peptide; NT-proBNP: N-terminal proBNP; O2: oxygen; RCT: randomized clinical trial;

1.6 Study Endpoints

A critical step of trial design is finding an outcome measure that is appropriate for the research question. An endpoint could be a biomarker, symptoms, quality of life, survival or health system exposures such as ambulance or emergency department use or hospitalization, or a composite of those components, etc. There are exhaustive discussions and deliberations in the literature on the characteristics of an appropriate endpoint for every disease condition and trial phase and setting.[44]

1.6.1 Surrogate endpoints

Food and Drug Agency (FDA) defines a surrogate endpoint as "a laboratory [or radiographic] measurement or physical sign that is used in therapeutic trials as a substitute for a clinically

meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy".[45] The surrogate outcome needs to have a strong correlation with and to capture all important impacts of the intervention on the clinically relevant outcome.[45,46]

In the late 1980s, the regulatory agencies took a flexible approach towards using surrogate markers for drug approvals.[47,48] Approximately half of the therapeutic agents approved by the FDA were based on trials that used surrogate markers as the primary outcome.[49] These markers are critical in shortening the time that we spend on narrowing down the long list of experimental therapies (plus appropriate doses) that could be taken to the next phase trials for being investigated against clinically-relevant outcomes.[45,50] Roughly a third of CV RCTs published in high impact factor journals from 2001 to 2012 used surrogate endpoints.[51] These trials had faster patient enrolment and completion and were more likely to be positive for their primary outcome.[51] Hence, surrogate markers facilitate trial efficiency with earlier completion and lower cost expenditure.

1.6.1.1 Biomarkers in Heart Failure RCTs

The ubiquitous availability of biomarkers provides the opportunity to adopt those for identifying eligible patients, as a part of the intervention, or as the primary endpoint and surrogate marker in the trials. Natriuretic peptides, including Brain-type Natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) have emerged as strong biomarkers for diagnosis and prognostication of patients suspected of having heart failure. BNP was originally isolated from the porcine brain but in humans, it has been synthesized in the heart in response to ventricular wall stress and volume/pressure overload from the cleavage of proBNP(1-108).[52,53] NT-proBNP is the other, biologically-inactive fragment and result of the proBNP cleavage. Elevated levels are shown to be associated with poorer prognosis [54] and New York Heart Association (NYHA) functional class, higher intraventricular pressures and pulmonary pressures, and inversely correlated with cardiac output.[55,56] Even when added to contemporary heart failure risk prediction models, natriuretic peptides are shown to improve discriminatory performance and prognostication.[57]

Biomarkers can help in identifying the target patients and those who can benefit the most from the intervention under study. In the HiLo-HF (High versus Low Oxygen therapy in acute

Heart Failure) trial which was a pilot RCT about the effects of supplemental oxygen therapy in patients presenting to the ED with AHF (Chapter 5), the serum BNP level above or equal to 400 pg/mL was defined as an inclusion criterion to increase the chance of identifying patients who are experiencing a true AHF episode.[58]

The GUIDE-IT (Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure) trial, besides several other trials, used serial NT-proBNP testing with targeting an NT-proBNP level <1,000 pg/mL to guide heart failure treatment in the intervention group and compared that to usual care in the control group.[59] Natriuretic peptides have been widely used as the primary or secondary endpoint in HF RCTs. Larger decreases in the NT-proBNP levels were linked to lower risk of mortality at 6 months in the phase III trials of Serelaxin, a recombinant human relaxin-2 drug (RELAX-AHF).[60,61] In the HiLo-HF trial (Chapter 5), the primary endpoint was the change of serum NT-proBNP levels from randomization to 72 hours.[58]

Province-wide access to natriuretic peptide testing was provided by Alberta Health Services for all Alberta EDs in 2012. In chapter 2, we investigated the uptake of natriuretic peptide testing in these EDs and evaluated factors that were associated with natriuretic peptide testing. Knowing about these factors may help us understand the logistics and strategies required for conducting large RCTs that apply natriuretic peptides either for participant identification, intervention, or outcome ascertainment.

1.6.2 Endpoint Adjudication

The use of centralized endpoint adjudication is now a common practice in many RCTs that consider clinical events as primary or secondary endpoints, and central endpoint committees (CEC) are routinely used for adjudicating events in CV trials. A review of 314 RCTs from various medical disciplines have reported CEC in one-third of RCTs with clinical event endpoints, with a significantly higher use (>80%) in CV RCTs.[62]

The rationale behind endpoint adjudication is to ensure the systematic application of definitions for events with potentially subjective and heterogeneous nature. Events such as all-cause mortality do not require adjudication, however, for primary or safety endpoints such as

myocardial infarction (MI), bleeding, stroke, or HF hospitalization, an independent, blinded CEC can classify events systematically based on the definition that is determined in the study protocol.

Systematic reviews of RCTs have shown treatment effects to be exaggerated and misleading in trials with non-blinded versus blinded outcome assessors (ascertainment bias).[63,64] However, other studies have reported the treatment effects to become more significant [65-67] or less significant [68-73] by applying the CEC.

Adjudication could vary from confirming the events reported by the site to screening charts, biomarkers and imaging reports to detect events that were missed by the site investigators. The level of variability, reproducibility, and complexity of the clinical event, and the presence of standard definitions are some of the factors that should be considered when contemplating about a CEC during the trial design.[74] A consensus statement by Cardiac Safety Research Consortium and the US FDA recommended adjudicating CV endpoints only when a trial is conducted by non-CV physicians, or if it's conducted by CV physicians but it is unblinded or requires determination of subcategories of major adverse cardiovascular events (MACE) comprising CV death, non-fatal MI, and non-fatal stroke or MACE+ (i.e. MACE plus ≥1 other event e.g. HF hospitalization) endpoints[75] (Table 1.1).

A meta-analysis of ten CV RCTs found no effects of outcome adjudication on the number of events or the treatment effect, regardless of the masked or unmasked nature of trials.[76] Another study concluded that the adjudication is not improving the ability to determine treatment effect.[74] When we don't have standard definitions for the event such as the case with AHF presentations at ED,[77] the adjudication may not improve accurate classification of events.[78]

Table 1.1. Recommendations on planning and reporting of central endpoint adjudication in RCTs[62]

Points to consider	Recommendations for planning	Recommendations for reporting
When to use an AC	In all RCTs having clinical event involving some subjectivity as primary outcome and especially, if the intervention is not delivered in a blinded fashion	Report the use of an AC in the Materials and Methods section of the report
Method for selecting cases to adjudicate	Provide a definition for suspected events	
	Use sensible methods to capture suspected events including those that were not identified by local investigators (e.g., core laboratories, registries…, algorithm)	Report these methods as well as who collected the data and whether they were blinded
Information provided to the AC	For each case, complete medical files, including results of tests performed. Forecast other sources of information if possible (e.g., national registries).	Report the type of information provided to the AC
	Remove all information that could withdraw blinding of treatment arm	Report that all data related to the treatment arm were removed of the information provided to the AC
Composition of the AC	At least three clinical experts in the field of the primary outcome	Report the name, expertise, and training of members of the AC in the appendix of the report
	If primary outcomes are in different medical areas, use several ACs	Give the composition of each AC in an appendix section
Blinding/independency	Members of the AC should be independent of the trial sponsor and blinded to the treatment arm while assessing outcomes	Report in the method section that the AC is independent of the trial sponsor and blinded to the treatment arm
Reviewing process	Define all the adjudicated outcomes	Report in an appendix the definition of adjudicated outcomes
	Train the reviewers to adjudicate the outcomes before the beginning of the trial and resolve any problems	
	Define a method to reach consensus	Report how the consensus was reached
Assess the reliability of results	Readjudicate a random number of cases	Report any method used to assess the reliability of results

AC: adjudication committee;

Despite being the standard for classifying events in RCTs, there is a paucity of studies investigating the optimal setting and operational approaches for the use of event adjudication.[79] It's not clear yet whether the purported improvement in the credibility of results with centralized adjudication of endpoints outweighs the added complexity and increased costs.[80] Careful planning might solve some of the issues related to CEC in trials, such as the delay in publishing results due to delay in dataset lock. Further studies are needed to determine when and what level of endpoint adjudication is helpful and efficient. In chapter 3, we explored the data from Providing Rapid Out of Hospital Acute Cardiovascular Treatment 3 (PROACT-3) trial[81] to compare the differential alignment of site versus CEC decisions for the ascertainment of angina, acute MI and AHF diagnoses.[78]

1.7 Key limitations of RCTs

Randomization in RCTs evenly distributes the known and unknown confounding factors among intervention and control groups, hence reducing the risk of confounding. Despite the indisputable

role of RCTs in providing minimally-biased and reliable evidence for important research questions, impediments such as high cost, the need for large sample size, long study duration and so on, limit their ability to answer our persistently-growing clinical dilemmas.[82] The cost of a single phase 3 RCT is estimated to be around 30 million US dollars.[83] This comes in parallel to a flourished clinical trial industry with contract research organizations accounting for a net worth of 25 billion dollars just in the last quarter of the twentieth century.[84]

Due to the long times from the design phase to the publication of results, RCTs sometimes cannot keep up with the fast pace of the medical discoveries and innovations, leaving a gap in our knowledge about optimal practice. An excellent example of the RCT data falling behind medical/clinical innovations is bare metal stents (BMS) for percutaneous coronary intervention (PCI) of patients with acute ST-segment elevation myocardial infarction (STEMI). By the time that the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial reported the disappointing results of PCI with the use of BMS in 2007,[85] the new drug-eluting stents (DES) were introduced, dictating a need for new controlled trials, etc.[86,87]

Inadequate (not long enough) follow-up in trials prevents the detection of rare but severe adverse events of new investigational drugs that are usually identified post-approval during the post-marketing long-term surveillance. History of clinical research is full of examples in which an investigational drug was reported to be effective in early phase trials using surrogate markers as the primary endpoint, whilst this was not confirmed in later trials where the drug was tested against clinical outcomes, showing that the investigated surrogate markers were not strongly correlated with the clinical outcomes of interest.

Identification and enrollment of high-risk patients, done to increase the possibility of events and power, could endanger the generalizability of study results for the target population.[87-89] The issue of generalizability of the target population and the dissimilarities between RCT and non-RCT (e.g. registry) patient populations have been well documented.[90]

1.8 Evolution of innovative RCTs

Although in some cases, well-designed and well-implemented observational studies still hold some promise, many settings, e.g. approving new medicinal products for use in clinical care, require evidence from clinical trials. It seems inevitable for regulatory agencies, and trialists in

academia and industry to seek creative, innovative and collaborative ways to streamline the implementation of RCTs whilst keeping them up to regulatory standards.[91,92]

With the pervasiveness and advances of electronic health records (EHR), new doors are opened for RCTs. Harmonizing classification of diseases using International Classification of Diseases (ICD) codes paved the way for the use of these electronic health data in identifying eligible patients and completing patient follow-up. Using data that are collected for administrative purposes simplifies the conduct of RCTs. As an example, the high cost of long-term follow up for patients recruited in an RCT can be mitigated using administrative health data with the condition that those data are being collected in a systematically-reliable manner. There are problems associated with using administrative data collection for outcome assessment in trials. These include the uncertainties about the reliability of billing codes, possibility of clerical errors, challenges of working with claims databases, etc.

Registry-based RCT that profits from the existing participant identification and data collection systems in national or local registries is another approach to take advantage of existing resources.[19] For instance, the DETO2X-AMI trial that was mentioned earlier in this chapter, used the SWEDEHEART (Swedish Web System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry, which is the national comprehensive inpatient and outpatient registry of heart disease to enroll patients and for data collection.[31]

Comparative effectiveness trials that are integrated into routine clinical operations of the healthcare systems can provide answers while retaining both the minimal intrusiveness of observational studies and the strengths offered by randomization. Finding suitable study interventions that are in common use and have well-described adverse event profiles, simplified methods of informing and consenting patients, and leveraging electronic health records for patient screening and follow-up allow the minimal perturbation of study operations from routine clinical practice in these trials.[93]

Randomizing groups of people (patients or providers) instead of individuals, as is done in cluster-randomized trials, provides some level of simplification in terms of participant identification and recruitment and prevents the contamination bias that occurs when members of the control group are inadvertently exposed to the intervention and may arise from individual

randomizations in a cluster of patients. Another method, called stepped-wedged design introduces the intervention over time in a way that all clusters receive the experimental intervention eventually.[94]

1.9 Pragmatic RCTs

Despite the increasing number of RCTs being published every year, the majority of these RCTs are aimed to respond to the questions raised by the advent of new technologies and procedures in medicine. Nevertheless, many of the long-standing questions in clinical medicine and cardiology lack a definitive answer and the knowledge gap is widening with a considerable pace.

A method that is now widely accepted as one of the approaches to resolve the above-mentioned limitations of traditional RCTs is the pragmatic approach which is embodied in the so-called "effectiveness" or "pragmatic" trials. The terminology and concept of pragmatic vs explanatory trials was first coined by Schwartz and Lellouch in 1967,[95,96] but it was neglected for decades until recently, when several international initiatives such as the PRACTIHC (Pragmatic Randomized Controlled Trials in HealthCare),[97] and the National Institute of Health (NIH) Collaboratory [98] promoted the pragmatic trials to generate trial results that are more applicable to the population in which the intervention will be eventually applied. Thereafter, trialists tried to ensure that their RCT design decisions are aligned with the intended purpose of the trial, be to inform clinical decision-making (effectiveness of an intervention over the other in usual care setting) or to explain the efficacy of a specific intervention in an ideal condition (Table 1.2).

Broad eligibility for patients, broad eligibility for care providers and sites, simplified data collection, use of electronic health records for follow-up, some level of leniency on protocol violations such as nonadherence or loss to follow-up that is no more than what happens in the daily practice are some aspects of the pragmatic trials that simplify the design and conduct of RCTs.[97,99-101]

Table 1.2. Comparison between explanatory and pragmatic trials

Explanatory trials	Pragmatic trials
• Strict in/exclusion criteria	• Diverse / representative population
• Ideal setting	• Usual care setting
• Specialized centres	• Multiple, heterogeneous centres
• Slow recruitment	• Faster recruitment
• Comparison with Placebo	• Comparison with real-word alternatives
• Physiological endpoints	• Clinically-important outcomes
• More expensive	• May be less expensive

Pragmatic RCTs evaluate the effectiveness of the intervention in a way that it's going to be ultimately applied in the clinic, hence maximizing the generalizability of the trial findings. The concept of pragmatic trials will be explained and explored in greater details in chapter 4. We applied a newly-developed tool that is called "PRagmatic Explanatory Continuum Index Summary-2" or PRECIS-2 to investigate the level of pragmatism and its related factors in CV trials and to explore the change in pragmatism over a two decades period.

1.10 Objectives

Despite the improvements in the design and implementation of CV RCTs over the last several decades, there are still many unanswered questions that need to be addressed. Trialists are required to make multiple decisions in the trial design to ensure the validity and generalizability of the trial findings, whilst they rarely have the evidence at their disposal on the optimal practice for every single decision. In this thesis, we explored some of the important aspects of the trial design including the outcome assessment and the level of pragmatism in CV RCTs. Moreover, we performed a pilot RCT to investigate the feasibility of conducting a future larger RCT about the effects of supplemental oxygen therapy in patients with AHF. As the next step, we performed a meta-analysis to synthesize the findings of available RCTs in the literature about the effects of supplemental oxygen therapy in patients with acute myocardial infarction. The specific objectives of this thesis are as below:

1. To describe the natriuretic peptide testing in emergency departments of Alberta and to evaluate the factors associated with that testing in the emergency department (Registry data)

2. To assess the level of agreement between site investigators and adjudication committee for diagnosing conditions such as acute coronary syndrome or acute heart failure in patient presenting to emergency department with CV symptoms (PROACT-3 RCT)
3. To investigate the level of pragmatism in CV RCTs and to study the change in the trial design domains and overall level of pragmatism in CV trials over the past 2 decades (Systematic Review)
4. To investigate the feasibility of conducting an RCT about supplemental oxygen therapy in acute heart failure and to explore the effects of oxygen therapy in patients hospitalized with AHF
5. To explore the effects of oxygen therapy in patients with acute myocardial infarction by synthesizing and pooling the data from all available RCTs in the literature (Systematic review and meta-analysis)

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Chapter 2 : Factors associated with natriuretic peptide testing in patients presenting to emergency departments with suspected Heart Failure

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2.1 Abstract

Background: Testing for natriuretic peptides (NP) such as BNP or NT-proBNP in the emergency department (ED) assists in the evaluation of patients with acute heart failure (HF). The aim of this study was to investigate factors related to the utilization of NPs in the ED in a large population-based sample in Canada.

Methods: Retrospective cohort study using linked administrative data from Alberta in 2012. Patients were included if they had testing for an NP in the ED and a comparator group with HF but without NP testing was also included.

Results: Of the 16223 patients in the cohort, 5793 were patients with HF (n=3148 tested and n=2645 not tested for NP) and 10430 were patients without HF but tested for NPs. Patients without HF who were tested for NPs, had respiratory disease (34%), non-HF cardiovascular diseases (13%), and others (52%). Patients with HF who were tested had a higher rate of hospital admission from the ED (78.4 vs. 62.2%; $p<0.001$), and lower 7 day and 90 day re-ED visit rates compared to those who were not tested. Among patients with HF, being male, an urban resident, being seen by an emergency medicine or cardiology specialist, and being in hospitals with medium ED visit volumes were associated with increased likelihood of testing for NPs.

Conclusions: Several factors, including the type of provider and ED clinical volume, influenced the utilization of NPs in routine ED practice. Standardization of a NP testing strategy in clinical practice would be useful for healthcare systems.

Keywords: Natriuretic peptides, BNP, NT-proBNP, heart failure, biomarker

2.2 Introduction

Heart Failure (HF) is a major healthcare problem in Canada and worldwide. It is estimated that there are 500,000 Canadians living with symptomatic heart failure with 50,000 new patients diagnosed each year,[1] and heart failure's global burden is expected to double in the next 1-2 decades.[2-4]

The majority of patients with dyspnea or suspected HF present via the emergency department (ED), and thus, tools to rule-in or rule-out heart failure are usually deployed in the ED. Two blood markers, BNP and NT-proBNP [collectively called natriuretic peptides (NPs)], are produced predominantly by ventricular cardiomyocytes under conditions of volume overload and myocardial stretch.[5, 6] Major practice guidelines, including Canadian guidelines, recommend the use of NP testing for diagnosing acute HF in EDs in the appropriate clinical situation,[7-10] and use in that setting has been shown to improve diagnostic accuracy and reduce healthcare costs.[11-13]

Despite these guidelines, the majority of healthcare regions in Canada have restricted availability to NP testing due to concerns over cost to laboratory services. After a pilot project, province-wide access to NP testing was provided by Alberta Health Services for all Alberta EDs in 2012. However, little is known about the utilization of this HF biomarker in a wide spectrum of EDs in a publicly funded healthcare system. The objectives of this study were to describe NP testing in all EDs of Alberta, and evaluate the factors related to NP testing.

2.3 Methods

In this retrospective cohort study, administrative data was used to capture information on patients who attended any ED in Alberta, Canada between April 1st, 2012 and March 31st, 2013. Alberta provides universal healthcare coverage and all patients and healthcare facilities provide data as described below. Alberta has approximately 4 million residents, 107 acute care facility EDs, and an annual ED volume of over 2.3 million visits. This study was approved by the Health Ethics Research Board of the University of Alberta, Edmonton, Alberta.

2.3.1 Data sources

Data for the study were retrieved from databases described previously[14, 15] and maintained by Alberta Health Services –Analytics. This database contains data on all inpatient and outpatient interactions with the health system as described below. The databases are comprehensive and were linked using each individual's unique lifetime identifier (ULI).

The Alberta version of the National Ambulatory Care Reporting System (NACRS) database includes all visits to any ED in Alberta and captures the most responsible diagnosis and up to 9 other diagnoses per encounter. NACRS also includes patients brought by ambulance who died before arriving at the hospital. Data from the NACRS was merged with inpatient data from the hospital Discharge Abstract Database (DAD) to identify the most responsible diagnosis and up to 24 comorbid conditions coded using International Classification of Diseases (ICD) codes, 10th (ICD-10) revision.[16, 17] The information in these databases has been demonstrated to be highly accurate for research use.[18] Urban-rural residence was determined as per the methodology applied by Statistics Canada, using the second character of the forward sortation address for each patient's home address as reported in the Alberta Health Care Insurance Plan Registry file.[19, 20]

Our cohort included all patients older than 18 years who presented to the ED with either (1) an ED most responsible diagnosis of HF or (2) had a natriuretic peptide test done. HF was defined using ICD-10 code I50.x. Natriuretic peptide testing is outlined in Figure 2.1.

Hospital-specific variables were created by identifying clusters of hospitals based on the average annual ED visits with a main diagnosis of HF, categorizing them into three tertiles with small (<62 HF cases / year, n=87 ED), medium (62-320 cases, n=15 ED), and high (>320 cases, n=5 ED) ED visits volume.[21] The 3 largest tertiary care hospitals (2 in Edmonton, 1 in Calgary) were also explored in a secondary analysis given their high patient volume. The cost of each hospitalization was estimated using the Resource Intensity Weight (RIW) methodology.[22] An estimate of the expected province-specific, intensity-adjusted resource consumption was calculated and made available for each of the 528 case mix groups (CMG). CMGs are identified by Canadian Institute of Health Information (CIHI) and each is consisted of cases with similar characteristics including diagnosis, intervention, and resource use. In Alberta, a physician working in the ED may have a variety of certifications or training, and physician specialty was divided into 5 categories (cardiology and critical care medicine, internal medicine, emergency medicine, general practice, and others), as previously described.[23]

2.3.2 Laboratory data

The ULI was used to link each patient to the ED and hospital lab data from a province-wide laboratory repository, similar to a previous study.[24] The following test results were included: sodium, potassium, creatinine, hemoglobin, BNP, and NT-proBNP. In Alberta, the Alere BNP assay (Alere, San Diego, USA) is used for BNP testing and for NT-proBNP, the Roche assay

(Roche Diagnostics GmbH, Manheim, Germany) is used. The choice of NP test is dictated by the available laboratory equipment; all hospitals had access to one test or the other. Creatinine values were included if done within 2 days prior to index ED visit, and sodium, potassium and hemoglobin were included if done ± 2 days around the index ED visit. The majority of tests (90%) occurred on the same day as the ED visit, and NP testing was only used if done at the time of the ED visit. If multiple tests were available in the above-mentioned time-frames, the one that was closest to the ED presentation time was used.

2.3.3 Comorbidities

Comorbidities were identified using ICD-10 codes for all acute care hospitalizations in the prior 3 years. For the purposes of risk adjustment, the Charlson Comorbidity Index score was calculated using the prior 3-years data.[25]

2.3.4 Primary and Clinical Outcomes

The primary outcome was testing for NPs in ED. Clinical outcomes of interest included all-cause mortality, hospitalization, re-hospitalization and repeat ED visits in the next one year.

2.3.5 Statistical Analysis

The continuous variables in each group were presented as mean± standard deviation (SD) or median and interquartile range (IQR), where appropriate, and the categorical variables were provided as frequency and percentage. The patient characteristics were compared between groups using Wilcoxon test and chi-square tests, where appropriate.

A series of logistic regression models were created to estimate the adjusted effects of demographics, comorbidities, laboratory data and NP testing, on the specified outcome variables as well as likelihood of being tested, based on urban/rural split, number of cases at a hospital, and physician speciality. Adjusted models were built using the backward stepwise selection method with a p-value of 0.20 for removal. Hosmer-Lemeshow goodness of fit was used to examine the appropriateness of the fitted models. Statistical significance was set at p=0.05 and all statistical tests were 2-sided. All statistical analysis was done using SAS statistical software (version 9.4; SAS Institute, Cary, North Carolina).

2.4 Results

From April 1st, 2012 to March 31st, 2013, there were 2.33 million ED visits by 1.15 million Albertans. Of those, 862,805 (74.8%) were over 18 years of age. 5793 unique patients (0.7% of all adult patients in the ED) had a most responsible diagnosis of HF, and a total of 13578 (1.6%)

patients had testing for a NP. Of those tested for NP in the ED, 76.8% (10430 patients) did not receive a final most responsible diagnosis of HF. 2645 patients were not tested for NPs and received a most responsible diagnosis of HF (Figure 2.1).

Mean age was similar between HF groups who were or were not tested for NPs (77.2±12.5 and 77.2±12.7 years, respectively; p = 0.83) and they were older than those without a diagnosis of HF who were tested for NPs (72.3±14.4, p <0.001; Table 2.1). The proportion of patients with male sex was higher (53.0% vs 50.2%, p=0.003) and the proportion of rural residence was lower (17.9% vs 27.0%, p<0.001) among patients with HF who were tested for NPs compared to HF patients who were not. Based on the Charlson Comorbidity Index score, the patients with HF tested for NPs had a similar burden of comorbidities compared to HF patients who were not tested for NPs. There was no difference in terms of renal function between HF groups with and without tested NP. The NP testing patterns differed among hospitals with different levels of ED visits volume (p<0.001), and among different types of medical care providers (p<0.001).

2.4.1 Natriuretic peptide results

A total of 13578 patients had an NP test:10383 (76.4%) patients had a BNP test, and 3195 (23.5%) patients had a NT-proBNP test. The median values for both BNP and NT-proBNP for patients with HF were six fold higher than those without the diagnosis of HF (BNP: 649 pg/ml (IQR 324-1244) versus 123 pg/ml (IQR 44-318), respectively; p <0.0001; NT-proBNP 3408pg/ml (IQR 1654-7616) versus 605pg/ml (IQR 177-2033), p<0.0001). Other lab values are presented in Supplementary Table 2.1.

2.4.2 Geographic, hospital volume and specialty variability in NP testing

Of patients with HF, the proportion of rural residents tested for NPs was lower compared to urban patients (16.9% vs. 27.0%; p<0.001). In hospitals with Low, Medium or High ED visit volume, the rate of testing for NPs among patients with HF was 42.0%, 71.5% and 52.0%, respectively (p<0.001).The rate of testing for NPs in patients with HF varied from 0% to 100% across different hospitals (Supplementary Figure 2.1).The rate of patients with a primary ED diagnosis of HF not tested for NPs was higher in Calgary's tertiary care centre (67.6%) compared to the two tertiary care hospitals in Edmonton (8.0% and 11.6%; p<0.001).

A higher percentage of HF patients seen by Emergency Medicine specialists were tested for NPs (62.7%) compared to patients seen by other specialties (total 54.3%; p <0.001; 50.3% in

Cardiology and Critical Care Medicine, 56.8% in Internal Medicine, 50.9% for other specialties and 45.1% for general practitioners).

The top three diagnoses (by ICD-10 code) in the patients without HF who were tested for NPs included diseases of the respiratory system in 34.0%, diseases of the circulatory system other than HF in 13.1%, and signs and symptoms involving the respiratory and circulatory systems but not yet diagnosed in 17.0% of patients.

2.4.3 Clinical Outcomes

Of patients with a diagnosis of HF, 70.8% (n = 4107) were admitted to hospital. The admission rates were lower for those without testing for NP but with a diagnosis of HF (62.2%), and patients who had NP testing and a diagnosis other than HF (58.6%; n = 6097; $p<0.001$).

Thirty-eight patients (0.2%) died during their index ED visit and among patients who were hospitalized, 9.5% (n=977) died during their index hospitalization (Table 2.2). The rate of death at index hospitalization was numerically higher in those patients with HF but not tested for NPs. The patients with HF, regardless of testing for NPs, had a similar 7 day, 90 day and 1 year mortality rates (Table 2.2). Patients with HF who were not tested for NPs had a similar 7 day and 90 day re-hospitalization rates, but higher 7 day and 90 day re-ED visit rates compared to those patients with HF who were tested for NPs ($p<0.02$). These differences remained after adjusting for key patient and hospital related variables (Supplementary Table 2.2).

2.4.4 Multivariable modeling predicting NP testing

Among patients with the diagnosis of HF, being male, an urban resident, and having prior HF were associated with higher likelihood of being tested for NPs (Figure 2.2). The likelihood of being tested for NPs was higher if the care provider was an Emergency Medicine specialist (OR 2.29, 95%CI 1.97, 2.66), Cardiology/Critical Care Medicine specialist (OR 1.57, 95%CI 1.10, 2.24) or Internal Medicine specialist (OR 1.49, 95%CI 1.17, 1.90), when compared to General Practitioners. Compared to the hospitals with low volume of ED visits, the patients treated in hospitals with a Medium volume of ED visits had higher odds of NP testing (OR 2.43, 95%CI 2.07, 2.86). Patients with diabetes or treated in hospitals with High volume of ED visits had a lower likelihood of being tested for NPs (adjusted OR 0.76, 95%CI 0.68, 0.86 and 0.79, 95%CI 0.66, 0.94, respectively).

2.4.5 Resource Use

The resource intensity weight (RIW) related to index ED visit as well as the 90-day RIW were significantly different between HF groups with higher resources spent for the HF group who have been tested for NPs.

2.5 Interpretation

We found that ¾ of patients tested for NPs in the ED did not end up with a diagnosis of HF, likely consistent with clinicians' knowledge of the established high negative predictive value of NP testing. We also identified several factors influencing natriuretic peptide testing patterns, including some comorbidities, geographic location, ED volume, and physician specialty. Finally, patients who had NP testing done were more likely to be admitted to hospital during their index ED visit.

Urban and rural variation in testing for NPs within Alberta was evident despite a single payer and universal availability. In fact, there was even a difference between tertiary care centers in two urban settings. These variations in practice, despite strong endorsement in Canadian guidelines since 2007 for the role of NP testing in the ED, suggests a need for better knowledge dissemination efforts to standardize care and thereby optimize patient outcomes.[26] All the physicians across the province received the same educational materials developed by AHS Chemistry Laboratory Integration Network in conjunction with a group of cardiologists, internists and emergency physicians during the provincial implementation of NP testing.[27]

Our data showed that patients with HF who were tested for NPs were more often admitted to hospital from the ED compared to patients who were not tested for NPs. Additionally, this group (patients with HF and tested for NPs) had a lower rate of short-term or long-term re-ED visit rates compared to their counterparts with HF but not tested for NPs, even after adjusting for key patient and hospital related variables. In general, the length of stay in patients with HF, tested for NPs, who were admitted to hospital, was shorter – the cause for this is uncertain but remained after adjustment. Additionally, the subsequent lower repeat ED visit rate remained even after landmark analyses for the evaluated time periods out to 90 days after hospital or ED visit. Potential explanations include a shorter time to diagnosis with fewer tests and initiation of appropriate therapy,[28] unaccounted bias if patients with higher certainty of HF or are sicker are tested less often, or improved coordination of care given diagnostic certainty.

Previous randomized studies have demonstrated the cost-effectiveness of NT-proBNP testing in the ED, including a study done in Canada.[13, 29-31] Although the estimated cost saving by the use of NP testing varied between studies (from ~500 - 1800 USD cost reduction per case)[13, 30-32] and with varying time-frames, almost all have demonstrated a significant cost-saving by using this biomarker. For example, Moe *et al*. in the study of Improved Management of Patients with Congestive Heart Failure (IMPROVE-CHF), showed a significant cost-reduction ($949) in median costs at 60 days of follow-up, but no significant difference in the median costs of the initial ED visit or initial hospitalization between NT-proBNP-guided and usual care groups.[13]

Compared to previous reports from Europe, Canada and United States registries of patients with HF, the study population is similar in terms of patients' age, sex, and prevalence of comorbidities such as diabetes mellitus, and atrial fibrillation.[33-37] The BNP or NT-proBNP levels were also similar to those reported by registries where NPs were measured.[35, 38] Considering the similar patient characteristics, we believe our results are generalizable to other regions of Canada and other countries. For regions which are planning to introduce, extend or standardize their NP testing in the ED, the results of current study may help them to recognize and address the potential target groups (e.g. care providers who are more or less likely to order the test), patients groups that should be targeted for testing in the EDs, and particular hospitals where other services e.g. echocardiography is not easily available.

Some strengths and limitations are noteworthy. First, and as with all administrative data studies, we lacked clinical details such as blood pressure, heart rate, ejection fraction or patient-reported outcomes such as dyspnea. However, and unlike previous studies using population-level data, we linked laboratory values (both the testing and the result) and hospital and clinician-level variables together. Second, we did not have individual costing data and therefore used the RIW methodology, which may lack precision as well as focused mostly on hospitalization-related costs, however it does provide an overall estimate of costs where available. Third, we did not capture data on physician-level decision making i.e. the probability that a patient has HF may influence the likelihood of NP testing. This study is conducted in the year following the provincial program in Alberta for the province-wide access to NP testing in EDs, hence it should be noted that the results may be different if the study had been done several years after the provincial program. Finally, we included sites across a varying geographic regions and patient volume which may dilute the effect of individual outlier sites. However, by being inclusive

across an entire province in a single-payer system, this is likely to enhance the identification of opportunities for further study and knowledge dissemination for the ideal use of NP testing.

In conclusion, several factors, including the type of care provider and ED volume, influenced the utilization of NPs in routine ED practice. Despite having a single payer system and the universal availability of NP testing, there was substantial geographic variation in testing for NPs in Alberta EDs. Optimization of a NP testing strategy in clinical practice would be useful for healthcare systems to potentially improve patient outcomes and/or cost-efficiency of care.

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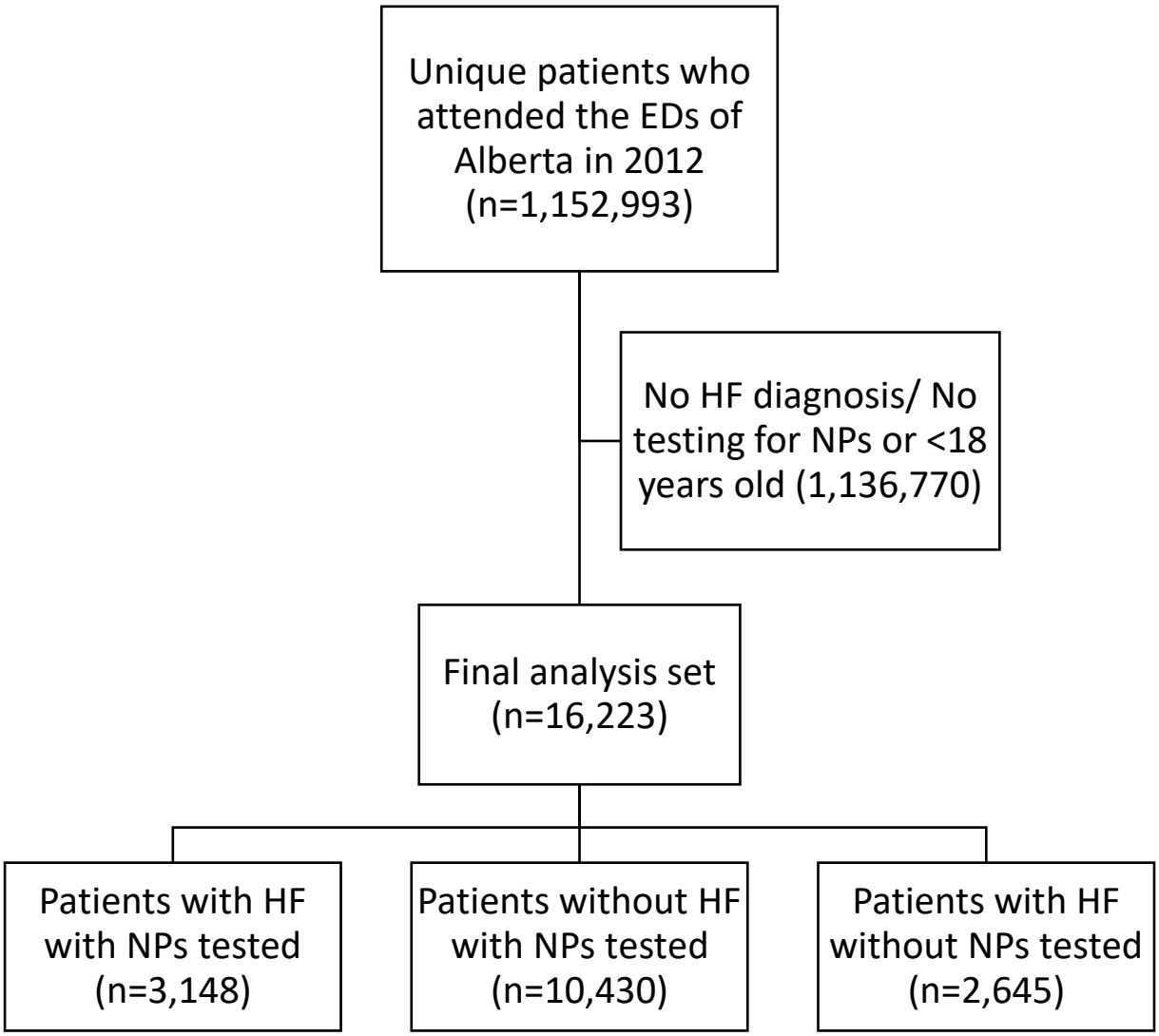


Figure 2.1. Patients flow and the study groups

Table 2.1. Baseline characteristics for patients with suspected HF by different study groups (N=16223)

	HF with tested NP	HF without tested NP	No HF with tested NP	p-value (HF tested NP vs HF without tested NP)	p-value (comparison among 3 groups)
	n=3148	n=2645	n=10430		
Demographics					
Age (y), mean (SD)	77.2 (12.5)	77.2 (12.7)	72.3 (14.4)	0.83	<.001
Male, %	53.0	50.2	50.3	0.03	0.02
Rural residence, %	17.9	27.0	16.6	<.001	<.001
Comorbidities, %					
Hypertension	59.0	57.7	52.4	0.32	<.001
Diabetes	34.3	37.1	29.7	0.03	<.001
Dyslipidemia	24.8	17.5	19.6	<.001	<.001
CAD	40.3	38.3	27.4	0.11	<.001
Myocardial infarction	21.9	19.1	14.9	0.01	<.001
Prior coronary artery revascularization	5.8	5.9	4.4	0.98	0.001
Prior HF	57.9	51.5	24.9	<.001	<.001
Atrial fibrillation	36.5	34.6	20.0	0.13	<.001
Cerebrovascular Disease	11.4	10.9	10.0	0.48	0.06
Peripheral vascular disease	10.1	9.2	7.1	0.26	<.001
COPD	33.6	32.4	38.8	0.34	<.001
Dementia	7.8	8.3	7.4	0.52	0.30
Anemia	22.8	22.0	18.6	0.46	<.001
Cancer	9.4	9.3	9.7	0.82	0.71
Charlson score, mean (SD)	2.9 (2.4)	2.8 (2.5)	2.3 (2.4)	0.13	<.001
Hospital and Provider characteristics					
Hospital, %				<.001	<.001

Tertiary care in Calgary	20.5	42.9	36.7		
Tertiary care in Edmonton	17.2	1.5	81.3		
Tertiary care in Edmonton	19.8	2.6	77.6		
All Urban	19.5	13.0	67.5		
ED visit hospital volume, n(%)				<.001	<.001
Low	767 (19.1)	1058 (26.3)	2201 (54.7)		
Medium	1165 (18.9)	464 (7.5)	4530 (73.6)		
High	1216 (20.1)	1123 (18.6)	3699 (61.3)		
Main provider in ED visit, n (%)				<.001	<.001
Emergency Medicine	1701 (54.0)	1009 (38.2)	7579 (72.7)		
General Practice	1131 (35.9)	1373 (51.9)	2570 (24.7)		
Internal Medicine	211 (6.7)	160 (6.1)	131 (1.3)		
Cardiology/Critical Care Medicine	78 (2.5)	77 (2.9)	19 (0.2)		
Other	27 (0.9)	26 (1.0)	129 (1.2)		
Timing of ED visit				0.99	0.30
Weekday, %	75.0	75.0	73.9		
Weekend, %	25.0	25.0	26.1		

Values are n(%) or mean (SD)/median as appropriate; Comorbidities are defined as 3 years prior to index ED visit; CAD: Coronary Artery Disease; COPD: Chronic Obstructive Pulmonary Disease; ED: Emergency Department; HF: Heart Failure; NP: Natriuretic Peptide; SD: Standard deviation;

Table 2.2. Clinical outcomes in each study group

	HF with tested NP (n=3148)	HF without tested NP (n=2645)	No HF with tested NP (n=10430)	p-value (HF tested NP vs HF without tested NP)	p-value (comparison among 3 groups)
Admission to hospital from index ED visit, n (%)	2467 (78.4)	1640 (62.2)	6097 (58.6)	<.001	<.001
LOS in index hospitalization, days				0.002	<.001
Median (25th-75th percentiles)	7.0 (4-13)	8.0 (4-15)	7.0 (3-13)		
Mean (SD)	11.5 (15.2)	14.2 (22.9)	12.5 (20.5)		
Repeat ED visit, n (%)[§]					
7 days	361 (12.3)	374 (15.2)	1218 (12.4)	0.002	<.001
90 days	1419 (48.3)	1370 (51.6)	4302 (43.9)	0.02	<.001
Repeat hospitalization, n(%)[§]					
7 days	145 (6.4)	109 (7.4)	343 (6.2)	0.23	0.25
90 days	821 (36.3)	523 (35.7)	1691 (30.7)	0.67	<.001
All-cause Death, n (%)					
Index ED visit	3 (0.1)	9 (0.3)	26 (0.3)	0.04	0.14
Index hospitalization	208 (8.4)	173 (10.6)	596 (9.8)	0.02	0.055
7 days	96 (3.1)	95 (3.6)	378 (3.6)	0.25	0.30
90 days	474 (15.1)	405 (15.3)	1318 (12.6)	0.79	<.001
1 year	869 (27.6)	732 (27.7)	2168 (20.8)	0.95	<.001
Economic burden (RIW)					
Index-ED visit RIW, Median (IQR25th-75th percentiles)	1.1 (0.7-1.6)	0.9 (0.1-1.4)	0.8 (0.1-1.4)	<.001	<.001

Total RIW within 90 days, Median (IQR25th-75th percentiles)	1.5 (0.9-3.3)	1.3 (0.4-2.9)	1.0 (0.1-2.4)	<.001	<.001

§ Excludes patients who died at index ED or hospitalization. 7-day or 90-day re-ED visit or re-hospitalization rates include those that admitted to hospital. Follow-up for re-hospitalization started after discharge from hospital. Follow-up for re-ED visit started after discharge from hospital for those who were hospitalized or from time of the ED visit for those who were not admitted to hospital.

ED: Emergency Department; HF: Heart Failure; LOS: Length of Stay; NP: Natriuretic Peptide; RIW: Resource Intensity Weight; SD: Standard deviation;

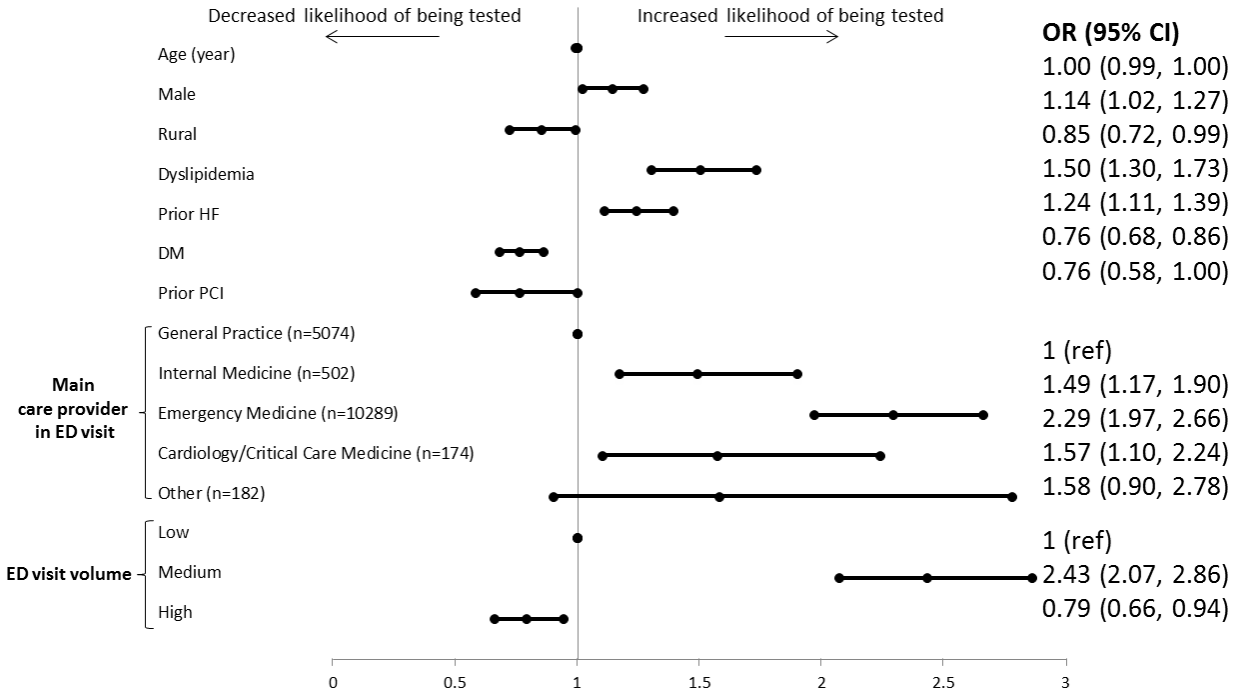


Figure 2.2. Likelihood of testing for NPs in patients with HF

2.7 Supplementary material

Supplementary Table 2.1. Laboratory findings in each group

	HF with tested NP (n=3148)	No HF with tested NP (n=10430)	HF without tested NP (n=2645)	p-value (HF tested NP vs HF without tested NP)	p-value (comparison among 3 groups)
Laboratory test					
BNP test, n(%)	2195 (69.7)	8188 (78.5)	--	--	<.001
BNP (pg/mL), median (IQR 25th-75th percentiles)	649 (324-1244)	123 (44-318)	--	--	<.001
NT-proBNP test, n(%)	953 (30.3)	2242 (21.5)	--	--	<.001
NT-proBNP(pg/mL), median (25th-75th percentiles))	3408 (1654-7616)	605 (177-2033)	--	--	<.001
Creatinine (µmol/L)	125.0 (81.8)	112.6 (102.5)	132.7 (119.1)	0.36	<.001
eGFR (ml/min)	54.2 (24.4)	65.0 (27.5)	54.1 (25.9)	0.77	<.001
eGFR group, %				0.08	<.001
>=60	39.6	57.1	40.6		
30-59.9	42.4	31.0	39.5		
<30	18.1	11.9	19.9		
Sodium (mmol/L)	137.9 (4.8)	137.6 (4.6)	138.0 (4.9)	0.18	<.001
Potassium (mmol/L)	4.2 (0.6)	4.1 (0.6)	4.3 (0.6)	<.001	<.001
Hemoglobin (g/L)	123.3 (20.9)	127.4 (21.5)	122.6 (21.0)	0.54	<.001

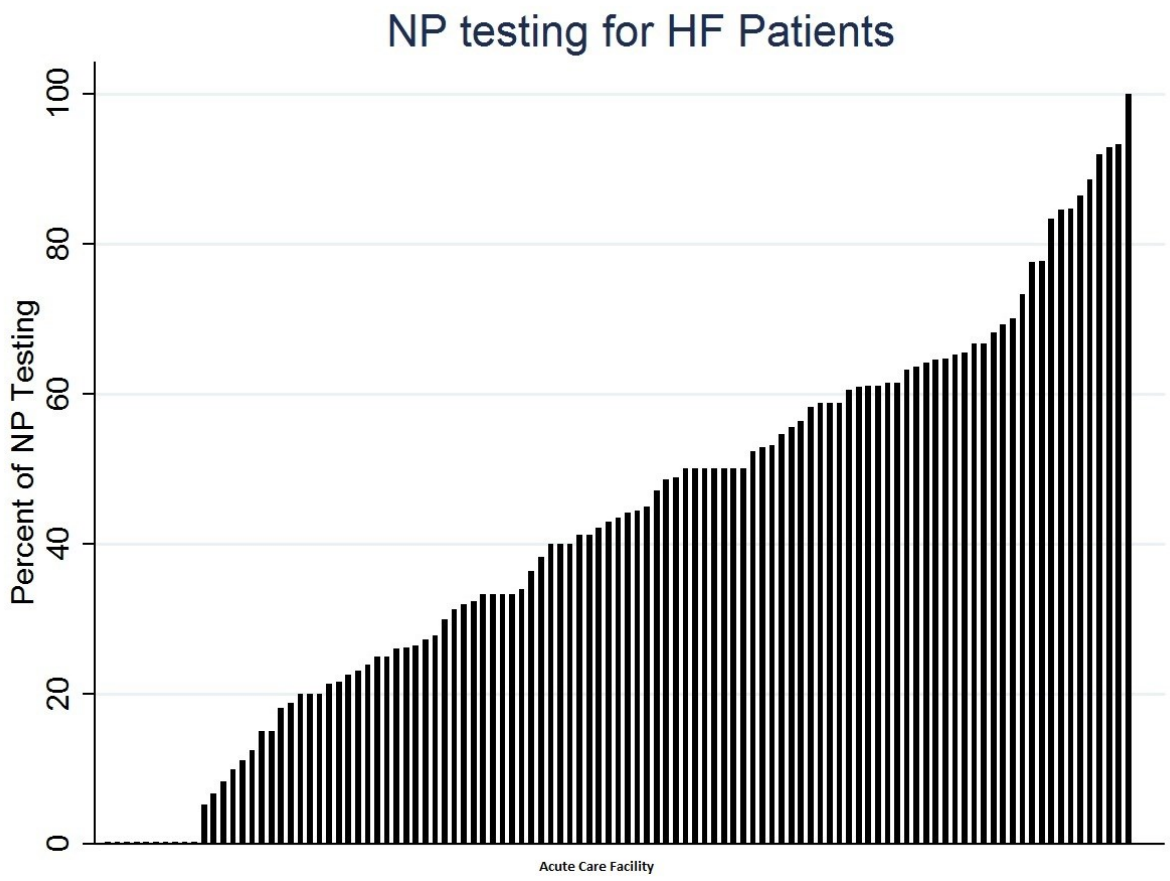
Creatinine and eGFR are defined as within 2 days prior to index ED visit; Sodium, potassium and hemoglobin are defined as ± 2 days of index ED visit; BNP: Brain-type Natriuretic Peptide; eGFR: estimated Glomerular Filtration Rate; HF: Heart Failure; NP: Natriuretic Peptide

Supplementary Table 2.2. Adjusted clinical outcomes

	HF with tested NP (n=3148)	HF without tested NP (n=2645)	No HF with tested NP (n=10430)
All-cause death			
7 days	1 (ref)	1.12 (0.81, 1.53)	1.57 (1.23, 2.01)
30 days	1 (ref)	1.05 (0.86, 1.29)	1.19 (1.01, 1.39)
90 days	1 (ref)	1.07 (0.91, 1.25)	1.02 (0.90, 1.16)
1 year	1 (ref)	1.08 (0.94, 1.23)	0.88 (0.80, 0.97)
Re-hospitalization[§]			
7 days	1 (ref)	1.13 (0.86, 1,48)	0.98 (0.79, 1.20)
30 days	1 (ref)	1.08 (0.91, 1.28)	0.91 (0.80, 1.04)
60 days	1 (ref)	1.03 (0.88, 1.19)	0.83 (0.74, 0.94)
90 days	1 (ref)	1.02 (0.88, 1.18)	0.81 (0.73, 0.91)
Re-ED visit[§]			
7 days	1 (ref)	1.22 (1.03, 1.44)	0.98 (0.86, 1.13)
30 days	1 (ref)	1.18 (1.04, 1.33)	0.94 (0.85, 1.03)
60 days	1 (ref)	1.13 (1.01, 1.28)	0.89 (0.81, 0.97)
90 days	1 (ref)	1.14 (1.02, 1.28)	0.91 (0.83, 0.99)
Economic burden (RIW)[#]			
Index-ED visit RIW	0 (ref)	-0.11 (-0.23, -0.01)	-0.11(-0.20, -0.02)
Total RIW within 90 days	0 (ref)	-0.12 (-0.21, -0.04)	-0.23 (-0.30, -0.16)

§ 7-day, 30-day, 60-day and 90-day re-ED visit or re-hospitalization rates include those that admitted to hospital. Follow-up for re-hospitalization started after discharge from hospital. Follow-up for re-ED visit started after discharge from hospital for those who were hospitalized or from time of the ED visit for those who were not admitted to hospital. Except re-hospitalization, all of the outcomes were adjusted by age, gender, rural residence, comorbidities, eGFR group, care provider, hospital ED volume, and hospitalization in index ED visit. For re-hospitalization, models were adjusted by age, gender, rural residence, comorbidities, eGFR group, care provider, hospital ED volume. #Generalized linear model (log transformed) were used for RIW.ED: Emergency Department; HF: Heart Failure; NP: Natriuretic Peptide; RIW: Resource Intensity Weight;

Supplementary Figure 2.1. The rate of testing for NPs among HF patients in different acute care facilities of Alberta



Supplementary Table 2.3. Main diagnosis in the patients without HF who were tested for NPs

	No HF with tested NP (n=10430)
Main diagnosis, # (%)	
Respiratory System diseases	3548 (34.0%), ICD-10 J**
Symptoms related to Respiratory and Circulatory Systems –NYD	1776 (17.0 %), ICD-10 R00-R09
Circulatory system diseases	1367 (13.1%), ICD-10 I**
Symptoms related to other systems–NYD	1323 (12.7%), ICD-10 R10-R94
Genitourinary system diseases	387 (3.7%), ICD-10 N**
Endocrine, nutritional and metabolic diseases	382 (3.7%), ICD-10 E**
Injuries and poisoning	263 (2.5%), ICD-10 S** & T**
Infectious and parasitic diseases	243 (2.4%), ICD-10 A** & B**
Digestive system diseases	244 (2.3%), ICD-10 K**
Musculoskeletal system diseases	191 (1.9%), ICD-10 M**
Skin diseases	163 (1.6%), ICD-10 L**
Blood diseases	135 (1.3%), ICD-10 D**
Mental, behavioural and neurodevelopmental disorders	124 (1.2%), ICD-10 F**
Factors influencing health status	97 (0.9%), ICD-10 Z**
Neoplasms	75 (0.7%), ICD-10 C**
Diseases of nervous system	75 (0.7%), ICD-10 G**
Pregnancy, child birth and related conditions	20 (0.2%), ICD-10 O**
Ear diseases	13 (0.1%), ICD-10 H**
Congenital malformations and abnormalities	3 (0.03%), ICD-10 Q**

ICD: International classification of diseases; NYD: Not yet diagnosed;

Supplementary Table 2.4. Codes used for identifying comorbidities

Comorbidities	ICD-10 codes	Health Interventions [CCI] codes
Hypertension	I10 - I15	
Diabetes	E10 - E14	
Dyslipidemia	E78	
CAD	I20 - I25	
Myocardial infarction	I21, I22, I25.2	
Prior coronary artery revascularization		1.IJ.76, 1.IJ.26, 1.IJ.50, 1.IJ.57
Prior HF	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0,I42.5-I42.9, I43, I50, P29.0	
Atrial fibrillation	I48	
Cerebrovascular Disease	G45, G46, H34.0, I60-I69	
Peripheral vascular disease	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	
COPD	I27.8, I27.9, J40-J47, J60-J67, J68.4, J70.1, J70.3	
Dementia	F00-F03, F05.1, G30, G31.1	
Anemia	D50 - D64	
Cancer	C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97	

CAD: Coronary artery disease; CCI: Canadian classification of health interventions; COPD: Chronic obstructive pulmonary disease; ICD: International classification of diseases;

Chapter 3 : Alignment of Site versus Adjudication Committee-based diagnosis with patient outcomes: Insights from the Providing Rapid Out of Hospital Acute Cardiovascular Treatment 3 (PROACT-3) trial

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3.1 ABSTRACT

Background: Adjudication by an adjudication committee (CEC) in clinical trials, plays an important role in the assessment of outcomes. Controversy exists regarding the utility of adjudication committee versus site-based assessments and their relationship to subsequent clinical events.

Methods: This study is a secondary analysis of the Providing Rapid Out of Hospital Acute Cardiovascular Treatment 3 (PROACT-3) trial, which randomized patients with chest pain or shortness of breath for biomarker testing in the ambulance. The emergency department physician diagnosis at the time of emergency department disposition was compared with an adjudicated diagnosis assigned by an adjudication committee. The level of agreement between emergency department and adjudication committee diagnosis was evaluated using Kappa coefficient, and compared to clinical outcomes (30-day re-hospitalization, 30-day and 1-year mortality).

Results: Of 477 patients, 49.3% were male with a median age of 70 years; hospital admission rate was 31.2%. The emergency department physicians and the adjudication committee disagreed in 55 cases (11.5%) with a kappa of 0.71 (95%CI 0.64, 0.78). The 30-day re-hospitalization, 30-day mortality and 1-year mortality was 22%, 1.9%, and 9.4%, respectively. Although there were similar rates of re-hospitalization irrespective of adjudication, in cases of disagreement compared to agreement between adjudication committee and emergency department diagnosis, there was a higher 30-day (7.3% vs. 1.2%, p=0.002) and 1-year mortality (27.3% vs. 7.1%, p<0.001)

Conclusions: Despite substantial agreement between the diagnosis of emergency department physicians and adjudication committee, in the subgroup of patients where there was disagreement, there was significantly worse short-term and long-term mortality.

Clinical Trial Identifier: NCT01634425

Key words: PROACT-3, Adjudication, Emergency department, agreement

3.2 Introduction

Adjudication is the process of independent and blinded review of key clinical data by a group of expert physicians in order to provide validation and consistency on the diagnosis or a key trial endpoint (event adjudication). As many clinical trials utilize non-fatal events as part of a composite endpoint or as key secondary endpoints, the adjudication committee is perceived as a necessary process for accurate trial interpretation. Adjudication committees have become an integral part of the clinical trials and adjudicate endpoints in studies, blindly, objectively and systematically.[1-3] Adjudication committees are often thought to provide greater certainty and reduce the variability in the classification of events.[3]

There are a paucity of studies which have compared adjudication committee and Site investigators endpoint assessments and the relationship to subsequent clinical outcomes.[1, 3-5] The disagreement between site investigators and adjudication committee may be substantial in some studies,[6] leading to uncertainty in the role of adjudication committees. In clinical studies testing the application of a new diagnostic test, an adjudication committee can help to determine the gold standard comparator for a new biomarker. Specifically, in acute cardiovascular disease, this strategy has been deployed in a number of trials testing plasma natriuretic peptides in acute heart failure and troponins in patients with chest pain.[7-9]

The Providing Rapid Out of Hospital Acute Cardiovascular Treatment 3 (PROACT-3) trial was conducted to test the role of pre-hospital biomarker testing in patients with symptoms of acute cardiovascular disease.[10] Because of the open-label use of the biomarker testing, an adjudication committee was used to determine patient diagnosis using similar information available to the emergency department physician. Since the value of an adjudication committee when used for this purpose is uncertain, we explored the level of agreement between emergency department and adjudication committee and compared the relationship between the emergency department and adjudication committee diagnosis with subsequent clinical outcomes.

3.3 Methods

3.3.1 PROACT-3 Trial

The PROACT-3 study was a prospective, open-label, blinded-endpoint (PROBE) randomized trial conducted to evaluate the role of pre-hospital testing of biomarkers such as troponin and b-type natriuretic peptide (BNP) in reducing the time from first medical contact to final disposition from emergency department in patients with symptoms of acute cardiovascular disease. Patients

with either chest pain or shortness of breath were randomized to usual care or assessment of biomarkers analyzed on a point-of-care device in the ambulance. Patients with the ST-elevation myocardial infarction were excluded. Details of the rationale, inclusion and exclusion criteria and the results of PROACT-3 have been published.[10] Since no significant difference was observed between the primary and secondary endpoints of patients in the pre-hospital biomarker versus control group, we pooled the two arms of PROACT-3 study for the present analysis. All patients provided informed consent, and the study was approved by the Health Research Ethics Board at the University of Alberta.

3.3.2 Adjudication process

All enrolled subjects underwent usual standard of care which included assessment by an emergency department physician, who subsequently recorded the patients' emergency department disposition diagnosis on the medical record. The adjudication committee in the PROACT-3 trial (made up of members of the Executive and Steering committee with experience and expertise in clinical practice, a total of 7 adjudicators) evaluated the diagnosis for subjects, blinded to the randomized assignment. Adjudication was done independently and prospectively. Each adjudication file was prepared by a project lead in a batch of 10, sent to each reviewer, and returned (without discussion) to the coordinating centre. A guidance manual of operation was drafted and shared with the adjudication committee which included standardized definitions for each diagnosis, based on national and international guidelines, where available.[11, 12] In order to simulate the clinical scenario, only information from the emergency department (or records from the first 24-hours after emergency department presentation) were available to adjudicators including emergency department physician notes, consultation notes, admission orders, electrocardiograms, and hospital-based labs. No additional information was gathered from Sites during the adjudication process. The pre-hospital biomarker results from the ambulance were available to the emergency department physicians but not the adjudicators. However, both emergency department physicians and adjudication committee had access to laboratory test results, which were done at emergency department. In the event of a disagreement amongst adjudicators, the Committee Chair reviewed the case and assigned a diagnosis. Adjudication was done prior to database lock on a rolling basis and without any knowledge of interim data. The final diagnosis of patients was summarized into four categories: Angina, Acute Coronary

Syndrome, Acute Heart Failure, and Other; each of these groups had subcategories allowing for a more specific diagnosis.[10]

3.3.3 Follow-up/end points

All subjects were followed for vital status for one year after enrollment, and there was no loss to follow-up. Events captured included repeat emergency department visits, hospitalization and re-hospitalization up to 30 days, and death up to 30 days and one year.

3.3.4 Cardiovascular Risk scoring

In order to provide external comparisons of the risk of the patient population enrolled in PROACT-3, we assessed each patient's risk score using GRACE score.[13] If the required variable was not available in our database, the related variable was used when the risk score was calculated (details in supplementary table 3.5).

3.3.5 Statistical Analysis

Continuous variables were presented as median and 25th and 75th percentiles. Categorical variables were reported as counts or percentages. The Kappa coefficient with corresponding 95% confidence intervals (CI) was used to measure the level of agreement between emergency department diagnoses and adjudication committee diagnoses. The agreement of <20%, 21-40%, 41-60%, 61-80%, 81% or higher were interpreted as slight, fair, moderate, substantial, and almost perfect agreements, respectively.[14] All-cause mortality within 30 days and 1 year of enrollment was examined according to agreement or disagreement between emergency department and adjudication committee diagnoses by Kaplan-Meier survival analysis; differences in survival estimates were tested via the log-rank test. The association between agreement and mortality at 1 year was also examined using Cox proportional hazard regression. To account for imbalances in key patient characteristics, the GRACE risk score was used for adjustment in the regression model. A sensitivity analysis was also performed by adjusting for other differences in baseline characteristics (age, prior angina, prior myocardial infarction, prior percutaneous coronary intervention, time from triage to emergency department discharge, pre-hospital troponin, and pre-hospital b-type natriuretic peptide) between groups with and without emergency department/ adjudication committee agreement (once alone and then in addition to the GRACE risk score) in a multivariable model predicting 1-year mortality. The adjusted associations were expressed as hazard ratio and 95% confidence interval.

All statistical tests were two-sided with p-value<0.05 considered statistically significant. No adjustments were made for multiple comparisons. Statistical analyses were performed using SAS, version 9.3 (Cary, North Carolina).

3.4 Results

3.4.1 Baseline characteristics

A total of 491 patients were enrolled and randomized in PROACT-3 but 11 patients were excluded because of missing data; thus, the final analytical dataset consisted of 480 patients. Among these 480 patients, 3 subjects lacked an emergency department diagnosis, and they were excluded from analyses of the level of agreement between emergency department and adjudication committee diagnosis.

The baseline characteristics of the patients are provided in Table 3.1 (and additional data in Supplementary Table 3.1). The median age was 70 (25th, 75th percentiles: 56, 81) years, 49.3% were male, 32.3% had a prior myocardial infarction. The admission rate was 31.2% (n=149/477) in this study cohort. The median GRACE risk score was 130 (25th, 75th percentiles: 104, 161); 25.8% of the study population had a GRACE score ≥160 (Supplementary Table 3.2 & 3.3).

3.4.2 Level of agreement

The emergency department physicians and the adjudication committee disagreed in 55 cases (11.5%) and agreed in 422 cases (88.5%), resulting in a kappa of 0.71 (95%CI 0.64, 0.78). By excluding the 'Other' group and comparing the Angina/Acute coronary syndrome/Acute heart failure group between emergency department physician and adjudication committee, the kappa was 0.77 (95%CI 0.65, 0.89). Likewise, the agreement of the Other group between emergency department physicians and the adjudication committee was 0.75 (95%CI 0.68, 0.82). Of the cases identified by the adjudication committee as either angina, acute coronary syndrome, acute heart failure or Other, the emergency department physicians labeled 37.5%, 63.1%, 83.8% and 96.6% of these cases, respectively, with the same diagnosis as the adjudication committee (Table 3.2). There was no difference between groups with and without emergency department/adjudication committee agreement in terms of their trial group allocation (P=0.19; Table 3.1). Case-by-case review of the 55 cases with emergency department/adjudication committee disagreement revealed no distinct trend for the effect of pre-hospital troponin and b-type natriuretic peptide testing favoring the pre-hospital biomarker testing group as a potential source of disagreement. The majority of these patients also received biomarker testing in the emergency department:

82.3% of 17 cases with emergency department/adjudication committee disagreement for acute heart failure underwent b-type natriuretic peptide testing and 96.7% of 31 cases with emergency department/adjudication committee disagreement for acute coronary syndrome underwent troponin testing.

3.4.3 Emergency Department/Adjudication Committee Agreement and Relationship to Outcomes

The overall 30 day repeat emergency department visit or re-hospitalization rate, 30-day mortality rate, and 1-year mortality rate was 22.0%, 1.9%, and 9.4%, respectively. The 30-day re-hospitalization rate was not different between patients from different diagnoses categories identified by emergency department physicians (P=0.57) or the adjudication committee (P=0.62), regardless of whether the adjudication committee and emergency department physician agreed or disagreed on the diagnosis (P=0.62). The 30-day and 1-year mortality rate differed between patients with different diagnoses by the emergency department physician (both P<0.001) or the adjudication committee (P=0.014 and P<0.001, respectively). As shown in Figure 3.1, among patients for whom the emergency department and adjudication committee disagreed, the 1-year death rate was significantly higher compared to those patients where the emergency department and adjudication committee agreed on their final diagnosis (P<0.001). Among the 16 cases which were adjudicated from Other group to acute coronary syndrome, only one died within one year, whilst all 4 cases who were adjudicated from acute heart failure to acute coronary syndrome and also 6 of 8 cases who were adjudicated from acute heart failure to Others, died in 1 year. After multivariable adjustment for differences in baseline cardiovascular risk (shown in supplementary Table 3.3), the difference in 1-year mortality between patients with and without emergency department/adjudication committee agreement persisted (unadjusted hazard ratio 4.21; 95%CI 2.26, 7.82; P<0.001; adjusted hazard ratio 2.25; 95%CI 1.16, 4.34; P=0.01). Further adjustment for other differences in baseline characteristics did not attenuate the results (Hazard ratio 2.67; 95%CI 1.32, 5.37; P=0.006). Adjusting for both the above-mentioned baseline differences and GRACE risk score resulted in a hazard ratio of 2.20 (95%CI 1.05, 4.58; P=0.036).

For each diagnosis category, Table 3.3 shows the 1-year mortality rates and agreement. The 1-year mortality rate was higher in patients labeled as acute coronary syndrome by the adjudication committee but not by the emergency department physicians (25%) compared to

those patients for whom both emergency department physicians and adjudication committee agreed on the occurrence of acute coronary syndrome (12.5%). When site labeled the patients as acute heart failure but adjudication committee disagreed, the 1-year mortality rate was higher (83.3%) compared to when adjudication committee labeled the case as acute heart failure but site disagreed (40%), or compared to when both site and adjudication committee agreed on the diagnosis of acute heart failure (26.9%). The 1-year survival of patients with and without acute coronary syndrome or acute heart failure, according to diagnosis by emergency department physicians, the adjudication committee, both or neither is shown in Figures 3.2A and 3.2B, respectively.

3.5 Discussion

In PROACT-3 trial, an adjudication committee was used because of the open-label nature of the trial in order to adjudicate the patient diagnosis using similar information available to the managing emergency department physicians. Our two key findings were: (1) there was substantial agreement (88%) in the final diagnosis made by the emergency department physicians and the adjudication committee; and (2) the patients with emergency department/adjudication committee disagreement had a higher mortality compared to those in whom the emergency department and adjudication committee agreed on their final diagnosis. This difference persisted even after adjustment for baseline risk score, and other characteristics, suggesting that other factors are associated with this observation.

In our study, in almost 90% of cases with emergency department/adjudication committee disagreement for the diagnosis of acute coronary syndrome, the site had a different diagnosis, whilst adjudication committee assigned the diagnosis of acute coronary syndrome. These cases in which there was disagreement on acute coronary syndrome were associated with 22.5% one-year mortality rate, markedly higher than the cases of agreement (12.5%). In surveys of clinical practice, emergency department physicians discharge a percentage of patients with acute myocardial infarction or acute coronary syndrome ranging from 2-5% and 2-6% respectively.[15-19] Previous research has shown that patients with a 'missed' myocardial infarction have mortality rates twice of patients admitted to the hospital,[20] and missed acute coronary syndrome accounts for the largest share of dollars paid in malpractice claims, with nearly 40% of claims resulting in

payment.[21] In recent cardiovascular trials the rates of myocardial infarction reported by site investigators have differed from rates as adjudicated by adjudication committees.[22-25] Some studies have shown larger differences in observed treatment effects when adjudication committee data are used instead of site investigator-reported myocardial infarctions,[1, 23, 26] but others have not.[4, 27-30] Mahaffey et al hypothesized that those trials which rely only on investigator-reported myocardial infarction events, probably underestimate the true event rate.[1] These observations potentially undermine the use of emergency department or site for diagnosing the clinical condition in trials which focused on chest pain, acute coronary syndrome or myocardial infarction. It seems that adjudication committee adds value by adjudicating in this situation.

One conclusion from our study could be that the disease state may influence the ability for an adjudication committee to provide a more accurate determination of the outcome. Heterogenous disease states and presentations such as acute heart failure differ from that of acute coronary syndrome and thus the need for an adjudication committee or its influence on the eventual outcomes is critical to consider in the design of such projects. Since patients with acute heart failure tend to be older, have multiple comorbid conditions and overlapping clinical syndromes, this disagreement (between site and adjudication committee) may reflect clinical practice in challenging cases – lack of a clear diagnosis leads to poor outcomes. This area is in need of clear additional diagnostic tools – clinical, radiographic, biomarker – to aid clinicians (and ultimately adjudication committees).

There are several potential limitations to our study. The sample size is modest [based on 55 disagreements and 422 agreements] and should be considered hypothesis-generating. In PROACT-3, the adjudication committee had access to similar information available to emergency department physicians, so the findings may not be generalizable to all adjudication committees using other methods for adjudication. Considering that the aim of PROACT-3 trial was to investigate the role of pre-hospital biomarker testing, it is possible that the application of pre-hospital biomarker testing in biomarker arm may have provided additional information regarding the patient's clinical condition to the ED physicians, whilst these test results and patients' group allocation were not available to the adjudication committee members. However, there was no difference between groups with and without emergency department/adjudication committee agreement in terms of their group allocation (P=0.19). Moreover, we performed a case-by-case review of cases with emergency department/adjudication committee disagreement

to see if the pre-hospital biomarker testing has had any influence on these disagreements, and no distinct trend was observed favoring the effect of pre-hospital biomarker testing on emergency department/adjudication committee disagreement.

The studies that have evaluated the efficacy of adjudication committee versus site investigators in identifying trial endpoints have often been based upon trials that utilized strict inclusion and exclusion criteria or diagnosis criteria for the events (such as new definitions for procedure-related myocardial infarction). In such trials, the adjudication committee members are familiar with the protocol, trial definitions and classifications and clinical practice. However, in the PROACT-3 trial, the diagnostic criteria that were used by the emergency department physicians in clinical practice are less homogeneous and subject to individual patient and clinician variability.

3.6 Conclusion

Our study demonstrated that, despite the substantial agreement between the diagnosis of emergency department physicians and adjudication committee, among patients where the site and a adjudication committee disagreed on the final diagnosis, there was worse short-term and long-term mortality. When looking at key clinical outcomes, the value of adjudication committee seems to be modest and disease-dependent. The value of an adjudication committee should be carefully considered for each unique trial type and disease. Considering the added complexity of including an adjudication committee, its value in trials of diagnosis should be revisited by further studies.

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Tables and Figures

Table 3.1. Baseline characteristics in PROACT-3 Adjudication sub-study

	All	ED/Adjudication Agreement	ED/Adjudication Disagreement	p-value
N	477	422	55	
Age, years	70 (56, 81)	69.0 (55.0, 81.0)	76.0 (64.0, 84.0)	0.012
>75years, %	39	37.4	50.9	0.054
Female, %	50.7	51.7	43.6	0.263
Prior Angina, %	15.5	14.5	23.6	0.077
Prior MI, %	32.3	30.6	45.5	0.026
Prior PCI, %	21.4	20.1	30.9	0.067
Prior CABG, %	7.1	6.9	9.1	0.548
Prior HF, %	13.2	12.3	20	0.114
Diabetes, %	27.9	27.5	30.9	0.595
First heart rate, bpm	82 (70, 96)	83.0 (71.0, 96.0)	76.0 (63.0, 100.0)	0.204
First Systolic BP, mmHg	146 (129, 169)	147.0 (129.0, 168.0)	139.0 (123.0, 170.0)	0.391
Pre-hospital variables				
Symptom onset to EMS arrival, min	201 (100, 717)	185.5 (97.0, 711.0)	316.5 (100.0, 1072.5)	0.400
Triage to ED discharge, min	492 (344, 636)	485.0 (328.0, 612.0)	556.0 (414.0, 749.0)	0.010
Pre-hospital Biomarkers				
Troponin I, ng/ml				
Median (Q_1, Q_3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.1)	0.044

>0.03	26/192 (13.5)	19/167(11.4)	7/25(28.0)	0.024
>0.1	7/192 (3.6)	4/167(2.4)	3/25(12.0)	0.017
BNP, pg/ml				
Median (Q_1, Q_3)	53.5 (12.0, 154.0)	46.5 (11.0, 121.0)	157.5 (40.0, 687.0)	0.002
<100	125/196(63.7)	115/170(67.7)	10/26(38.5)	0.002
100-<400	52/196(26.5)	43/170(25.3)	9/26(34.6)	
≥400	19/196(9.6)	12/170(7.1)	7/26(26.9)	
Hospital Biomarkers				
Troponin I, ng/ml				
First, median (Q_1, Q_3)*	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.439
>0.1 ng/ml	452/453 (99.8)	398/399(99.8)	54/54(100.0)	0.713
Peak, median (Q_1, Q_3)	0.1 (0.1, 0.2)	0.1 (0.1, 0.1)	0.1 (0.1, 0.7)	0.172
>0.1 ng/ml	67/233 (28.8)	52/194(26.8)	15/39(38.5)	0.142
BNP, pg/ml				
First, median (Q_1, Q_3)	1290.0 (422.0, 2193.5)	177.5 (74.5, 724.0)	312.0 (136.0, 2075.0)	0.124
<100	27/99(27.3)	24/76(31.6)	3/23(13.0)	0.194
100-<400	33/99(33.3)	23/76(30.3)	10/23(43.5)	
≥400	39/99(39.4)	29/76(38.2)	10/23(43.5)	
Standard care + biomarkers	238/477 (49.8)	206/422(48.8)	32/55(58.2)	0.191
Hospital admission from ED	149/477 (31.2)	120 (28.4)	29 (52.7)	<0.001

Values are medians (25th, 75th percentiles [Q_1, Q_3]) unless otherwise stated. BP: Blood pressure; BNP: B-type natriuretic peptide; CABG: Coronary artery bypass grafting; ED: Emergency department; EMS: Ambulance; HF: Heart Failure; IQR: Interquartile range; MI: Myocardial Infarction; PCI: Percutaneous coronary intervention;

Table 3.2. Cross-tabulation of categorized diagnosis of emergency department versus Adjudication

		Adjudication Diagnosis				
		Angina	ACS	AHF	Other	Total
ED diagnosis, n	Angina	6	8	0	1	15
	ACS	0	48	0	3	51
	AHF	0	4	26	8	38
	Other	10	16	5	342	373
	Total	16	76	31	354	477

Kappa: 0.71(0.64-0.78); ACS: Acute coronary syndrome; AHF: Acute heart failure; ED: Emergency department;

Table 3.3. Patient outcomes by ED-Adjudication diagnosis agreement

	Site 'Yes'; Adjudication 'Yes'		Site 'Yes'; Adjudication 'No'		Site 'No'; Adjudication 'Yes'		Site 'No'; Adjudication 'No'	
	n	1-year death (KM%)	n	1-year death (KM%)	n	1-year death (KM%)	n	1-year death (KM%)
Angina	6	0.0	9	22.2	10	0.0	452	9.5
ACS	48	12.5	3	0.0	28	25.0	398	8.0
AHF	26	26.9	12	83.3	5	40.0	434	6.0
Others	342	5.0	31	9.7	12	50.0	92	20.7

KM: Kaplan-Meier estimate; ACS: Acute coronary syndrome; AHF: Acute heart failure; ED: Emergency department;

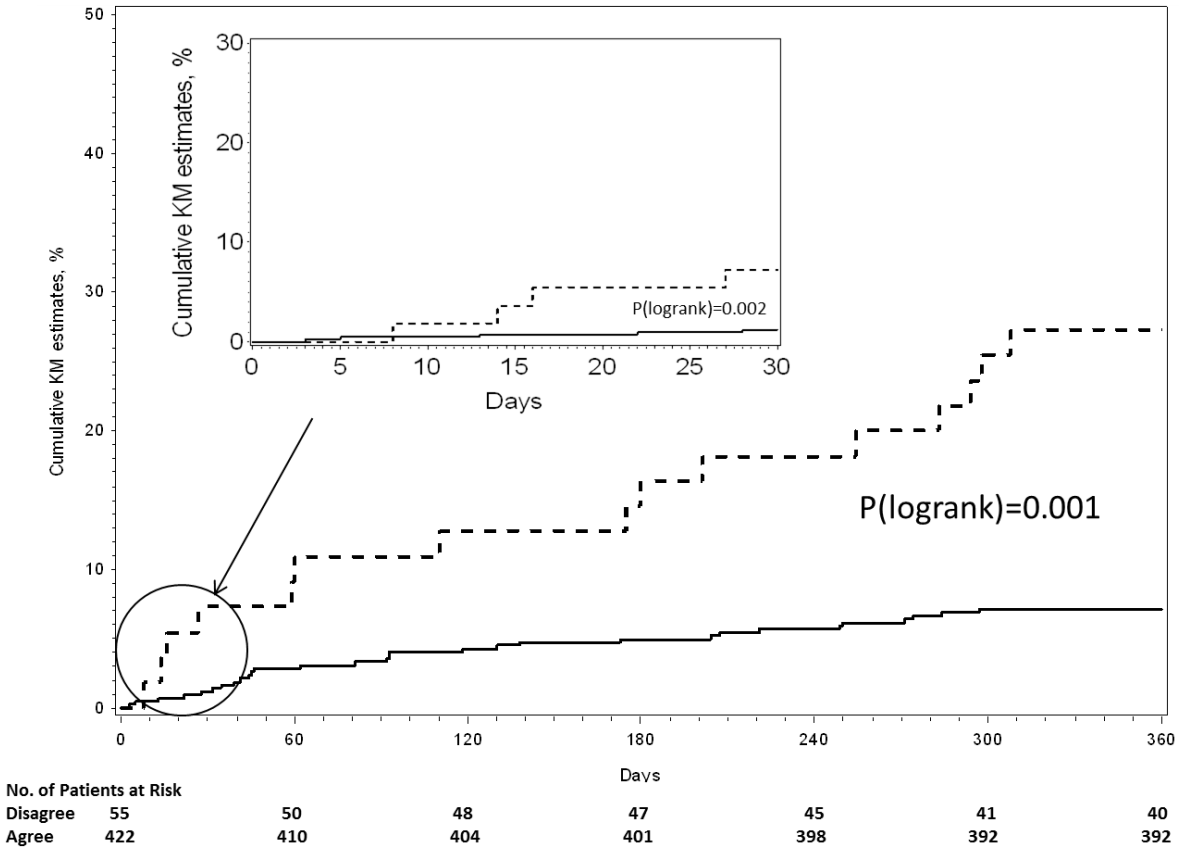
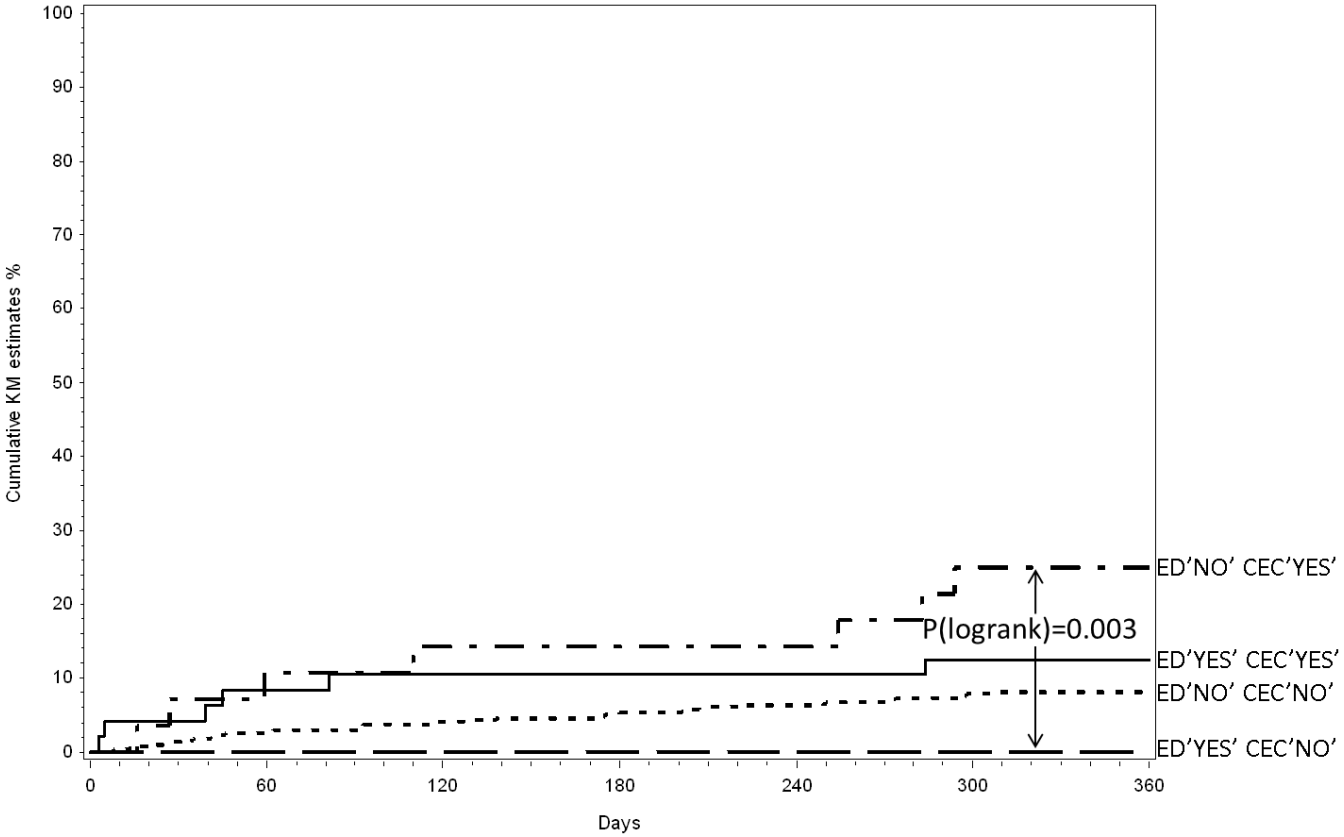
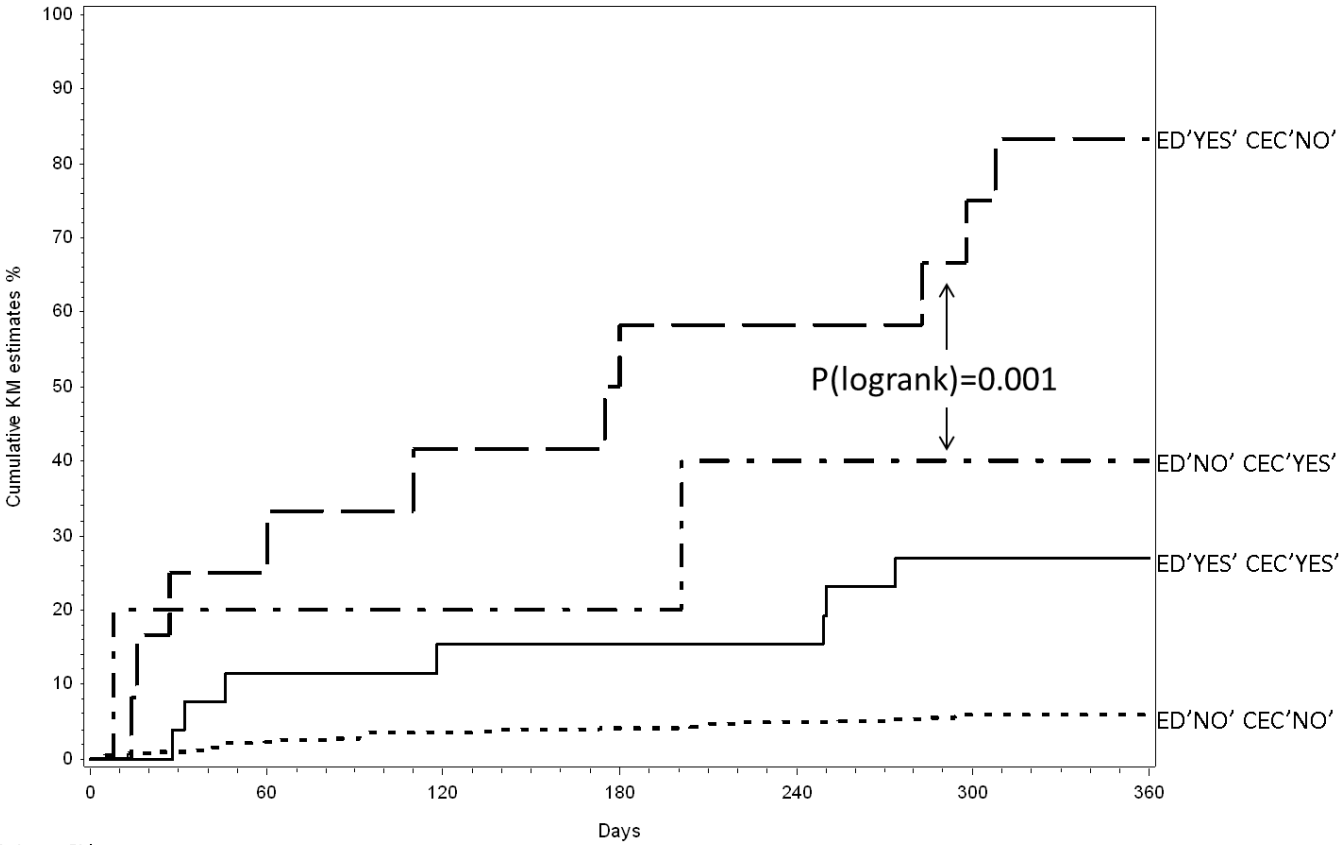


Figure 3.1. Kaplan-Meier curve for 30-day and 1-year mortality in groups with and without emergency department/adjudication committee agreement. Dotted line: disagree; solid line: agree



No. of Patients at Risk							
ED'NO'CEC'YES'	28	25	24	24	24	21	21
ED'YES'CEC'YES'	48	44	43	43	43	42	42
ED'NO'CEC'NO'	398	388	382	378	373	367	366
ED'YES'CEC'NO'	3	3	3	3	3	3	3

2A



No. of Patients at Risk							
ED'YES'CEC'NO'	12	9	7	6	5	3	2
ED'NO'CEC'YES'	5	4	4	4	3	3	3
ED'YES'CEC'YES'	26	23	22	22	22	19	19
ED'NO'CEC'NO'	434	424	419	416	413	408	408

2B

Figure 3.2. One-year death Kaplan-Meier curve according to different conditions of emergency department (ED)/adjudication committee (CEC) diagnosis for acute coronary syndrome (2A) and acute heart failure (2B)

3.8 Supplementary material

Supplementary Table 3.1. Baseline characteristics in groups identified by ED physicians versus Adjudication committee

	ED Diagnoses				Adjudication Diagnoses				
	Angina	**ACS**	**AHF**	**Other**	**Angina**	**ACS**	**AHF**	**Other**	**All**
n	**15**	**51**	**38**	**373**	**16**	**77**	**31**	**356**	**480**
Age, years	74 (53, 84)	68 (55, 82)	82 (74, 87)	68 (55, 80)	72.5 (62.5, 83.5)	69 (56, 82)	80 (72, 86)	68 (54.5, 80)	70 (56, 81)
>75years, %	7 (46.7)	21 (41.2)	28 (73.7)	130 (34.9)	7 (43.8)	32 (41.6)	20 (64.5)	128 (36.0)	187 (39.0)
Female, %	9 (60.0)	25 (49.0)	22 (57.9)	186 (49.9)	9 (56.3)	35 (45.5)	17 (54.8)	184 (51.7)	245 (51.0)
Prior Angina, %	2 (13.3)	10 (19.6)	4 (10.5)	58 (15.5)	3 (18.8)	19 (24.7)	1 (3.2)	51 (14.3)	74 (15.4)
Prior MI, %	5 (33.3)	24 (47.1)	17 (44.7)	108 (29.0)	7 (43.8)	39 (50.6)	14 (45.2)	95 (26.7)	155 (32.3)
Prior PCI, %	4 (26.7)	17 (33.3)	5 (13.2)	76 (20.4)	4 (25.0)	27 (35.1)	6 (19.4)	65 (18.3)	102 (21.3)
Prior CABG, %	0 (0.0)	6 (11.8)	8 (21.1)	20 (5.4)	0 (0.0)	9 (11.7)	6 (19.4)	19 (5.3)	34 (7.1)
Prior HF, %	1 (6.7)	7 (13.7)	25 (65.8)	30 (8.0)	1 (6.3)	9 (11.7)	22 (71.0)	31 (8.7)	63 (13.1)
Diabetes, %	2 (13.3)	20 (39.2)	20 (52.6)	91 (24.4)	2 (12.5)	30 (39.0)	18 (58.1)	84 (23.6)	134 (27.9)
First heart rate, bpm	77 (70, 82)	76.5 (70, 94)	89.5 (74, 108)	82 (70, 96)	79 (70.5, 87)	80 (70, 95.5)	87 (70, 98)	83 (70, 96)	82 (70, 96)

First Systolic BP, mmHg	152 (133, 174)	161 (136, 184)	141.5 (126, 171)	145 (128, 166)	151.5 (133.5, 173.5)	157 (135, 179.5)	148 (125, 171)	144.5 (129, 166)	147 (129, 169)
Pre-hospital variables									
Symptom onset to EMS arrival, min	266 (84.5, 490.5)	151 (104, 263)	2126 (968, 4303)	191 (95, 711)	143 (69, 375)	139 (100, 366)	2889 (620, 6650)	191 (97, 715)	191 (97, 717)
Triage to ED discharge, min	565 (452, 623)	469.5 (335, 738)	523.5 (414, 844)	488 (335, 605)	557.5 (507, 602)	493 (322.5, 743.5)	656 (438, 864)	478.5 (324.5, 590)	492 (342, 634)
EMS-Biomarkers									
Troponin I, ng/ml									
Median (Q_1, Q_3)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0.1)	0 (0, 0)	0 (0, 0)	0 (0, 0)
>0.03	1/7 (14.3)	6/18 (33.3)	3/12 (25)	16/155 (10.3)	1/8 (12.5)	9/29 (31.0)	2/10 (20)	14/147 (9.5)	26/194 (13.4)
>0.1	0/7 (0)	5/18 (27.8)	0/12 (0)	2/155 (1.3)	0/8 (0)	5/29 (17.2)	1/10 (10)	1/147 (0.7)	7/194 (3.6)
BNP, pg/ml									

Median (Q_1, Q_3)	38 (6, 93)	100.5 (35, 215)	721 (433, 1510)	40 (10, 114)	63 (39, 98.5)	94 (15, 215)	727 (259, 1880)	39.5 (10, 116)	53.5 (12, 154)
<100	6/7(85.7)	8/18(44.4)	0/12 (0)	111/159(69.8)	6/8(75)	15/29(51.7)	1/11(9.1)	104/150(69.3)	126/198(63.6)
100-<400	1/7 (14.3)	10/18 (55.6)	4/12 (33.3)	37/159 (23.3)	2/8 (25)	11/29 (37.9)	4/11 (145.5)	35/150 (23.3)	52/198(26.3)
≥400	0/7(0)	0/18(0)	8/12(66.7)	11/159(6.9)	0/8(0)	3/29(10.3)	6/11(54.6)	11/150(7.3)	20/198(10.1)
Hospital Biomarkers									
Troponin I, ng/ml									
First, median (Q_1, Q_3)*	0.1 (0.1, 0.1)	0.1 (0.1, 0.7)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.4)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)
>0.1 ng/ml	15/15 (100)	51/51 (100)	38/38 (100)	348/349 (99.7)	16/16 (100)	76/76 (100)	31/31 (100)	332/333 (99.7)	455/456 (99.8)
Peak, median (Q_1, Q_3)	0.1 (0.1, 0.1)	1.1 (0.1, 4.5)	0.1 (0.1, 0.2)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.8 (0.1, 3.3)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.2)
>0.1 ng/ml	2/12 (16.7)	36/48 (75.0)	10/29 (34.5)	19/144 (13.2)	0/9 (0)	47/69 (68.1)	5/24 (20.8)	16/132 (12.1)	68/234 (29.1)
BNP, pg/ml									
First, median	151.5 (142, 161)	853.5 (282.5,	891.5 (544.5,	116 (58, 210)	101 (47, 109)	196 (142, 1151)	1034.5 (561, 2151)	132 (58, 279)	1290 (422, 2193.5)

(Q_1, Q_3)		1456.5)	2257.5)						
<100	0/2(0)	1/4	1/32 (3.1)	25/61 (41)	1/3(33.3)	3/13(23.1)	1/26(3.9)	22/57(38.6)	27/99(27.3)
100-<400	2/2 (100)	0/4 (0)	5/32 (15.6)	26/61 (4.6)	2/3 (66.7)	4/13 (30.8)	4/26 (15.4)	23/57 (40.4)	33/99(33.3)
≥400	0/2(0)	3/4(75.0)	26/32 (81.3)	10/61 (16.4)	0/3(0)	6/13(46.2)	21/26(80.8)	12/57(21.1)	39/99(39.4)

ED: Emergency department; ACS: Acute Coronary Syndrome; AHF: Acute heart failure; MI: Myocardial Infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; Q_1: 25th percentile; Q_3: 75th percentile;

Supplementary Table 3.2. CV risk score of the patients according to their ED diagnoses or Adjudication diagnoses using GRACE risk score

		ED diagnosis					Adjudication diagnosis				
		All	**Angina**	**ACS**	**AHF**	**Other**	**All**	**Angina**	**ACS**	**AHF**	**Other**
n		**477**	**15**	**51**	**38**	**373**	**480**	**16**	**77**	**31**	**356**
GRACE score		130.0 (104.0, 161.0)	131.0 (86.0, 153.0)	138.0 (104.0, 166.0)	178.5 (161.0, 189.0)	126.0 (103.0, 152.0)	130.0 (104.0, 161.0)	140.5 (106.5, 153.5)	138.0 (104.0, 171.0)	176.0 (157.0, 187.0)	125.5 (102.0, 153.0)
GRACE score	<140	285 (59.7)	9 (60.0)	28 (54.9)	2 (5.3)	246 (66.0)	286 (59.6)	8 (50.0)	41 (53.2)	2 (6.5)	235 (66.0)
	140-160	69 (14.5)	4 (26.7)	7 (13.7)	7 (18.4)	51 (13.7)	70 (14.6)	7 (43.8)	10 (13.0)	7 (22.6)	46 (12.9)
	>=160	123 (25.8)	2 (13.3)	16 (31.4)	29 (76.3)	76 (20.4)	124 (25.8)	1 (6.3)	26 (33.8)	22(71.0)	75 (21.1)

ACS: Acute Coronary Syndrome; AHF: Acute heart failure; ED: Emergency department;

Supplementary Table 3.3. Patients risk score in groups with and without ED/ Adjudication agreement

		ED/Adjudication Agreement	ED/Adjudication Disagreement	p-value
n		**422**	**55**	
GRACE score		127 (104, 157)	148 (108, 185)	0.004
GRACE Score	<140	61.8	43.6	0.002
	140-160	14.9	10.9	
	≥160	23.2	45.5	

ED: Emergency department;

Supplementary Table 3.4. Cross-tabulation of non-categorized diagnosis in the emergency department versus Adjudication

	Adjudication Dx			
	Angina	**ACS**	**AHF**	**Other**
	16	**77**	**31**	**356**
Initial ED diagnosis, n				
NSTEMI	0	24	0	1
Heart failure	0	4	26	8
STEMI	0	2	0	0
COPD	0	0	1	15
ACS	0	7	0	1
Unstable angina	0	15	0	1
Angina	6	8	0	1
Non-cardiac chest pain	10	13	1	190
Other	0	3	3	137
Not done/reported	0	1	0	2

ACS: Acute Coronary Syndrome; AHF: Acute heart failure; COPD: Chronic obstructive pulmonary disease; ED: Emergency department; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction;

Supplementary Table 3.5. GRACE Risk scoring model and the way we've calculated risk score

Risk scoring Model	Population	Variables required	The way we addressed lacking variables
GRACE score	ACS	Age, Heart Rate, Systolic blood pressure, Creatinine, Cardiac Arrest at Admission, ECG ST segment deviation, Elevated Cardiac Enzymes, Killip class (I: no CHF, II: Rales and/or JVD, III: Pulmonary Edema, IV: Cardiogenic Shock)	JVP=or>4 was considered as jugular vein distension. We considered all the cases with crepitations as rales resulted from heart failure.

ACS: Acute Coronary Syndrome; ECG: Electrocardiogram; CHF: Congestive Heart Failure; JVD: Jugular vein distention; JVP: Jugular vein pressure;

Chapter 4 : Trends in the explanatory or pragmatic nature of cardiovascular clinical trials over two decades

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4.1 Abstract

Background: Pragmatic trials test interventions using designs that produce results that may be more applicable to the population in which the intervention will be eventually applied. This study was aimed to investigate how pragmatic or explanatory cardiovascular (CV) randomized controlled trials (RCT) are, and if this has changed over time.

Methods: All CV-related RCTs published during the years of 2000, 2005, 2010 and 2015 were identified and enrolled from six major medical and CV journals, including the New England Journal of Medicine, Lancet, JAMA: Journal of the American Medical Association, Circulation, European Heart Journal, and JACC: Journal of the American College of Cardiology. Included RCTs were assessed by two independent adjudicators with expertise in RCT and CV medicine. The outcome measure was the level of pragmatism evaluated using the PRECIS-2 tool, which uses a 5-point ordinal scale (ranging from very pragmatic to very explanatory) across 9 domains of trial design, including eligibility, recruitment, setting, organization, intervention delivery, intervention adherence, follow-up, primary outcome, and analysis.

Results: The mean (±SD) PRECIS-2 score was 3.26 ± 0.70 among 616 RCTs. The level of pragmatism increased over time from a mean score of 3.07 ± 0.74 in 2000 to 3.46 ± 0.67 in 2015 ($p < 0.0001$ for trend; Cohen's D relative effect size 0.56). The increase occurred mainly in the domains of eligibility, setting, intervention delivery, and primary endpoint. PRECIS-2 score was higher for neutral trials than those with positive results ($p = .0002$) and in phase III/IV trials as compared to phase I/II trials ($p < .0001$), but similar between different sources of funding (public, industry, or both; $p = 0.38$). More pragmatic trials had more sites, larger sample sizes, longer follow-ups, and mortality as the primary endpoint.

Conclusions: The level of pragmatism increased moderately over two decades of CV trials. Understanding the domains of current and future clinical trials will aid in the design and delivery of CV trials with broader application.

Keywords: Randomized clinical trial, pragmatic, explanatory, PRECIS-2, cardiovascular disease

4.2 Introduction

Pragmatic trials have the primary goal of informing decision-makers (patients, clinicians, healthcare administrators and policy-makers) about the comparative effectiveness of biomedical and behavioral interventions by enrolling a population relevant to the study intervention and representative of the populations in which the intervention will be eventually applied and by streamlining and simplifying the trial-related procedures.[1] They carry the potential to address some of the limitations of traditional randomized controlled trials (RCT) such as the lack of external validity, high cost and lengthy processes, often by streamlining the trial design and implementation. Since the concept of pragmatic and explanatory RCTs was first described in 1967,[2, 3] trialists have increasingly focused on how their trial design decisions can serve the intended purpose of their study. As a part of efforts to understand the nature of pragmatic RCTs,[4, 5] the PRagmatic Explanatory Continuum Index Summary (PRECIS) was developed to aid trialists make design decisions consistent with the intended purpose of a trial.[4]

The updated 2015 version of the PRECIS tool can be used to assess the trial decisions on 9 domains of trial design including the eligibility criteria, recruitment, setting, organization, the flexibility of intervention delivery, the flexibility of adherence to the intervention, follow-up, primary outcome and primary analysis.[6, 7] Several studies tested the role of the PRECIS tool in the trial design phase and its ability to provide a framework to stimulate discussion among study investigators, [5] and it has also been used retrospectively in evaluating RCTs.[8-12] However, there is a paucity of data on how the landscape of cardiovascular (CV) RCTs have changed over the past few decades in terms of their placement on the pragmatic-explanatory continuum. The aim of this study was to investigate how pragmatic or explanatory CV RCTs are and to study the change in the domains and overall level of pragmatism in CV trials over the past 2 decades.

4.3 Methods

CV RCTs that were published in six top-ranked medical and CV journals (based on impact factors) in the years of 2000, 2005, 2010, and 2015 were included in this study. Secondary analyses, sub-studies, follow-up studies, experimental and observational studies, commentaries, preliminary results, methodology papers and those that were not CV-related or not published in the mentioned time frame were excluded.

4.2.1 Search strategy and study selection

Based on impact factors, three top-ranked medical journals (i.e. New England Journal of Medicine, Journal of American Medical Association, and Lancet), as well as three top-ranked cardiovascular journals (i.e. Journal of American College of Cardiology, Circulation, European Heart Journal) were selected. As these CV journals publish the majority of CV RCTs, it was not feasible to assess all trials (4390 RCTs between 2000 to 2015 using the search strategy below; Supplementary Table 4.1), therefore we selected 4 full years of publications (i.e. 2000, 2005, 2010 and 2015) spanning a period of change that may reflect trials started or completed in the 1990s through 2015. These years were selected to show the trend of change in the publication of pragmatic versus explanatory trials. We searched the PubMed using the Journal name, the medical subject heading (MeSH) term of "Cardiovascular diseases" and the publication type of "Randomized Controlled Trial", filtered to the publication date between January 1st and December 31 of each year. For example: "Lancet"[jour] AND "Cardiovascular Diseases"[Mesh] AND "Randomized Controlled Trial" [Publication Type] AND ("2000/01/01"[PDAT] : "2000/12/31"[PDAT]).

4.2.2 Data extraction

All 1,185 abstracts were screened for the above-mentioned eligibility criteria by one adjudicator (NS) to ensure they were clinical trials. After excluding 517 articles (Figure 4.1), the full text of the remaining 668 studies were assessed by two independent adjudicators with expertise in RCT and CV medicine. All adjudicators were trained using the main relevant publications and the PRECIS toolkit from the precis-2.org website. Fifty-two additional studies were excluded in this phase for being identified as secondary analyses (n=5), follow-up (n=5), observational (n=2), non-CV (n=32), non-randomized (n=3), and experimental and pharmacokinetic (n=2) studies, and for not being published in the study timeframe (n=3). The final cohort consisted of 616 RCTs. Two adjudicators extracted information regarding study phase, sample size, numbers of involved sites and countries, follow-up duration, source of funding, trial design, and PRECIS-2 for each trial. In case of disagreement between adjudicators, the study was reviewed and arbitrated by the chair of the adjudication committee (JAE). Trials were categorized based on the results to 1) neutral (negative), 2) negative for primary endpoint but positive for secondary endpoints, and 3) positive trials. Non-inferiority trials that showed non-inferiority for the primary endpoint were considered as positive trial in this analysis.

4.2.3 PRECIS-2 tool

PRECIS-2 tool was used to score the different domains of trial design for each trial.[6] As demonstrated in Supplementary Figure 4.1, the tool is a 9-spoked wheel, each spoke representing one of nine domains of trial design (including eligibility criteria, recruitment, setting, organization, the flexibility of intervention delivery, the flexibility of adherence to the intervention, follow-up, primary outcome and primary analysis). Trials with an explanatory approach get scores nearer to the hub and those with pragmatic designs receive scores closer to the rim of the wheel. A 5-point Likert scale was used to rate the level of pragmatism in each trial design domain: 1. Very explanatory, 2. Rather explanatory, 3. Equally pragmatic/explanatory, 4. Rather pragmatic, 5. Very pragmatic. Although there are other tools to evaluate the level of pragmatism in RCTs,[13-15] the PRECIS-2 was used due to its standardization and more comprehensive domains. Adjudicators scored trials separately on a web-based form provided through REDCap.[16]

4.2.4 Statistical Analysis

Categorical variables were summarized as frequency and percentages and compared between groups using the Pearson Chi-square test or Fisher's exact test, as appropriate. Continuous variables were summarized as mean and standard deviation (SD) and compared applying the one-way analysis of variance (ANOVA). For each domain in an RCT, the average of the scores was taken as the PRECIS score. An RCT-specific summary PRECIS-2 score was calculated by averaging the scores over the nine domains, referred to as mean PRECISE-2 score. In case of missing data on a specific domain, the mean PRECISE-2 score was based on the remaining domains with non-missing score. The levels of pragmatism as quantified using the mean PRECISE-2 score were compared between different characteristics of RCTs using ANOVA. The Cohen's D was used to quantify the mean difference between groups relative to the variation.[17] The changes or difference between groups can be interpreted as small, medium, or large, if the Cohen's D is 0.2-0.49, 0.5-0.79, and ≥ 0.8 respectively.[17] Pearson's correlation coefficient was calculated to evaluate the degree of its linear relationship with continuous factors including sample size or the duration of follow up in the trial. A simple linear regression was fitted to test for linear trend in the temporal change over the years of publication. The assumption of normality has been checked for the analyses and (log) transformations were applied when appropriate. The relationship between the type of trial (explanatory versus pragmatic), the

internal validity and the trial result were evaluated using the Chi-squared test. P-value ≤0.05 was considered as statistically significant. Data analysis was performed using SAS version 9.4 software, and R package version 3.5 was used to generate the figures.

4.3 Results

4.3.1 Trial Characteristics

There were 616 RCTs in total, with 172, 168, 137, and 139 studies, published respectively in years 2000, 2005, 2010, and 2015. Among those, 423 (69.6%) studies involved more than one site, and 238 (38.8%) studies involved more than one country. Sources of funding were 'public only' in 210 (39.3%), private/industry in 215 (40.3%), and both public and private/industry funding in 109 (20.4%) RCTs. In 82 cases (13%), the funding was not reported.

Respectively, 7.5% and 1.1% were cross-over and cluster-randomized trials. Type of intervention was identified as pharmaceutical in 343 (55.7%) studies; procedure and device studies in 193 (31.3%), and behavioral and health system interventions in 80 (13%) studies. Trial phase was not clear for 16 studies, but among the others, 13 (2.2%), 254 (42.3%), 212 (35.3%), and 121 (20.2%) studies were identified as phase I, II, III, and IV, respectively. Among phase II trials, 105 (41.3%) and 110 (43.3%) studies were further classified as IIa and IIb, respectively.

Among 616 RCTs, 380 (61.7%) were positive for their primary endpoint. Fifty-six (9.1%) trials were positive for secondary endpoints but failed to achieve the primary endpoint, and 180 (29.2%) were identified as neutral or negative.

4.3.2 PRECIS-2 Scores

The PRECIS scores across 9 trial design domains as well as the summary PRECIS-2 score are presented in Supplementary Table 4.2 and Supplementary Figure 4.2. The mean (±SD) PRECIS-2 score was 3.26 ± 0.70 among 616 included RCTs. The primary endpoint and statistical analysis domains had the lowest and highest PRECIS-2 scores, respectively.

The level of pragmatism increased over time from a score of 3.07 ± 0.74 in 2000 to 3.46 ± 0.67 in 2015 ($p < 0.0001$ for trend; Cohen's D relative effect size 0.56) (Table 4.1). The increase in pragmatism occurred mainly in the domains of eligibility, setting, intervention delivery, and primary endpoint (Figure 4.2).

Although the level of pragmatism increased over time in both general medicine and CV journals, the general medicine category had a greater increase in the mean PRECIS-2 score, as compared to CV journals (p for trend <.0001). RCTs that were published in general medicine journals had a higher PRECIS-2 score as compared to those published in CV journals (Table 4.1 and Supplementary Figure 4.3). The domains of setting and primary outcome had the highest difference in pragmatism between trials published in general medicine and CV journals (Supplementary Figure 4.3D).

PRECIS-2 score was higher for neutral trials than those with positive results (p=.0002) and in phase III/IV trials as compared to phase I/II trials (p<.0001) (Figure 4.3). Furthermore, trials that involve more sites and countries, with larger sample sizes, longer follow-ups, and those with mortality (alone or in a composite) as their primary endpoint were found to be more pragmatic (Table 4.1 and Figure 4.4). There was no difference in the level of pragmatism between different sources of funding (public, private/industry, or both; p=0.38). Cross-over designed RCTs had a significantly lower PRECIS-2 as compared to their counterparts (2.69 vs 3.31, p<.0001). Cluster-randomized trials had a numerically higher PRECIS score than the RCTs with individual participant randomization, but the difference was not significant (3.66 vs 3.26, p=0.13). Trials with behavioral and health system interventions had higher (i.e. more pragmatic) PRECIS-2 score (3.48) than RCTs with pharmaceutical (3.14), and device or procedural (3.38) interventions (p<.0001). Although studies with a high risk of bias based on Cochrane risk of bias tool had higher PRECIS-2 score as compared to those with low bias risk, the difference was not clinically meaningful (Cohen's D effect size 0.19; Supplementary Table 4.3).

4.3.3 Sensitivity analysis

The results (increase in pragmatic RCTs from 2000 to 2015, difference between journal types, trial phases, types of intervention, and study endpoints, and larger sample sizes, more sites, and longer follow-up periods in pragmatic trials) remained consistent, when pragmatic trials were defined as those with PRECIS-2 scores of ≥4 in at least 4 domains, provided the scores of the other domains were ≥3[18] (Supplementary Table 4.4).

In total, 212 RCTs were identified as phase III, ranging from 46 phase III RCTs (21.7%) in 2000 to 62 trials (29.2%) in 2015. The PRECIS-2 score was similar between the years of study (mean score of 3.53 ± 0.56) and the trend over time was non-significant (p=0.65). We also

investigated phase III and IV trials combined, and the trend of change in pragmatism over time was not significant (p=0.43).

Twenty-three (3.7%) and 19 (3.1%) studies were self-identified by authors as pragmatic and explanatory RCTs, respectively. The PRECIS-2 score was respectively, higher (3.83 vs 3.25) and lower (2.92 vs 3.25) in the self-identified pragmatic and explanatory trials as compared to those that did not mention pragmatism or the explanatory nature (Supplementary Table 4.5 and Supplementary Figure 4.4). The self-identified pragmatic trials were more pragmatic than others in the primary outcome, setting, follow-up and eligibility domains of the trial design (Supplementary Table 4.6-4.7). Difference between two adjudications were evaluated and found to be insignificant (Supplementary Table 4.8).

4.4 Discussion

This study showed a moderate increase in the level of pragmatism in CV trials over 2 decades. The increase in pragmatism occurred mainly in the domains of eligibility, setting, intervention delivery, and primary endpoint. No RCT was completely explanatory or pragmatic in the trials sampled, consistent with the assumption of the developers of the PRECIS and PRECIS-2 tool, that trials are designed on a spectrum connecting these two extremes rather than dichotomous decisions of either pragmatic or explanatory nature.[6]

4.4.1 Pragmatic trials and guidelines

A recent study reviewed current recommendations of 2 major CV professional organizations' practice guidelines and found that only 8.5% - 14.2% recommendations were based on high-quality evidence, derived from multiple RCTs or meta-analyses of high-quality RCTs.[19] Despite attempts to simplify and improve the conduct of RCTs, the evidence gap remains with only 11.6% and 8.5% of recommendations being backed by high-quality evidence, respectively in 2009 and 2019.[19, 20] To fill the above-mentioned gap, streamlining the design of RCTs across all 9 domains is needed, in order to focus on key questions in CV medicine. Unlike explanatory trials, which are aimed to maximize internal validity to demonstrate that the intervention is indeed the cause of increased/decreased outcome, the main focus in pragmatic trials is often maximizing external validity or generalizability of findings by mimicking the real-world setting and minimizing the alterations to usual processes of care while preserving internal validity.

4.4.2 Trial characteristics and degree of pragmatism

Previous studies have suggested that the majority of pragmatic trials which explore research questions that are important for optimizing the care for patients and health systems, are commonly funded by public or public-private partnerships.[21] However, we did not find any difference in the level of pragmatism between different types of funding. There are fewer regulatory restrictions on interventions such as behavioral or health system interventions. In our study, behavioral or health system interventions had a higher level of pragmatism than medicinal or device/procedural interventions.

In the study of Dal-Ré *et al*, among 89 medicinal RCTs self-labelled as pragmatic or naturalistic, 36% had rather explanatory features and were placebo-controlled single-centre, or early phase trials.[18] Conversely, in our study, trials that identified themselves as pragmatic had higher PRECIS-2 scores.

There was an increase in the level of pragmatism by increase in the phase of the RCTs. In principle, the pragmatic RCTs are supposed to investigate the effectiveness of already-marketed drugs rather than those still in the process of regulatory licensing, which requires strict protocols aiming maximized internal validity.[18] Hence, it seems appropriate for the higher phase trials i.e. phase III/IV to be more pragmatic than phase I/II RCTs. We did not identify a trend of greater pragmatism over the 2 decades in Phase III or IV trials; however, it is plausible that a re-emphasis on pragmatic RCT has occurred in the more recent years and this change will be evident in the coming years. Conversely, the large simple trials that lead to changes in practice in e.g. acute myocardial infarction, were also very pragmatic.

We used the PRECIS-2 tool for appraising trials to assess their placement in the pragmatic-explanatory continuum. Knowledge translation and dissemination efforts, including journal publications, may want to include the PRECIS-2 wheel assessment with the rationale behind the assigned scores in the same way journals require reporting CONSORT checklist.[22]

4.4.3 Limitations

There are strengths and limitations requiring mention. As we only included RCTs that were published in the general medicine and CV journals, the findings might not be generalizable to trials published in other journals and there is a possibility of publication bias. The assessment of all published trials in a 2-decade period was not feasible for our group. We restricted the

adjudications to the main primary publication of trials. Pilot projects, methodology and rationale papers, although not available for all RCTs,[5, 21] may be able to provide in-depth information on the nuances of the trial design for further assessment. It was not feasible to contact over 600 investigative teams to clarify elements regarding their trial, so we relied on publication materials, however, it is unlikely this clarification would have shifted the results meaningfully.

4.4.4 Conclusion

The level of pragmatism increased moderately over time in CV trials. Greater focus on the design and delivery of CV trials will be required for filling the knowledge gap and for the broad application of the studied interventions.

4.5 References

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Figures and Tables

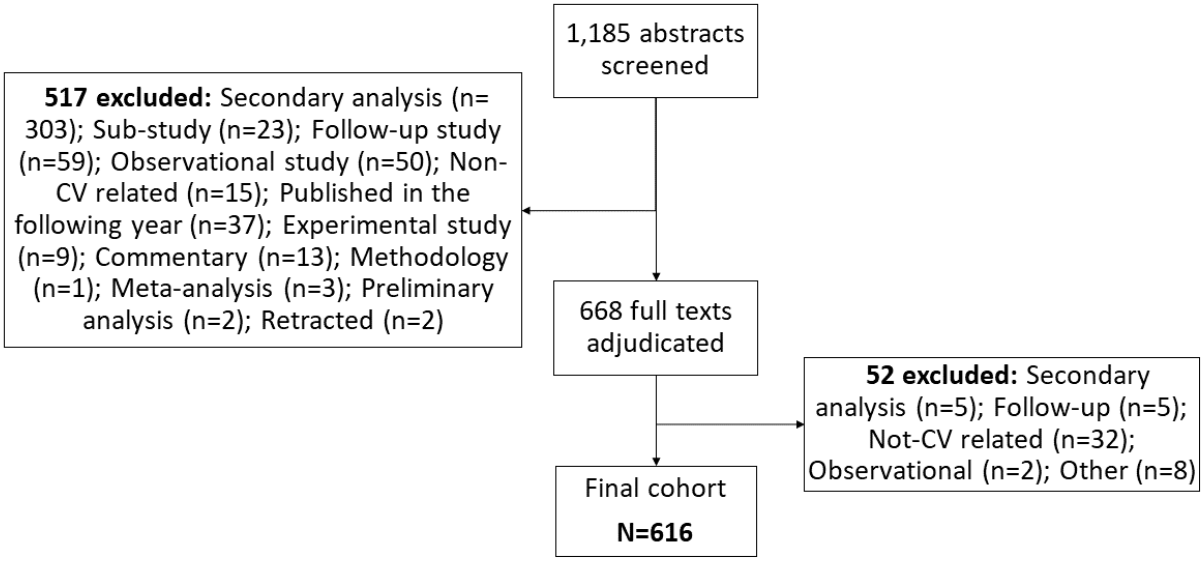


Figure 4.1. Study flow diagram

CV: cardiovascular;

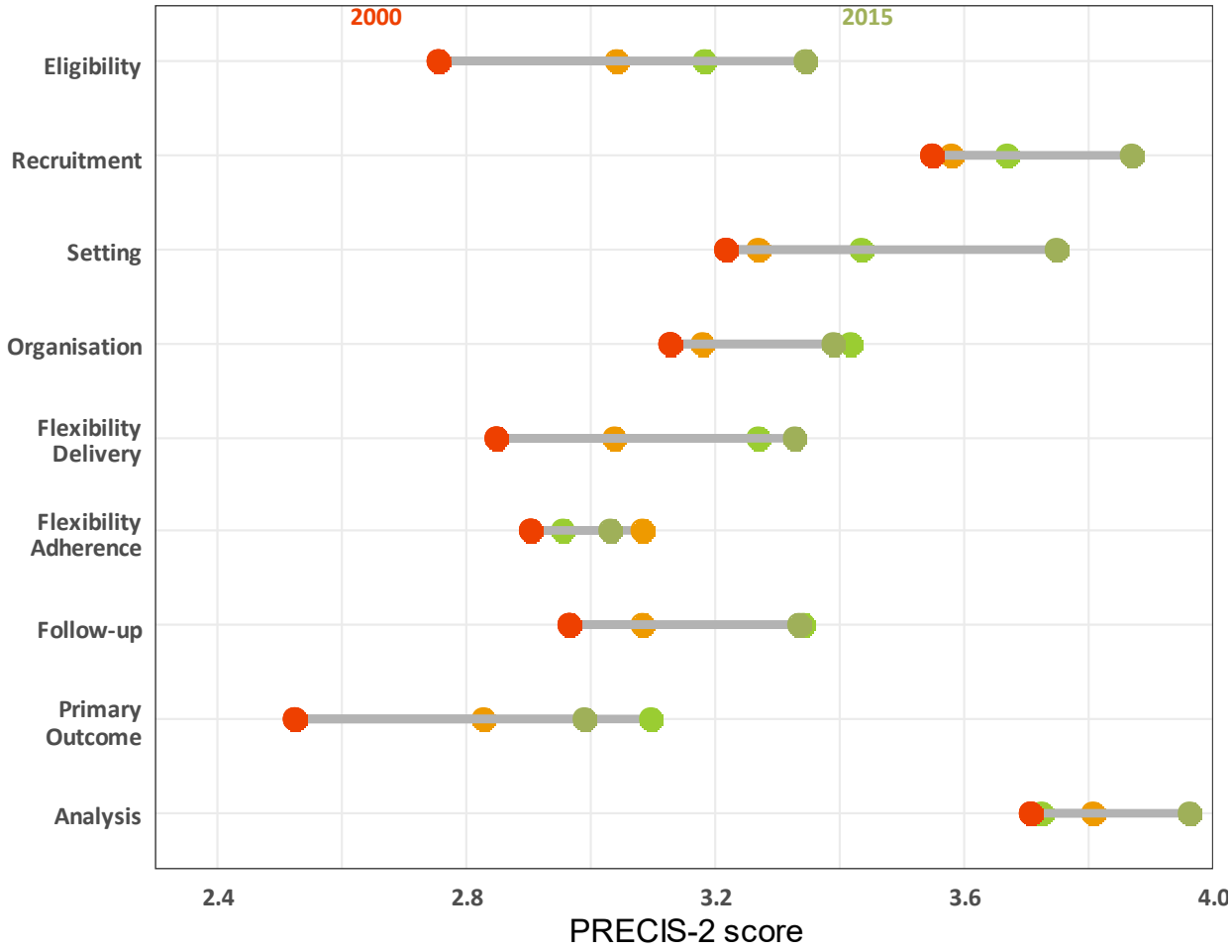


Figure 4.2. Change in pragmatism over time across different domains of trial design

Table 4.1. Study characteristics and level of pragmatism

Factors	N (%)	Mean Score (SD)	Effect size: Cohen's D	P-value
Overall	616	3.26(0.70)		
Year of publication				
2000	172(27.9)	3.07(0.74)	-ref-	<.0001*
2005	168(27.3)	3.21(0.64)	0.21	
2010	137(22.2)	3.37(0.66)	0.43	
2015	139(22.6)	3.46(0.67)	0.56	
Journal				
General Medicine: NEJM/Lancet/JAMA	224(36.4)	3.55(0.58)	0.67	<.0001
Cardiology: EHJ/JACC/Circulation	392(63.6)	3.10(0.71)	-ref-	
Trial phase				
I/II	267(44.5)	2.97(0.67)	-ref-	<.0001
III/IV	333(55.5)	3.49(0.63)	0.81	
Cross-over design				<.0001
No	568(92.5)	3.31(0.68)	Ref	
Yes	46(7.49)	2.69(0.59)	-0.92	
Cluster-randomized				0.13
No	609(98.9)	3.26(0.70)	Ref	
Yes	7(1.14)	3.66(0.59)	0.58	
Number of arms				0.0006
1-2	491(79.7)	3.31(0.69)	Ref	
≥3	125(20.3)	3.07(0.68)	-0.34	
Type of Intervention				<.0001
Medicinal	343(55.7)	3.14(0.69)	Ref	

Procedure or device	193(31.3)	3.38(0.67)	0.35	
Behavioral or Health system intervention	80(13.0)	3.48(0.67)	0.49	
Placebo-controlled				<.0001
No	382(62.0)	3.36(0.70)	Ref	
Yes	234(38.0)	3.11(0.66)	-0.37	
Blinding of participants and personnel				<.0001
No	312(51.2)	3.38(0.69)	Ref	
Yes	297(48.8)	3.14(0.69)	-0.34	
Blinding of outcome assessors				0.055
No	74(12.7)	3.41(0.62)	Ref	
Yes	507(87.3)	3.25(0.70)	-0.24	
Primary outcome				<.0001
Mortality	27(4.38)	4.05(0.37)	1.5	
Mortality in a composite	168(27.3)	3.63(0.53)	0.89	
Other	421(68.3)	3.07(0.67)	-ref-	
Central adjudication for primary endpoint				<.0001
No	370(60.1)	3.11(0.72)	Ref	
Yes	246(39.9)	3.50(0.59)	0.59	
Trial results				0.0002
Neutral (negative)	180(29.2)	3.42(0.66)	-ref-	
Negative for primary but positive for 2º outcomes	56(9.09)	3.38(0.67)	0.07	

Positive for 1º outcome	380(61.7)	3.17(0.70)	0.36	
Type of Funding				0.38
Public Only	210(39.3)	3.34(0.71)	Ref	
Private Only	215(40.3)	3.25(0.69)	-0.13	
Public + Private	109(20.4)	3.30(0.60)	-0.07	

EHJ: European Heart Journal; JACC: Journal of American College of Cardiology; JAMA: Journal of American Medical Association; N: number; NEJM: New England Journal of Medicine; ref: reference; SD: standard deviation; In the type of funding, the private category includes both private and industry types of funding.

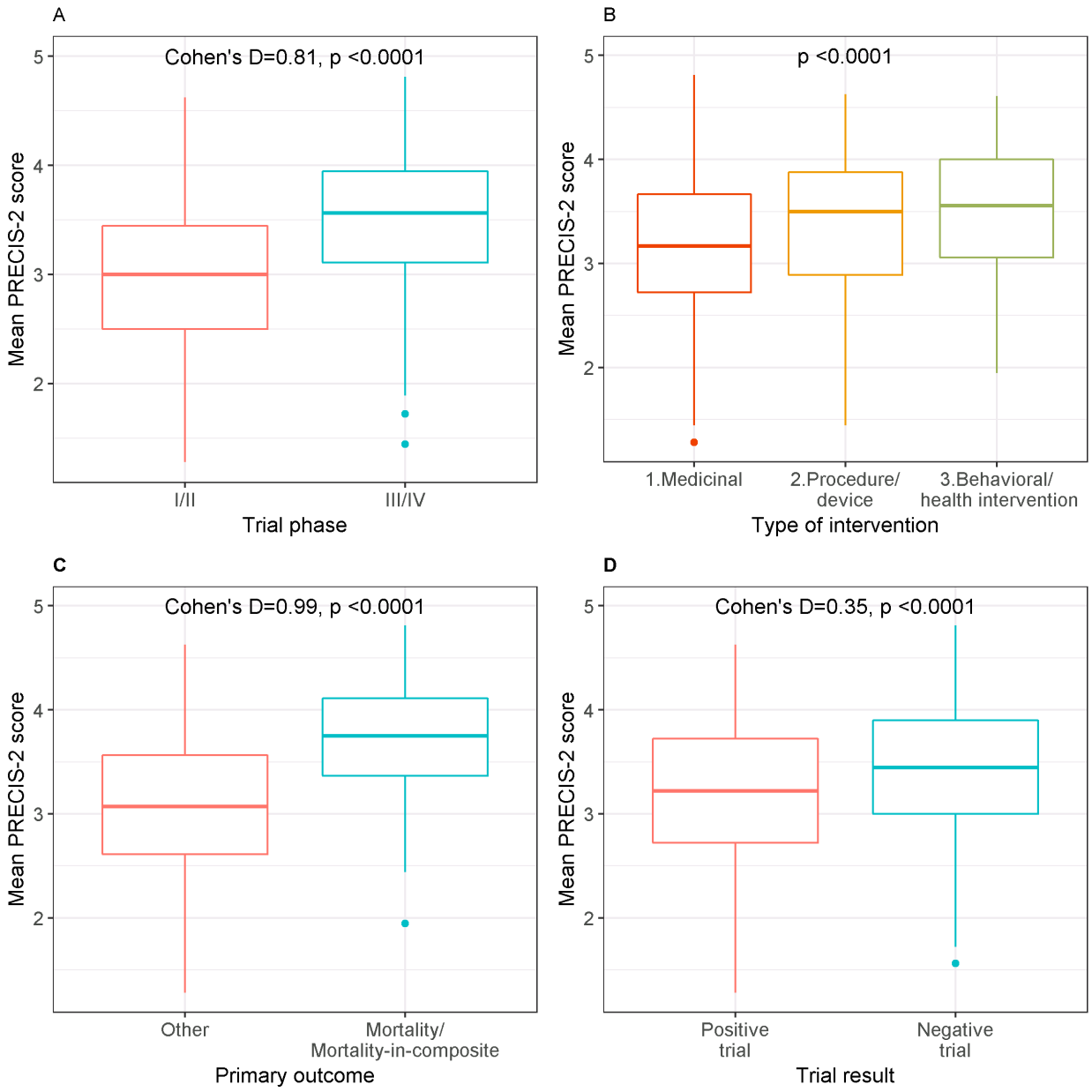


Figure 4.3. The level of pragmatism by trial phase, type of intervention, primary outcome, and trial results

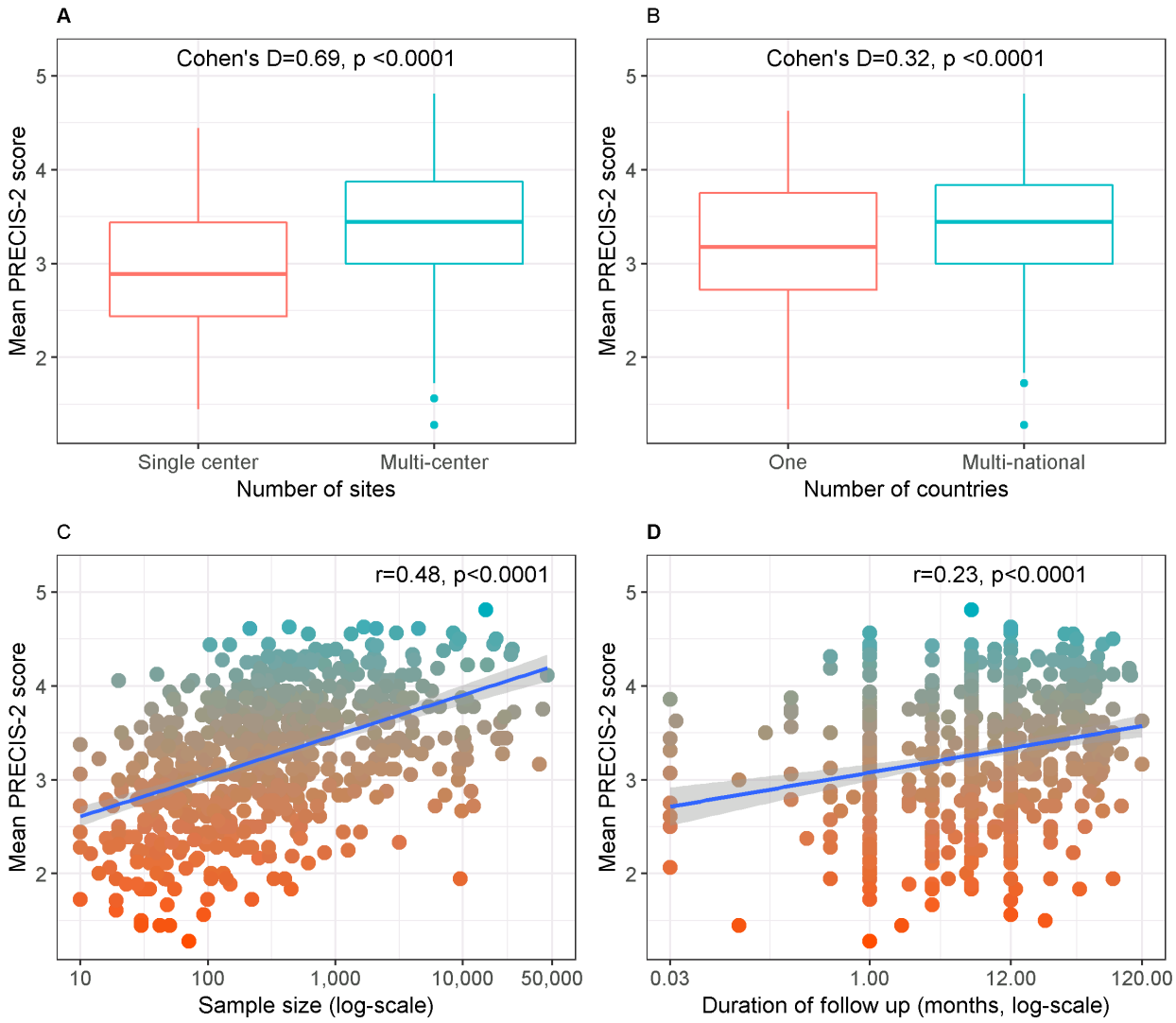


Figure 4.4. Correlation between PRECIS-2 score with sample size, number of sites and countries, and follow-up period

4.6 Supplementary material

Supplementary Table 4.1. Number of randomized clinical trials identified with including different study publication years

Journal Name	RCTs (2000-2015)	RCTs (2006-2015)	RCTs (2011-2015)	2006, 2009, 2012, 2015	2000, 2005, 2010, 2015
NEJM	578	407	209	170	161
JAMA	314	185	99	66	63
Lancet	396	240	119	102	123
JACC	1206	706	358	277	308
Circulation	1142	541	256	224	309
EHJ	754	487	223	235	221
Total	**4,390**	**2,566**	**1,264**	**1074**	**1185**

EHJ: European Heart Journal; JACC: Journal of American College of Cardiology; JAMA: Journal of American Medical Association; NEJM: New England Journal of Medicine; RCT: randomized clinical trial;

Supplementary Table 4.2. Level of pragmatism across different design domains

Design domains	N (%)	Mean (SD)
Eligibility Criteria	615	3.06 (0.98)
Very explanatory (1)	11 (1.8)	
Rather explanatory (>1 and <3)	233 (37.8)	
Equally pragmatic/ explanatory (3)	111 (18.0)	
Rather pragmatic (>3 and <5)	233 (37.8)	
Very pragmatic (5)	27 (4.4)	
Unclear	1 (0.2)	
Recruitment path	543	3.65 (1.18)
Very explanatory	31 (5.0)	
Rather explanatory	90 (14.6)	
Equally pragmatic/ explanatory	55 (8.9)	
Rather pragmatic	248 (40.3)	
Very pragmatic	119 (19.3)	
Unclear	73 (11.9)	
Setting	616	3.40 (1.10)
Very explanatory	20 (3.2)	
Rather explanatory	146 (23.7)	
Equally pragmatic/ explanatory	93 (15.1)	
Rather pragmatic	289 (46.9)	
Very pragmatic	68 (11.0)	
Organizational intervention	613	3.26 (1.02)
Very explanatory	15 (2.4)	
Rather explanatory	176 (28.6)	
Equally pragmatic/ explanatory	106 (17.2)	
Rather pragmatic	277 (45.0)	
Very pragmatic	39 (6.3)	
Unclear	3 (0.5)	
Flexibility of Intervention-Delivery	614	3.10 (0.99)
Very explanatory	15 (2.4)	
Rather explanatory	209 (33.9)	
Equally pragmatic/ explanatory	114 (18.5)	
Rather pragmatic	255 (41.4)	
Very pragmatic	21 (3.4)	
Unclear	2 (0.3)	
Flexibility of Intervention-Adherence	358	2.99 (1.18)
Very explanatory	34 (5.5)	
Rather explanatory	119 (19.3)	
Equally pragmatic/ explanatory	61 (9.9)	
Rather pragmatic	105 (17.0)	
Very pragmatic	39 (6.3)	
Unclear or NA	258 (41.9)	
Follow-up	615	3.16 (1.00)
Very explanatory	13 (2.1)	

Rather explanatory	197 (32.0)	
Equally pragmatic/ explanatory	116 (18.8)	
Rather pragmatic	263 (42.7)	
Very pragmatic	26 (4.2)	
Unclear	1 (0.2)	
Outcome	616	2.84 (1.24)
Very explanatory	74 (12.0)	
Rather explanatory	228 (37.0)	
Equally pragmatic/ explanatory	88 (14.3)	
Rather pragmatic	174 (28.2)	
Very pragmatic	52 (8.4)	
Analysis	611	3.79 (1.03)
Very explanatory	13 (2.1)	
Rather explanatory	85 (13.8)	
Equally pragmatic/ explanatory	80 (13.0)	
Rather pragmatic	317 (51.5)	
Very pragmatic	116 (18.8)	
Unclear	5 (0.8)	
PRECIS Summary Score, mean ± SD	616	3.26 (0.70)

SD: standard deviation; For all domains, the very explanatory, rather explanatory, equally explanatory/pragmatic, rather pragmatic, and very pragmatic categories were defined as the PRECIS-2 score =1, >1 and <3, =3, >3 and <5, and =5, respectively.

4.6.1 The Cochrane Risk of Bias score

The risk of bias in each RCT was assessed using the Cochrane Risk of Bias tool which assesses trials for the sequence generation, allocation sequence concealment, blinding of participants, personnel and outcome assessors, completeness of outcome data, selective outcome reporting, etc. This tool categorizes the risk of bias in each trial to one of the three categories: high, low, and unclear.

Risk of bias was adjudicated to be low, high, and unclear, respectively in 178, 211, and 227 studies. The PRECIS-2 score was higher in the high-risk studies as compared to low-risk RCTs (Supplementary Table 4.3).

Supplementary Table 4.3. PRECIS-2 scores in studies with different levels of risk determined by Cochrane risk of bias tool

Factors	N (%)	Mean Score (SD)	Effect size: Cohen's D	P-value
Overall	616	3.26(0.70)		
Cochrane Risk of Bias				<.0001
Low risk	178(28.9)	3.29(0.66)	Ref	
High risk	211(34.3)	3.42(0.67)	0.19	
Unclear risk	227(36.9)	3.09(0.71)	-0.29	

SD: standard deviation;

Supplementary Table 4.4. Study characteristics between pragmatic and non-pragmatic randomized clinical trials

Factors	N (%)	Pragmatic	Not Pragmatic	P-value
Overall	**616**	**105**	**511**	
Year of publication				0.0898
2000	172 (27.9)	24 (22.9)	148 (29.0)	
2005	168 (27.3)	24 (22.9)	144 (28.2)	
2010	137 (22.2)	24 (22.9)	113 (22.1)	
2015	139 (22.6)	33 (31.4)	106 (20.7)	
Journal				<.0001
General Medicine: NEJM/Lancet/JAMA	224 (36.4)	64 (61.0)	160 (31.3)	
Cardiology: EHJ/JACC/Circulation	392 (63.6)	41 (39.0)	351 (68.7)	
Trial phase				<.0001
I/II	267 (44.5)	21 (20.8)	246 (49.3)	
III/IV	333 (55.5)	80 (79.2)	253 (50.7)	
Single Centre	185 (30.4)	15 (14.4)	170 (33.7)	<.0001
Multi-national	238 (38.8)	54 (51.9)	184 (36.1)	0.0025
Sample size, median (IQR)	297 (92, 922)	897 (304, 2332)	221 (66, 652)	<.0001
Follow-up duration, months, median (IQR)	6 (3, 16)	12 (5, 36)	6 (2, 13)	0.0011
Cross-over design				0.0169
No	568 (92.5)	103 (98.1)	465 (91.4)	
Yes	46 (7.5)	2 (1.9)	44 (8.6)	
Cluster-randomized				0.8452
No	609 (98.9)	104 (99.0)	505 (98.8)	
Yes	7 (1.1)	1 (1.0)	6 (1.2)	
Number of arms				0.5388
1-2	491 (79.7)	86 (81.9)	405 (79.3)	
≥3	125 (20.3)	19 (18.1)	106 (20.7)	
Type of Intervention				0.0031
Medicinal	343 (55.7)	43 (41.0)	300 (58.7)	
Procedure or device	193 (31.3)	42 (40.0)	151 (29.5)	
Behavioral or Health system intervention	80 (13.0)	20 (19.0)	60 (11.7)	
Placebo-controlled				0.0044
No	382 (62.0)	78 (74.3)	304 (59.5)	
Yes	234 (38.0)	27 (25.7)	207 (40.5)	
Blinding of participants and personnel				0.0269
No	312 (51.2)	63 (61.2)	249 (49.2)	
Yes	297 (48.8)	40 (38.8)	257 (50.8)	

Blinding of outcome assessors				0.9058
No	74 (12.7)	12 (12.4)	62 (12.8)	
Yes	507 (87.3)	85 (87.6)	422 (87.2)	
Primary outcome				<.0001
Mortality	27 (4.4)	14 (13.3)	13 (2.5)	
Mortality in a composite	168 (27.3)	51 (48.6)	117 (22.9)	
Other	421 (68.3)	40 (38.1)	381 (74.6)	
Trial results				0.0883
Neutral (negative)	180 (29.2)	37 (35.2)	143 (28.0)	
Negative for primary but positive for 2° outcomes	56 (9.1)	13 (12.4)	43 (8.4)	
Positive for 1° outcome	380 (61.7)	55 (52.4)	325 (63.6)	
Type of Funding				0.2637
Public Only	210 (39.3)	44 (45.8)	166 (37.9)	
Private Only	215 (40.3)	32 (33.3)	183 (41.8)	
Public + Private	109 (20.4)	20 (20.8)	89 (20.3)	

EHJ: European Heart Journal; IQR: interquartile range; JACC: Journal of American College of Cardiology; JAMA: Journal of American Medical Association; NEJM: New England Journal of Medicine; ref: reference; SD: standard deviation; In the type of funding, the private category includes both private and industry types of funding.

Supplementary Table 4.5. Self-identified pragmatic and explanatory trials

Self-identified pragmatism	N (%)	PRECIS-2 score Mean (SD)	Effect size; Cohen's D	P-value
Not reported	574 (93.2)	3.25 (0.68)	-ref-	<.0001
Self-identified explanatory	19 (3.08)	2.92 (0.69)	0.49	
Self-identified pragmatic	23 (3.73)	3.83 (0.78)	0.84	

SD: standard deviation; N: number;

Supplementary Table 4.6. PRECIS-2 score across different domains of trial design in self-identified pragmatic or explanatory randomized clinical trials and others

Domain	Self-identified Pragmatic	Self-identified Explanatory	Not reported	Δ PRECIS-2 between self-identified pragmatic group vs others
1. Eligibility	3.67	2.55	3.05	0.62
2. Recruitment	4.24	2.50	3.67	0.57
3. Setting	4.15	3.18	3.38	0.78
4. Organization	3.73	2.87	3.26	0.47
5. Intervention delivery	3.43	3.00	3.09	0.35
6. Intervention adherence	3.18	3.00	2.98	0.20
7. Follow-up	3.85	2.76	3.15	0.70
8. Primary outcome	3.63	2.71	2.81	0.82
9. Analysis	4.11	3.66	3.79	0.32

Supplementary Table 4.7. Trial phase, placebo use and number of sites in self-identified pragmatic and explanatory trials compared to others

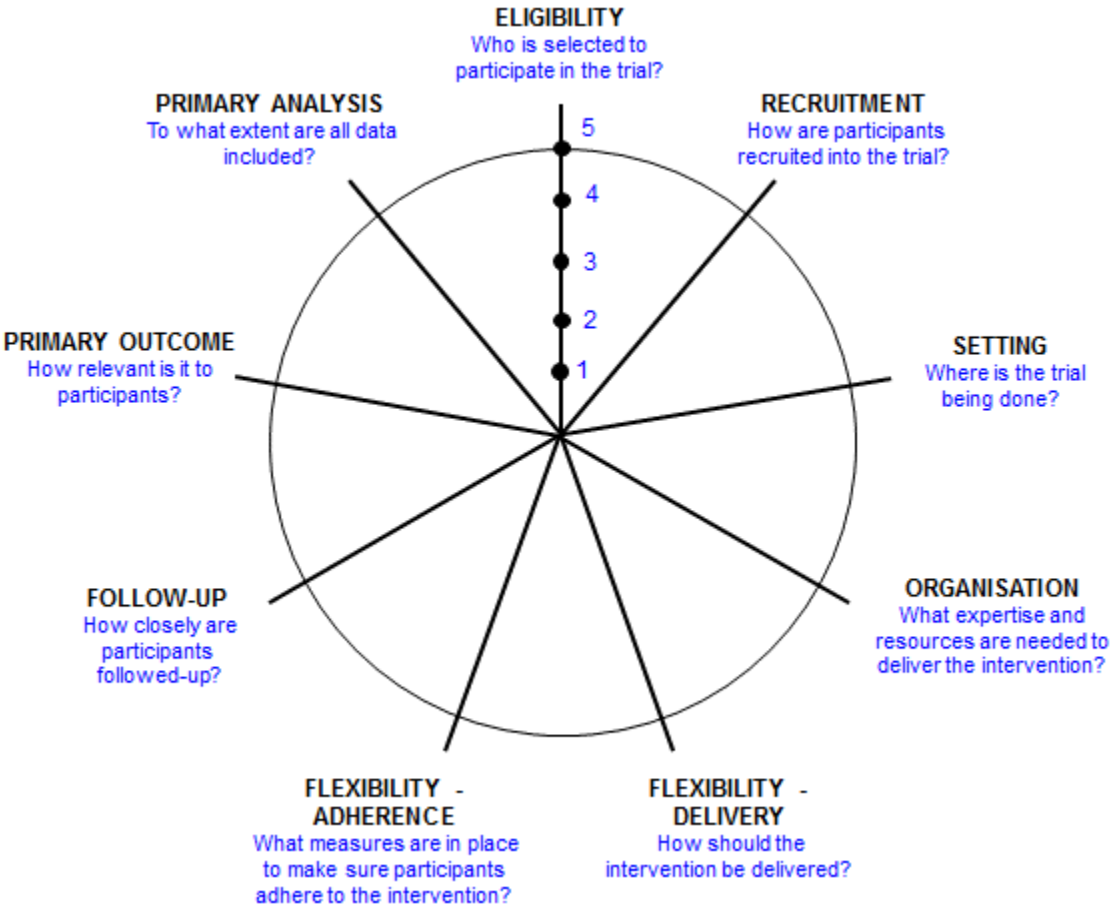
	Total	Self-identified pragmatic	Self-identified explanatory	Not reported	P-value
Total N	616	23	19	574	
Trial phase					0.0811
I/II	267 (44.5)	5 (21.7)	8 (44.4)	254 (45.4)	
III/IV	333 (55.5)	18 (78.3)	10 (55.6)	305 (54.6)	
Single site, n(%)	185 (30.4)	8 (36.4)	5 (29.4)	172 (30.2)	0.8248
Placebo controlled, n(%)	234 (38.0)	6 (26.1)	10 (52.6)	218 (38.0)	0.2109

Supplementary Table 4.8. Number of studies with ≥1, ≥2, and ≥3 difference between two adjudicators for each PRECIS-2 domain

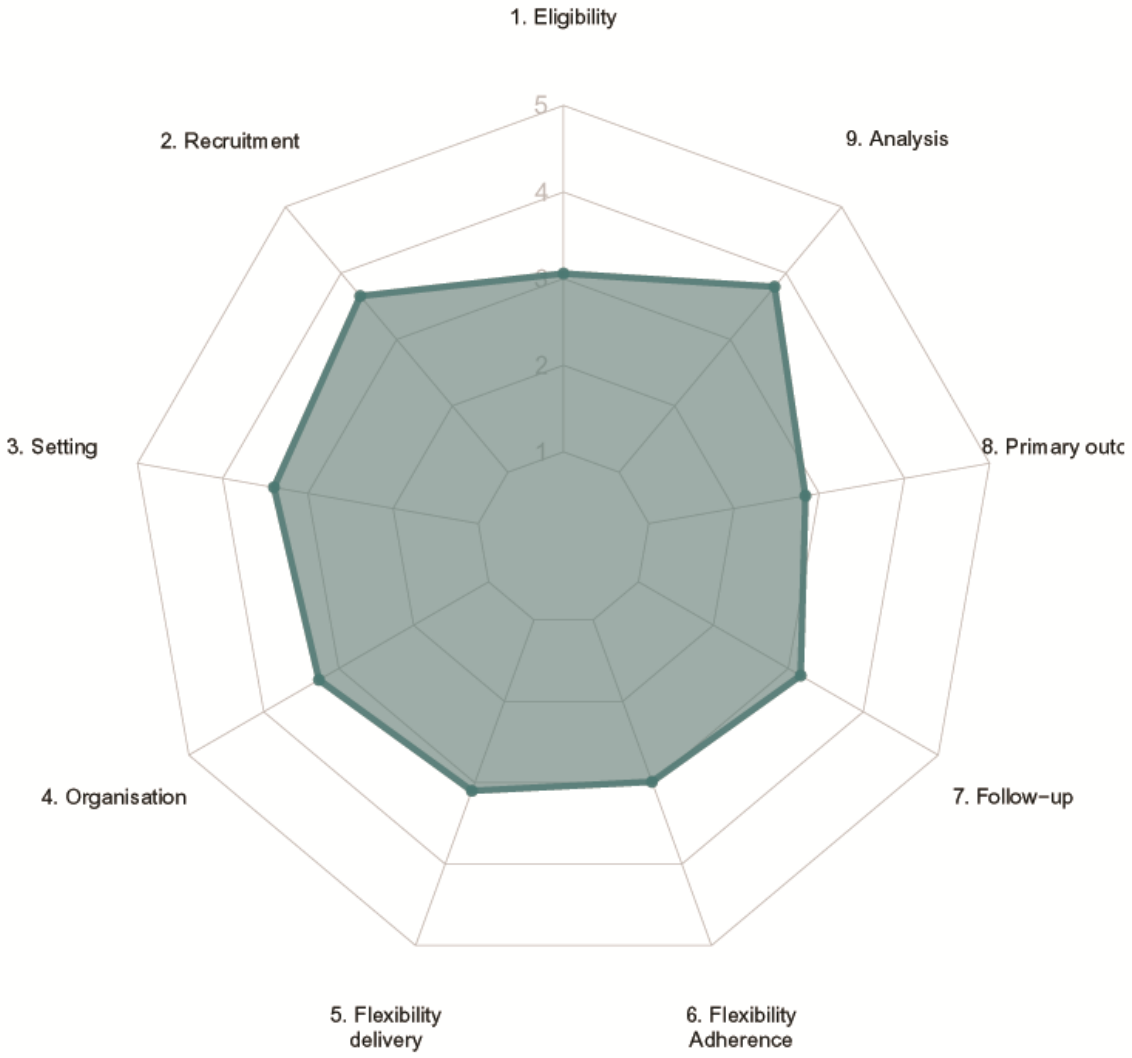
	Agreement		Difference between adjudicators			Mean (SD) difference
PRECIS domains	**Equal score**	**Both unclear**	**≥ 1**	**≥ 2**	**≥ 3**	
Eligibility Criteria	186 (30.2)	1 (0.2)	429 (69.6)	226 (36.7)	107 (17.4)	1.27 (1.34)
Recruitment path	350 (56.8)	73 (11.9)	193 (31.3)	97 (15.7)	44 (7.1)	0.62 (1.0)
Setting	218 (35.4)	-	398 (64.6)	197 (32.0)	82 (13.3)	1.13 (1.10)
Organizational intervention	212 (34.4)	3 (0.5)	401 (65.1)	205 (33.3)	87 (14.1)	1.15 (1.1)
Flexibility of Intervention-Delivery	220 (35.7)	2 (0.3)	394 (64.0)	178 (28.9)	57 (9.3)	1.03 (0.98)
Flexibility of Intervention-Adherence	230 (37.3)	258 (41.9)	128 (20.8)	73 (11.9)	35 (5.7)	0.68 (1.06)
Follow-up	218 (35.4)	1 (0.2)	397 (64.4)	177 (28.7)	56 (9.1)	1.04 (1.0)
Outcome	196 (31.8)	-	420 (68.2)	234 (38.0)	121 (19.6)	1.31 (1.20)
Analysis	237 (38.5)	5 (0.8)	374 (60.7)	175 (28.4)	65 (10.6)	1.04 (1.08)

In a sensitivity analysis we evaluated studies with a difference between the assigned scores for each domain by two adjudicators and 20.8-69.6%, 11.9-38.0%, and 5.7-19.6% of studies respectively had a difference between adjudicated scores equal or greater than 1, 2, and 3 across different domains of trial design (Supplementary Table 4.8).

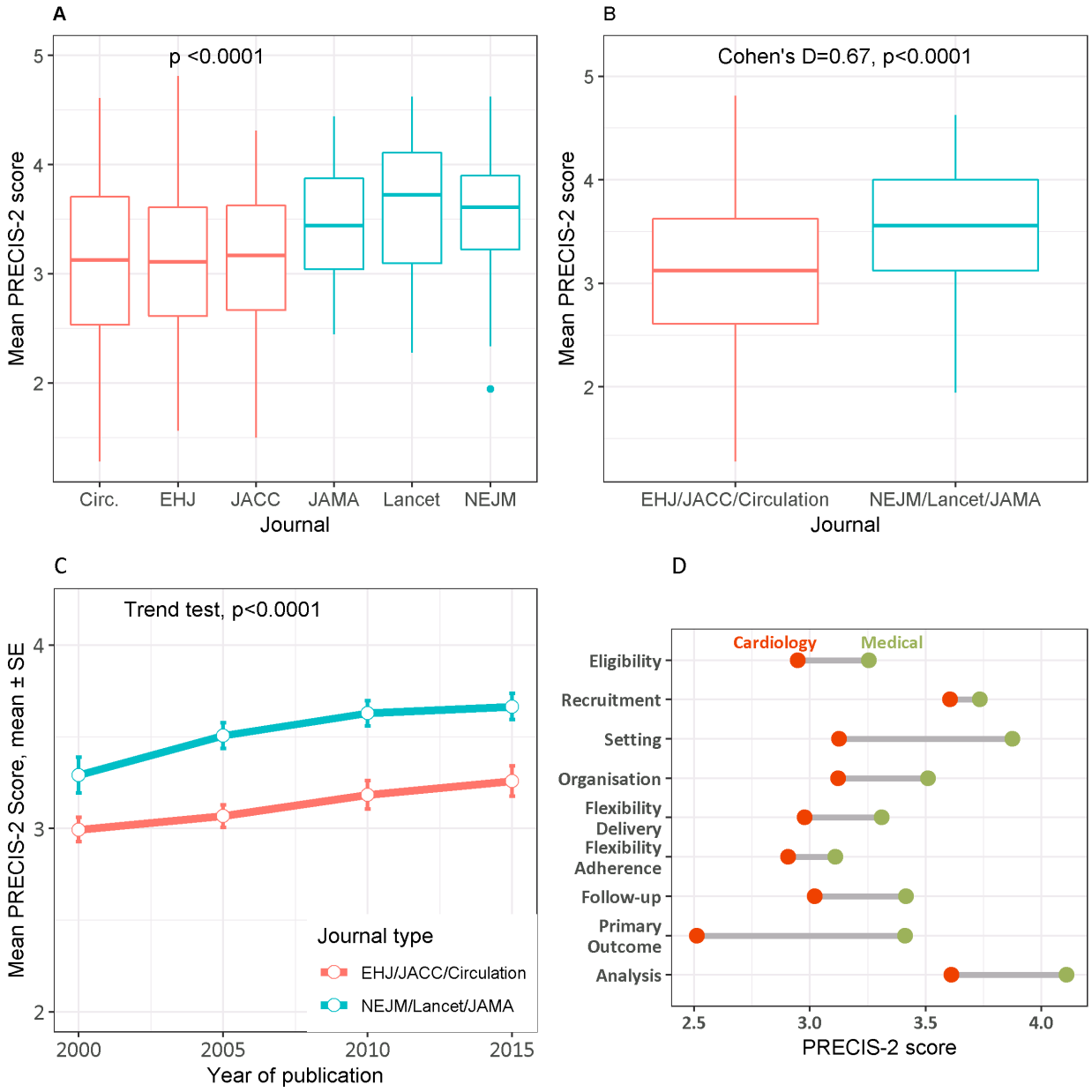
Supplementary Figure 4.1. The PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel



Supplementary Figure 4.2. PRECIS-2 score across different domains of trial design

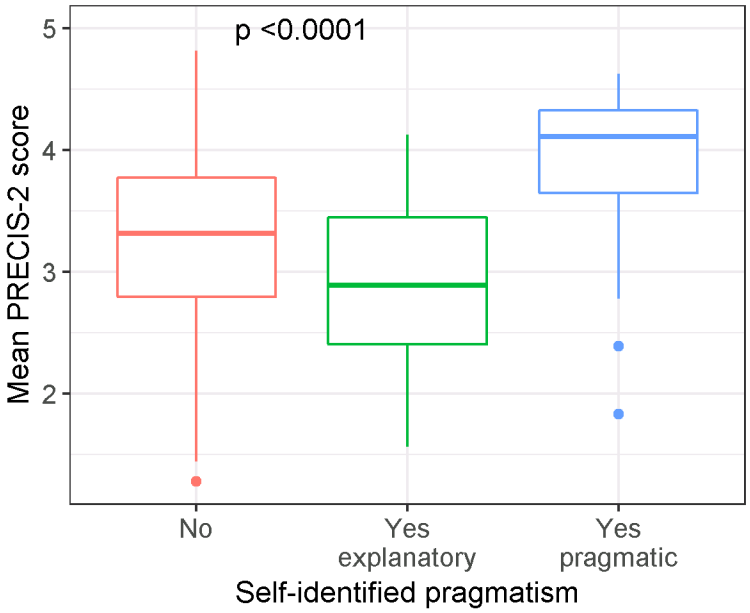


Supplementary Figure 4.3. The level of pragmatism between trials published in different journals (4.3A) and journal categories (4.3B), the trend over time of pragmatism (4.3C), and PRECIS-2 scores across different domains between general medicine and cardiology journals (4.3D)



EHJ: European Heart Journal; JACC: Journal of American College of Cardiology; JAMA: Journal of American Medical Association; NEJM: New England Journal of Medicine;

Supplementary Figure 4.4. PRECIS-2 score between self-identified pragmatic and explanatory trials compared to others



Chapter 5 : High versus Low oxygen therapy in patients with acute Heart Failure: HiLo-HF Pilot trial

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5.1 Abstract

Background: Most patients with acute heart failure (AHF) are treated with supplemental oxygen during hospitalization. In this study, we investigated the effect of oxygen titrated to high versus low pulse oximetry targets in patients hospitalized with AHF.

Methods: In a pilot, open-label, randomized controlled trial, 50 patients who were admitted for AHF were randomized to either high (≥96%) or low (90-92%) SpO_2 targets. Oxygen was manually titrated to the assigned target ranges for 72 hours. The primary endpoint was the change in NT-proBNP from randomization to 72 hours, and secondary endpoints included patient-reported dyspnea by visual analogue scale (VAS), patient global assessment (PGA), peak expiratory flow (PEF) within 72 hours, and clinical outcomes up to 30 days following hospital discharge.

Results: The median age was 73.5 years, and 42% were women. The change in NT-proBNP was -6,963 (-13,345, -1,253) pg/ml in the high SpO_2 group and -2,093 (-5,692, -353) pg/ml in the low SpO_2 group (p=0.46), and the 72-hour to baseline NT-proBNP ratio was similar between groups (0.7 vs 0.6; p=0.51). There were no differences between arms in change in dyspnea VAS (p=0.86), PGA (p=0.91), PEF (p=0.52), in-hospital mortality (4.0% vs. 8.0%, p=0.50), or 30-day heart failure readmission rates (20.8% vs. 8.7%, p=0.22).

Conclusions: In this study, no differences were observed in the primary or secondary outcomes for patients randomized to high versus low SpO_2 targets. Further RCTs with larger sample sizes are warranted to determine the efficacy and safety of oxygen therapy in patients with AHF.

ClinicalTrials.gov Identifier: NCT03110042.

Keywords: supplemental oxygen, heart failure, randomized clinical trial

5.2 Introduction

Supplemental oxygen (O_2) therapy is a routine treatment in the management of many patients with dyspnea, including those with acute heart failure (AHF).[1] Regardless of the arterial O_2 saturation levels, O_2 is often administered in these patients based on the clinicians' or patients' belief that it will ameliorate dyspnea, or that improving oxygenation of the myocardial tissue will improve cardiac function.[2, 3] However, given the lack of high-quality evidence, there is an ongoing debate regarding the role that O_2 plays in the treatment of patients with AHF.

Whilst there is consensus among clinicians regarding the treatment of hypoxemia (low O_2 saturation levels or SpO_2) in the acute setting, it is unclear whether O_2 should be administered in AHF patients who have normal O_2 saturation. Several physiologic studies have suggested deleterious effects of hyperoxia (i.e. high O_2) on cardiac function.[4-7] These effects are thought to be due to high O_2 stimulating the overproduction of reactive O_2 species (ROS), and hyperoxia-induced vasoconstriction that can lead to decreased coronary blood flow, and eventually to cardiac dysfunction.[3] Previous studies have shown that the patients' perception of dyspnea is not directly correlated with SpO_2.[2]

Several major randomised clinical trials (RCT) have shown O_2 therapy to have no clinical benefits in patients without hypoxemia presenting with acute myocardial infarction,[8, 9] and others suggested possible harms.[10] Recent heart failure guidelines have taken a cautious, yet variable, approach regarding recommendations on the use of supplemental O_2 therapy in normoxemic patients with AHF.[11-13]

We designed the High versus Low SpO_2 oxygen therapy in patients with acute Heart Failure (HiLo-HF) pilot trial to investigate the feasibility of conducting an RCT as well as to explore the effects of supplemental O_2 therapy in patients who were hospitalized with AHF.

5.3 Methods

HiLo-HF trial was a single-centre pilot open-label RCT designed to test the feasibility, efficacy and safety of targeting a high (High SpO_2) versus low (Low SpO_2) O_2 saturation range. The study was approved by the Health Research Ethics Board of The University of Alberta and written informed consent was obtained from all subjects prior to study participation. The

Canadian VIGOUR Centre (CVC; thecvc.ca) managed the trial. The trial was registered at clinicaltrials.gov (NCT03110042).

5.3.1 Participants

Patients who presented to the emergency department (ED) at University of Alberta Hospital with AHF were screened for this study. The inclusion and exclusion criteria of the HiLo-HF pilot RCT were as follows:

Inclusion criteria: Patients >40 years of age presenting to the ED with objective AHF (BNP>400 pg/mL and/or chest x-ray with pulmonary congestion) and with a planned admission for the treatment of heart failure (HF) as the primary diagnosis. Patients were eligible for randomization within 16 hours of presenting to the ED.

Exclusion criteria: Patients on home O_2, known prior hypercapnic failure ($PaCO_2$>50 mmHg), asthma, primary pulmonary hypertension, requiring urgent positive pressure ventilation or intubation, or on >10 L/min O_2 were excluded.

Patients who did not meet the inclusion criteria for the HiLo-HF trial were potentially eligible for the HiLo-HF registry (eligibility criteria for HiLo-HF registry provided in supplementary table 5.1). The pilot RCT included 50 patients (25 patients in each arm) as a demonstration of feasibility (Figure 5.1).

5.3.2 Intervention

Patients were randomized in the ED to either High SpO_2 or Low SpO_2 groups after providing informed written consent (Figure 5.2). All patients had nasal cannula placed as the usual standard of care, and patients were titrated to the pre-specified target ranges according to the detailed instructions provided in supplementary material.

1. High SpO_2 group: **In the High SpO_2 arm, patients were manually titrated by a trained research coordinator to a target SpO_2 range of ≥96%.**
2. Low SpO_2 group: **In the Low SpO_2 arm, patients were manually titrated by a trained research coordinator to the target SpO_2 range of 90-92%.**

Consented patients were randomly allocated to study groups via the automated web-based system within REDCap.[14] The allocation was concealed. Time at randomization was considered as study time zero (T0). All patients received usual standard of care with the exception of their O_2 management. After 72 hours, patients were switched over to usual care for O_2 therapy at the

discretion of the treating physician. We selected the 72 hours timeframe since in previous studies most patients with AHF were no longer on O_2 by 72 hours.[2]

5.3.3 Follow-up

Patients were assessed on a daily basis while in hospital and on day of discharge to assess for in-hospital safety events (clinically-assessed worsening heart failure, or other clinical events). Patients were followed up by telephone and health records review for a period of 30 days after hospital discharge.

5.3.4 Endpoints

The primary endpoint of this study was the change in NT-proBNP from baseline to 72 hours (expressed as an absolute change and as a ratio of the baseline value).[15] Secondary endpoints included: 1) Change in dyspnea on visual analogue scale (VAS) from baseline to 72 hours (area under the curve; AUC, mm/hr);[16, 17] 2) Change in global symptoms using Patient Global Assessment (PGA) measure to 72 hours (AUC, mm/hr);[18] 3) Change in Peak Expiratory Flow (PEF) at 72 hours (L/min);[2] 4) Worsening heart failure at 7 days; 5) diuresis response as defined by weight loss up to 72 hours per 40 mg furosemide or equivalent;[19] and 6) clinical event at 30 days following hospital discharge (all-cause mortality, HF readmission).

Worsening heart failure (WHF) was defined as signs and/or symptoms of HF that require intensification of intravenous therapy for HF, or new institution of mechanical ventilator support (CPAP, NIV or intubation) or circulatory support (mechanical circulatory assist devices).[16, 17]

Directly measured patient-reported outcomes (e.g. dyspnea VAS, PGA) were collected at set time points as per Figure 5.2. For Dyspnea VAS, patients were asked to evaluate their breathing by marking a 10-cm vertical line, with the top labeled “best you have ever had” and the bottom labeled “worst you have ever had.” We scored the patients' markings on a scale of 0 to 100 by measuring the distance in millimeters from the bottom of the line. Similar approach was used for PGA to evaluate patients’ general well-being. Given the open-label design, a research coordinator who was blinded to the patient's group allocation was assigned to perform or record the subjective endpoints evaluations (i.e. dyspnea VAS and PGA). Samples for NT-proBNP were collected via standardized laboratory procedures, processed and frozen for batch analysis at the end of the trial. The Roche NT-proBNP assays were performed by the University of Alberta Clinical Trials laboratory on the Elecsys 2010 (Roche Diagnostics, Manheim, Germany; reporting range 5 to 35000 pg/ml).

5.3.5 Statistical analysis

All analyses were performed based on intention-to-treat principle. Categorical variables were summarized as frequency and percentages and compared between groups using the Pearson Chi-square test or Fisher's exact test, as appropriate. Continuous variables were summarized as median with interquartile range (IQR) and compared using the Mann-Whitney test. No data imputation has been performed when data missing in one or more data points. Analysis of Covariance (ANCOVA) was applied for the primary endpoint analysis. Given the non-normal distribution, the values were log-transformed prior to ANCOVA analysis. Summary results were reported in the original scale, while the significance test result was that of the changes in log-scale with applying Wald-statistic.

The area under the curve (AUC) representing the change in VAS, PGA and PEF from baseline to 72 hours was computed according to the trapezoidal rule for each patient,[18] and was compared between the study arms using ANCOVA. Similarly, ANCOVA was applied to compare the relative changes of dyspnea VAS AUC, PGA and PEF from baseline to 72 hours. The 30-day clinical events were estimated using Kaplan-Meier method and were compared between the intervention arms using the log-rank test. Patients who remained alive and without hospital readmission were censored at their last available study date. All statistical analysis was conducted using SAS statistical software (version 9.4; SAS Institute, Cary, North Carolina).

5.4 Results

Two-hundred thirty-three patients who presented to ED with AHF were screened for eligibility between November 24, 2016 and February 27, 2018, and 50 patients were enrolled into the HiLo-HF pilot trial (25 per arm). Patients excluded are presented in Figure 5.1.

The patients enrolled in the trial had a median age of 73.5 years old, 42% were women, 70% had prior history of HF, 56% had coronary artery disease (CAD), 18% had COPD, and 62% were current/past smokers (Table 5.1). There were no clinically important differences in demographic or clinical features between arms.

Twenty-two (44%) patients presented via ambulance, and the median rate of administered O_2 in the ambulance was 5.5 L/min among the 12 who received O_2 before the ED.

Pre-randomization SpO_2 was 94% (IQR 92, 96) and 96% (IQR 93, 98), respectively, in the high and low SpO_2 groups with 11 (44%) and 10 (40%) patients receiving O_2 (median 2 L/min O_2; IQR: 2, 3).

The median time from triage to disposition from ED was 12.8 (IQR: 9.0, 15.7) hours, which was not different between study arms (p=0.24).

5.4.1 Adherence to study protocol

At individual assessment timepoints, 83-94% of patients in the high SpO_2 group and 5-30% of patients in the low SpO_2 group were at the assigned SpO_2 ranges. However, when we accounted for supplemental O_2 volumes, only 14.5%, 18.7%, 6.9%, and 10.2% had non-adherence to the study protocol (defined as SpO_2 levels out of the target range ±1% with inappropriate O_2 volumes administered) at 6, 24, 48, and 72 hours after randomization, respectively. The rate of non-adherence was not significantly different between study groups (Table 5.2 and Supplementary Figure 5.1).

5.4.2 Primary endpoint

Follow-up (i.e., 72 hour) NT-proBNP tests were missed in 14 patients: 7 patients were discharged before 72 hours, 1 patient left against medical advice, 1 patient refused further blood tests, 1 was withdrawn from the study for safety reasons, and 4 were because of staff error. Hence the analysis for primary endpoint was limited to the remaining 36 patients with available baseline and follow-up NT-proBNP results.

Baseline and 72-hour NT-proBNP levels were not statistically significantly different between groups with high and low SpO_2 targets (Table 5.3 and Figure 5.3A). Although numerically higher in the high SpO_2 arm, NT-proBNP change was not significantly different between study arms. Ratio change of NT-proBNP to 72 hours was also similar between trial arms (p=0.51). Moreover, there was no difference between groups in terms of change in NT-proBNP after adjustment for age, sex, past history of DM, CKD, COPD, CVA and prior HF (p=0.74).

5.4.3 Secondary endpoints

Dyspnea Scores: The dyspnea VAS was not different between study arms in different study timepoints from 6 hours to 72 hours after randomization (all p>0.05) (Table 5.3). The change in

dyspnea from baseline to 72 hours was not different between study groups, and VAS AUC was similar between groups with high and low SpO_2 setpoints (Figure 5.3B).

Patient Global Assessment: Similarly, the patient symptoms according to PGA were not different between study arms in different study timepoints from 6 hours to 72 hours after randomization (all p>0.05). The change in PGA from baseline to 72 hours was not different between study groups and PGA AUC was similar between two arms of the trial (Table 5.3 and Figure 5.3C).

Peak expiratory flow: The peak expiratory flow was not significantly different between study groups in different timepoints (Figure 5.3D). In ANCOVA analysis adjusting for baseline values, the change in PEF from baseline to 72 hours (p=0.52) and PEF AUC (p=0.19) were not different between two study arms.

Diuresis response: Data for both the baseline and 72-hour weight was only available for 39 patients. Follow-up/Baseline weight ratio was similar between study groups (median (IQR): 0.97 (0.94, 0.98) vs 0.96 (0.93, 0.97) in the high and low SpO_2 arms, respectively; p=0.55).

Worsening HF: WHF occurred in one patient (4%) from the low SpO_2 group and there was no difference between study arms in terms of WHF (p=1.0).

Clinical outcomes: For 30-day clinical events, no missing patient values occurred following health records surveillance, so the analysis included all 50 patients. One patient in the high SpO_2 arm and two patients in the low SpO_2 arm died in hospital (4.0% vs 8.0%, p=0.50). Among those who survived to be discharged, 5 patients in the High SpO_2 arm and 2 patients in the low SpO_2 arm were re-hospitalized within 30 days after hospital discharge (20.8% vs 8.7%, p=0.22). Kaplan-Meier curve showed no difference between study groups in death/rehospitalization at 30 days following hospital discharge (p-value for log-rank test=0.36) (Supplementary Figure 5.3).

Length of Stay: The median length of hospital stay (LOS) was 6.3 (IQR 3.7, 11.0) days in the pilot RCT and it was significantly longer in the low SpO_2 group than in the high SpO_2 group (9.5 vs 4.7 days, p=0.011) (supplementary figure 5.2). However, after adjusting for age, sex, residence type (home vs long-term care facility), prior history of HF, CAD, diabetes mellitus (DM), hypertension (HTN), CKD, cerebrovascular disease (CVA), atrial fibrillation and the use of cardiac devices, the difference in the LOS was not significant between groups (p=0.070).

Safety: One patient in the high SpO_2 group was withdrawn after randomization because of high partial pressures of CO_2 and potential risk of hypercapnic failure. Epistaxis related to the use of nasal cannula was reported in one patient in the high SpO_2 arm, but no significant adverse event was reported in any of the two groups.

5.4.4 HiLo-HF registry

Patients in the registry (n=60) had a median age of 77 years old, and 35% were women. Thirty-four (56.7%), 26 (43.3%), and 19 (31.7%) patients had past medical history of heart failure, CAD, and COPD, respectively. The median time from triage to enrolment was 19.2 (IQR 7.2, 21.5) hours, which was longer than that among the trial patients (median 11.4; IQR 7.3, 13.5, $p<0.001$). Baseline symptoms were similar between registry and trial populations and there was no difference in terms of VAS AUC, PGA AUC, PEF AUC, and diuresis response (all p-values > 0.05).

5.4.5 Pooled cohort

Given that the trial was neutral for primary and secondary endpoints, as the next step, we pooled both trial arms and the HiLo-HF registry to form a cohort of 110 patients who presented to ED with AHF.

In the first 24 hours after randomization, SpO_2 levels were inversely correlated with patients' perception of symptom measured either by dyspnea VAS or PGA ($r= -0.36$, $p=0.014$), but there was no correlation after that. At 24h, patients with $SpO_2<94\%$ had a higher (i.e. better) dyspnea VAS (84 vs 67, $p=0.003$) and PGA (82 vs 57, $p<0.001$) than those with SpO_2 levels $\geq 94\%$.

Baseline BNP (n=110) or NT-proBNP (n=50) levels had no correlations with SpO_2 levels, dyspnea VAS, PGA, or PEF at baseline. There was no correlation between NT-proBNP levels and SpO_2 levels, dyspnea VAS, PGA, or PEF at follow-up (i.e. 72 hours) (Supplementary Table 5.6).

There was no correlation between ΔSpO_2 and ΔNT-proBNP from baseline to 72 hours in the pilot cohort (Supplementary Figure 5.4). There was no correlation between O_2 administered from baseline to 72 hours and the change in NT-proBNP levels (ΔNT-proBNP) or the ratio change of NT-proBNP (Δ / baseline NT-proBNP) at the same study period (supplementary figure 5.5).

5.5 Discussion

The HiLo-HF pilot trial is the first RCT to explore the effects of supplemental O_2 therapy in patients with AHF. In this trial, titrating O_2 therapy to high or low SpO_2 targets did not result in changes in biomarkers, symptoms or clinical outcomes. Regardless of group allocation, NT-proBNP levels, patient reported symptoms (e.g. VAS and PGA), and pulmonary function (i.e. PEF) improved over time. In addition, while the pilot demonstrated success in recruitment, the protocol resulted in missing information for a variety of reasons. Overall, these lessons suggest that while a definitive trial is warranted, the protocol and operation of the trial should be further adjusted for pragmatic implementation.

Three small studies provided the foundation of what we know currently about the possible effects of hyperoxygenation in patients with heart failure. A study by Mak *et al*. including patients with stable coronary artery disease (N=12) and those with HF (N=16), showed that extreme hyperoxia (FiO_2 = 1.0, PaO_2 ~300 mmHg) was associated with impairment of cardiac relaxation and increased left ventricular filling pressures in patients with and without HF.[6] Another study showed that high-flow O_2 (~5L/min, FiO_2 ~ 0.40) reduced both cardiac output and heart rate, and caused a trend towards increased systemic vascular resistance when compared to room air (FiO_2 0.21).[7] Finally, the study of Haque *et al*. showed a decrease in stroke volume and an increase in pulmonary capillary wedge pressure with hyperoxia in patients admitted with AHF and this effect started at an FiO_2 level of 0.24 – equivalent to 1 L/minute of supplemental O_2.[5]

The SpO_2 levels in the high SpO_2 arm of this study rose over time with AHF treatment, but it remained steady in the low SpO_2 arm from baseline to 72 hours. The manual SpO_2 titration method did not induce a proper separation in SpO_2 levels between the two trial arms. There were some adherence issues, mostly related to the healthcare professionals' non-adherence to follow the protocol in down-titrating O_2 for those with SpO_2 levels above the assigned range. These issues could be partially addressed by utilizing automated closed loop systems for controlling supplemental O_2 delivery. These systems provide a potential solution to this problem with near constant adjustments and less variability of blood O_2 saturations.[20] They can regulate the flow of O_2 on a second-by-second basis through a sophisticated closed-loop algorithm that receives data input regarding peripheral O_2 saturation level from pulse oximetry and reacts to that immediately with increasing or decreasing O_2 flow in order to prevent under or over-delivery of O_2.

Other studies have attempted to understand the effects associated with supplemental O_2 therapy in other clinical settings.[21-23] A recent meta-analysis, pooling 7,998 patients with acute myocardial infarction from 8 RCTs, showed no clinical benefits on mortality or infarct size with supplemental O_2 therapy as compared to room air.[9] Although the only two small RCTs in patients with cardiac arrest showed no mortality difference between groups treated with high ($FiO_2 = 1.0$) versus conservative levels of O_2,[24, 25] large cohort studies and meta-analysis of observational studies suggested decreased survival after resuscitation from cardiac arrest with hyperoxia.[26, 27] Studies from the stroke setting demonstrated no benefit of liberal O_2 therapy in those patients.[28, 29] A total of 11 RCTs including 6,366 patients with acute stroke showed a non-significant increase in mortality at 3, 6, and 12 months with normobaric O_2 as compared to room air.[30] A study in the critical care setting reported an absolute risk reduction of 8.6% for the primary outcome of ICU mortality with conservative O_2 therapy (PaO_2 70-100 mm Hg or SpO_2 94-98%) as compared to usual care ($FiO_2 \geq 0.40$, PaO_2 100-150 mm Hg and $SpO_2 \geq 97\%$).[31] A multi-centre RCT in patients with stable COPD and moderate desaturation at rest or during exercise, showed no benefit of long-term supplemental O_2 therapy in terms of time to death or hospitalization.[32] A meta-analysis of 25 RCTs (16,037 patients) compared the outcomes of liberal versus conservative O_2 treatment in acutely ill patients, and showed liberal oxygenation to increase mortality by roughly 20% in a dose-dependent way, without improving other patient-important outcomes such as disability or LOS.[33]

These findings have both clinical and health policy implications. Changes in SpO_2 levels might be a harbinger of patients' deterioration in patients with AHF and hence hyperoxygenation, with masking those changes, decreases the likelihood of timely detection and intervention.[33] On the other hand, given the cost of O_2 therapy and the ubiquitous use of O_2 in hospitalized or ED patients with AHF,[2, 34] a lack of clinical benefit could mean that by departing from this practice, healthcare systems could save significant amount of funds from being wasted on a potentially futile intervention and directed towards other treatments with proven efficacies.

There are several limitations to this study that are noteworthy. The study is a pilot trial and hence, it is underpowered to detect small differences between study groups. We used a relatively cautious approach of titrating O_2 delivery to a specific saturation. Hence, even patients in the high SpO_2 group did not experience extreme hyperoxia. The use of manual titration method and

reliance on the treating team to do that was not associated with proper separation of SpO_2 levels in this study. A device approach using automated closed loop systems has the potential to solve that issue. In this study, we did not restrict the patient population to patients with AHF who were normoxemic at presentation and have included patients with hypoxemia as well. This will increase the representativeness of our study population to the actual AHF population. However, there is less controversy about the use of O_2 in hypoxemic patients compared to those with normoxemia at rest or minimal activity. We lacked data regarding patients' baseline SpO_2, given that patients were recruited at ED and a proportion of patients had already received O_2 in ambulance or in the ED prior to recruitment. Finally, a change in the timeline for follow-up NT-proBNP test from a fixed timeline (72 hours) to sampling at 72 hours or at discharge if earlier, could have prevented a significant proportion of missing data on primary endpoint in this study.

In conclusion, we found no differences in improvements in NT-proBNP or patient symptoms between high and low SpO_2 targets in the first 72 hours after admission for AHF. Further RCTs with larger sample size are warranted to determine the comparative efficacy and safety of treatment with supplemental O_2 in patients with AHF.

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Figures and Tables:

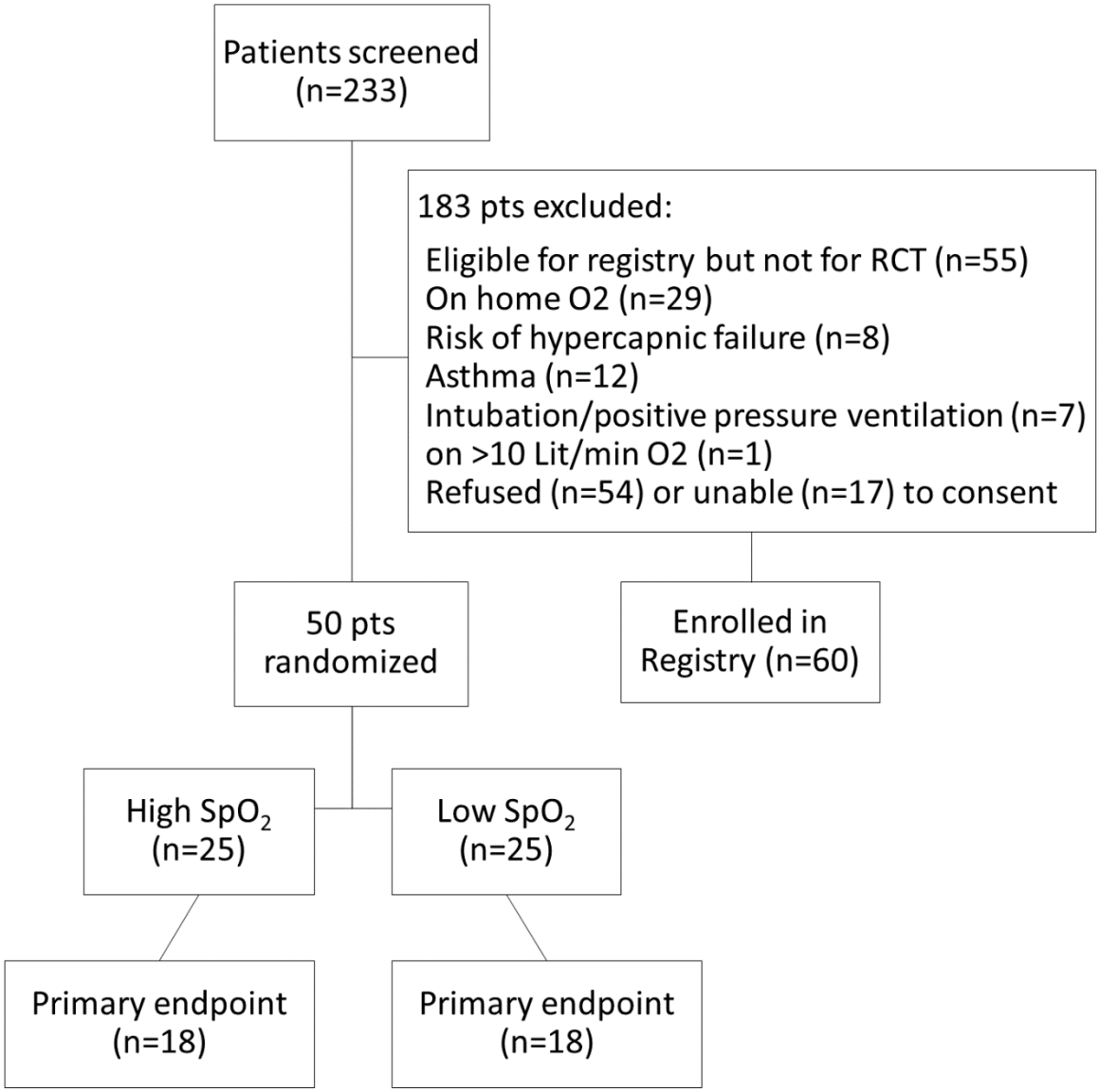


Figure 5.1. Patient flow diagram

Note: pts: patients; O_2: oxygen; SpO_2: peripheral oxygen saturation level;

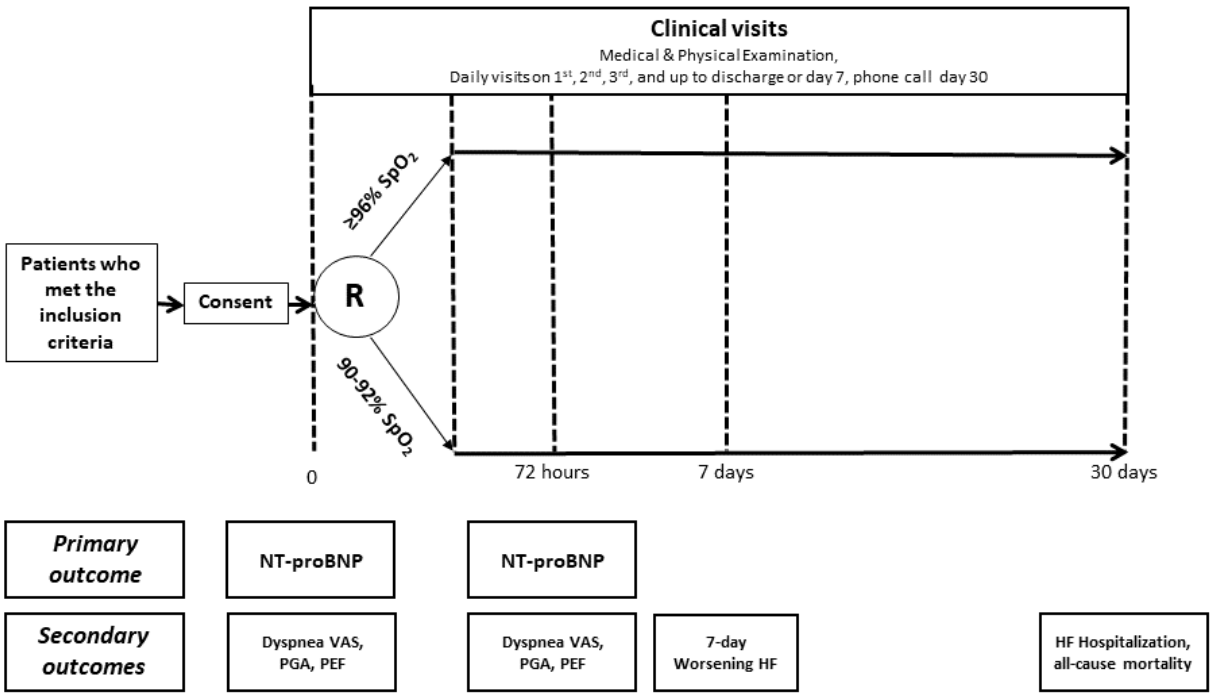


Figure 5.2. Study groups and primary/secondary endpoints

Note: HF: heart failure; NT proBNP: N-terminal pro brain-type natriuretic peptide; PEF: peak expiratory flow; PGA: patient global assessment; R: randomization; SpO_2: peripheral oxygen saturation level; VAS: visual analogue scale.

Table 5.1. Baseline Characteristics of the Patients in HiLo-HF Trial and Registry

	HiLo Registry (n=60)	HiLo pilot RCT			
		All (n=50)	High SpO_2 target (n=25)	Low SpO_2 target (n=25)	p-value
Age, yr	77 (65.5, 86)	73.5 (67, 84)	73.0 (70, 77)	74 (59, 86)	0.75
Women, n(%)	21 (35)	21 (42)	11 (44)	10 (40)	0.77
Race					
Aboriginal	1 (1.7)	1 (2)	0 (0)	1 (4)	0.14
Caucasian	49 (81.7)	39 (78)	20 (80)	19 (76)	0.73
Other	10 (16.6)	10 (20)	5 (20)	5 (20)	0.27
Medical History					
Heart failure	34 (56.7)	35 (70)	15 (60)	20 (80)	0.12
Ischemic	21 (35)	22 (44)	9 (36)	13 (52)	0.25
Non-ischemic	13 (21.7)	13 (26)	6 (24)	7 (28)	
AF/Flutter	35 (58.3)	26 (52)	12 (48)	14 (56)	0.57
Cardiac devices*	11 (18.3)	10 (20)	5 (20)	5 (20)	1.00
CAD	26 (43.3)	28 (56)	14 (56)	14 (56)	1.00
MI	11 (42.3)	14 (50)	8 (57.1)	6 (42.9)	0.45
PCI	11 (42.3)	10 (35.7)	4 (28.6)	6 (42.9)	0.43
CABG	11 (42.3)	9 (32.1)	5 (35.7)	4 (28.6)	0.68
Prior Stroke	15 (25)	10 (20.4)	6 (25)	4 (16)	0.43
Diabetes	21 (35)	22 (44)	8 (32)	14 (56)	0.08
HTN	45(75)	35 (70)	16 (64)	19 (76)	0.35
COPD	19 (31.7)	9 (18)	6 (24)	3 (12)	0.27
Asthma	2 (3.3)	0 (0)	0 (0)	0 (0)	n/a
Smoking	36 (60)	31 (62)	18 (72)	13 (52)	0.14
Current	4 (11.1)	9 (29)	6 (33.3)	3 (23.1)	0.53
Pack/year	20 (7.3, 38.8)	27.5 (10, 40)	33.8 (12.5, 45)	25.0 (6.3, 31)	0.14
Cancer within past 5 years	11 (18.3)	4 (8)	2 (8)	2 (8)	1.00
Charlson Index	4 (3.5, 6)	4 (3, 6)	4 (3, 5)	5 (4, 6)	0.10
Baseline LVEF, n(%)					0.33
≤ 20%	8 (13.3)	4 (8)	1 (4)	3 (12)	
21-40%	12 (20)	20 (40)	9 (36)	11 (44)	
41-45%	7 (11.7)	3 (6)	3 (12)	0 (0)	
46-50%	3 (5)	5 (10)	3 (12)	2 (8)	
≥ 51%	24 (40)	16 (32)	9 (36)	7 (28)	
Missing	6 (10)	2 (4)	0 (0)	2 (8)	
Mode of ED arrival, n(%)					0.59
Direct admission from clinic	1 (1.7)	1 (2)	0 (0)	1 (4)	
Self-presentation	30 (50)	27 (54)	14 (56)	13 (52)	

EMS	29 (48.3)	22 (44)	11 (44)	11 (44)	
O_2 in EMS, n (%)	16 (55.2)	12 (54.5)	7 (63.6)	5 (45.5)	0.39
O_2 in EMS, L/min	2.0 (2, 4)	5.5 (3, 7)	5.5 (4, 8)	4.0 (2, 6)	0.61
Pre-randomization SpO_2, %	95 (93, 97)	94.5 (93, 97)	94 (92, 96)	96 (93, 98)	0.12
Pre-randomization O_2, n (%)	26 (43.3)	21 (42)	11 (44)	10 (40)	0.77
Pre-randomization O_2, L/min	2 (2, 3.2)	2 (2, 3)	2 (2, 3)	2.2 (2, 4)	0.37
Time					
From triage to admission order, hour	11.2 (8, 13.8)	7.2 (5, 11.7)	7.5 (4.7, 11.7)	7.0 (5.1, 10.6)	0.67
From triage to enrollment, hour	19.2 (7.2, 21.5)	11.4 (7.3, 13.5)	11.4 (6.2, 13.5)	11.3 (8.1, 14.2)	0.47
From triage to first NT-proBNP test	-	13.2 (8.0, 15.3)	13.1 (7.5, 15.4)	13.2 (8.2, 15.3)	0.44
From triage to disposition from ED, hour	16.2 (11.3, 21.8)	12.8 (9, 15.7)	12.7 (6.6, 15.3)	14.6 (9.4, 16.8)	0.24
From triage to discharge from hospital, days	6 (2.8, 12.4)	6.3 (3.7, 11)	4.7 (2.7, 6.7)	9.5 (4.9, 19.9)	0.01

Note: AF: atrial fibrillation; CABG: coronary artery bypass grafting; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; ED: emergency department; EMS: emergency medical services; HTN: hypertension; HiLo: high-dose oxygen/low-dose oxygen; MI: myocardial infarction; NT proBNP: N-terminal pro brain-type natriuretic peptide; O_2: oxygen; PCI: percutaneous coronary intervention; SpO_2: peripheral oxygen saturation level; yr: years. * Cardiac devices including pacemaker, implantable cardioverter defibrillator and cardiac resynchronization therapy. Unless described otherwise, median (25percentile,75th percentile) are reported.

Table 5.2. Adherence to study protocol in HiLo-HF pilot RCT

	All (n=50)	**High SpO_2 target (n=25)**	**Low SpO_2 target (n=25)**
% on determined SpO_2 range ±1%, n(%)			
6 hour	27 (56.2)	20 (83.3)	7 (29.2)
24 hour	25 (53.2)	20 (87)	5 (20.8)
48 hour	25 (58.1)	18 (85.7)	7 (31.8)
72 hour	18 (46.1)	17 (94.4)	1 (4.8)
% on O_2, n(%)			
6 hour	27 (56.2)	18 (75)	9 (37.5)
24 hour	18 (38.3)	12 (52.2)	6 (25)
48 hour	17 (39.5)	13 (61.9)	4 (18.2)
72 hour	16 (41)	12 (66.6)	4 (19)
O_2 Volume in pts treated w/ O_2, n(%)			
6 hour	2 (2, 3)	2.5 (2, 4)	2 (2, 3)
24 hour	2.5 (2, 4)	3 (2, 4)	2 (1.3, 2.6)
48 hour	2 (2, 3.5)	2.5 (2, 4.7)	2 (1.2, 3.1)
72 hour	2.2 (1.1, 3.5)	2.5 (1.6, 6.1)	1.7 (1, 3.2)
Number of pts w/ SpO_2 out of target range ±1% w/ inappropriate O_2 volume, n(%)			
6 hour	7/48 (14.5)	3/24 (12.5)	4/24 (16.6)
24 hour	9/48 (18.7)	3/24 (12.5)	6/24 (25)
48 hour	3/43 (6.9)	2/21 (9.5)	1/22 (4.5)
72 hour	4/39 (10.2)	1/18 (5.5)	3/21 (14.2)

Note: HiLo: high-dose oxygen/low-dose oxygen; pts: patients; O_2: oxygen; SpO_2: peripheral oxygen saturation level.

Table 5.3. Primary and Secondary End Points

	HiLo-HF Registry	HiLo-HF pilot RCT			
		All (n=36)	**High SpO_2 target (n=18)**	**Low SpO_2 target (n=18)**	**p-value**
NT-proBNP					
Baseline, pg/mL	-	14,140.1 (5,570.6, 27,806.6)	15,987.9 (6,025.6, 29,785.5)	10,262.5 (4,355.3, 27,223.0)	0.45*
72 hour, pg/mL	-	7,108.9 (4,310.5, 17,007.0)	6,479.7 (4,529.5, 12,304.9)	10,156.8 (4,001.8, 17,133.8)	0.72*
Δ NT-proBNP, pg/mL	-	-3,971.4 (-11,194.5, -1,049.5)	-6,963.5 (-13,345.1, -1,253.3)	-2,093.1 (-5,692.1, -353.5)	0.46*
72h to baseline ratio	-	0.7 (0.5, 0.8)	0.7 (0.3, 0.8)	0.6 (0.5, 0.9)	0.51**
Secondary endpoints					
	HiLo-HF Registry (n=43)	**All (n=39)**	**High SpO_2 target (n=18)**	**Low SpO_2 target (n=21)**	**p-value**
VAS					
Δ VAS, mm	15 (5, 35)	10 (5, 25)	10 (5, 25)	10 (7, 20)	0.86**
VAS AUC, mm × h	5,295 (4,537, 5,983)	5,160 (4,380, 5,932)	5,160 (4,050, 6,150)	5,167 (4,552, 5,703)	0.73
PGA					
Δ PGA, mm	20 (10, 30)	10 (0, 20)	5 (0, 20)	10 (0, 15)	0.91**
PGA AUC, mm × h	4,320 (3,360, 5,280)	4,620 (3,840, 5,760)	4,860 (4,290, 5,775)	4,320 (3,795, 5,670)	0.63
PEF					
Δ PEF, L/min	45 (0-80)	47.5 (20, 75)	52.5 (20, 90)	42.5 (25, 67.5)	0.52**
PEF AUC, L/min × h	19,920 (12,795, 24,840)	16,740 (14,610, 22,110)	15,660 (12,540, 19,500)	18,960 (16,080, 24,840)	0.19
Diuresis Response					
72h/Baseline weight ratio	0.96 (0.94, 0.98)	0.96 (0.94, 0.98)	0.97 (0.94, 0.98)	0.96 (0.93, 0.97)	0.55

Note: AUC: area under the curve; HiLo: high-dose oxygen/low-dose oxygen; NT proBNP: N-terminal pro brain-type natriuretic peptide; PGA: patient global assessment; PEF: peak expiratory flow; RCT: randomized controlled trial; VAS: visual analogue scale; * p-value based on comparison of High and Low SpO_2 groups on logarithmic scale; ** test of difference at 72 hours adjusting for baseline applying the ANCOVA model. Unless described otherwise, median (25percentile,75th percentile) are reported.

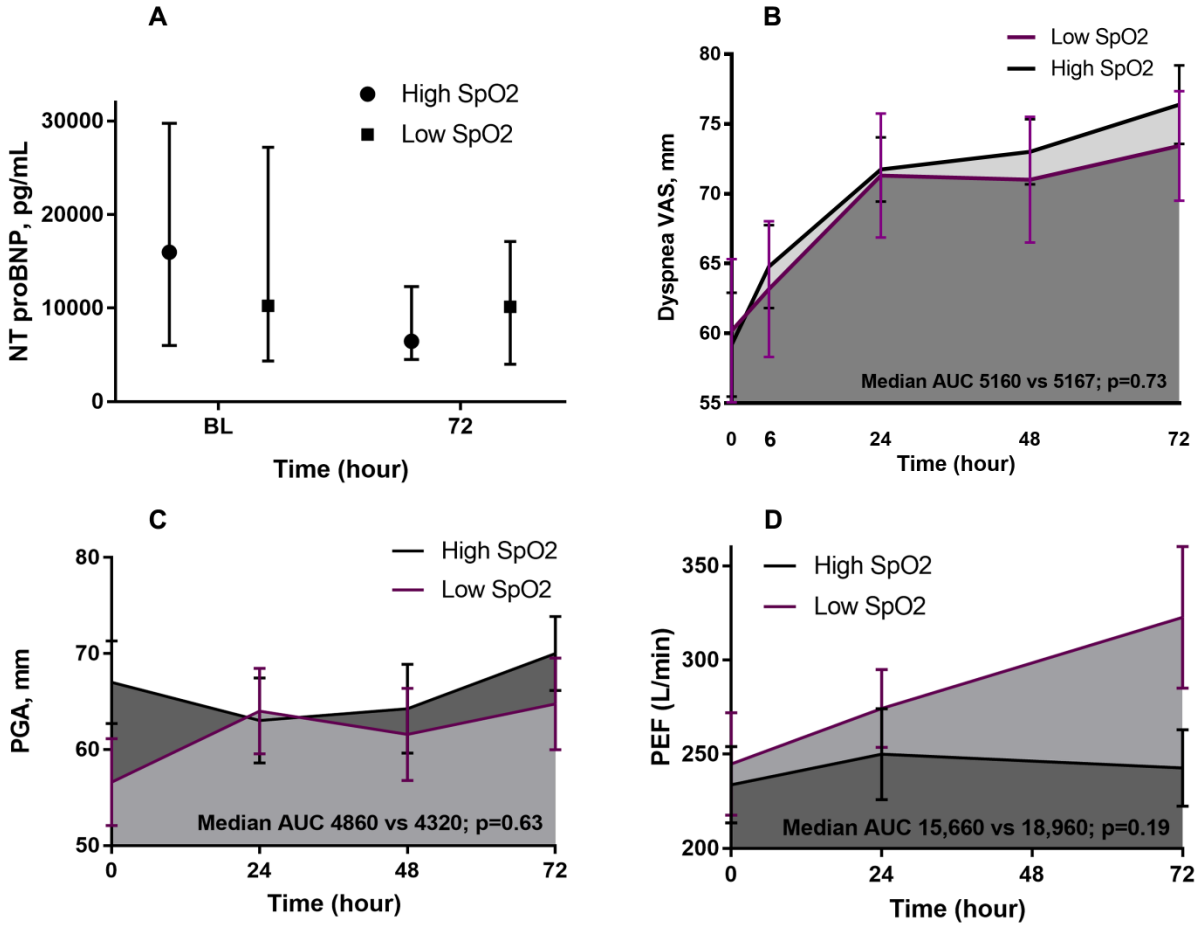


Figure 5.3. Change in NT-proBNP levels (A), Dyspnea VAS (B), Patient Global Assessment (C), and Peak Expiratory Flow (D) from baseline to 72 hours in groups with high and low SpO2 targets

Note: AUC: area under the curve; BL: baseline; PEF: peak expiratory flow; PGA: patient global assessment; SpO_2: peripheral oxygen saturation level; VAS: visual analogue scale;

5.7 Supplementary material

5.7.1 Appendix 1. Oxygen dose adjustment in the SpO_2 titration arms of study

The patients will be monitored based on their clinical condition. Saturations will be measured after one hour of oxygen therapy and then 4-hourly. Critically-ill patients will receive continuous monitoring of oxygen saturation, besides other usual care-related assessments. Stable patients, however, could be monitored four times a day. **Oxygen therapy should be increased if the saturation is below the desired range and decreased if the saturation is above the desired range (and eventually discontinued as the patient recovers). Adjustments should only be made by research coordinators or medical staff who have been trained to adjust the administration of oxygen if the oxygen saturation falls below or rises above the pre-specified range.[1]**

When to increase the oxygen therapy dose:

When the patient fails to achieve the desired oxygen saturation range, the research coordinator or the clinician in-charge needs to increase the dose of oxygen in association with checking for other potential reasons.

- Checking all the aspects of oxygen delivery system for faults and errors.
- In case that the patient's oxygen saturation is consistently lower than the pre-specified target range, after medical assessment, the oxygen therapy needs to be increased.
- The patients should be observed for 5 minutes after oxygen dose was increased.
- If the oxygen saturation fails to rise after 5-10 minutes of increased oxygen therapy, the dose could be increased if there is no risk of hypercapnia and no clinical concern in medical assessment. Otherwise, an assessment with blood gas analysis 30-60 minutes after increase in oxygen dose is warranted.

When to lower the oxygen dose:

Most of the patients will be stabilized in 24 hours by the medical treatment provided in ED and in ward.

- Reduce the oxygen dose if the saturation is higher than the prescribed range

- Reduce the oxygen dose if the patients are clinically stable and the oxygen saturation has been in the upper zone of the target range for quite some time (e.g. 4-8 hours).
- Saturations should be monitored for 5 minutes following a change of oxygen therapy or at least should be re-checked after 5 minutes on the lower dose of oxygen
- If the target saturation is maintained properly after lowering the dose, the new flow rate should be continued. The patients should be re-evaluated at the next visit and in case of being stable, the process of dose reduction could be repeated and the patient can eventually be weaned off oxygen.

Supplementary Table 5.1. Eligibility criteria for HiLo-HF RCT and registry

HiLo-HF Pilot	HiLo-HF Registry
Inclusion criteria	**Inclusion criteria**
Patients >40 years of age presenting to the ED with AHF	Patients >40 years of age presenting to the ED with AHF
with an objective finding (BNP>400 pg/ml or chest x-ray with pulmonary congestion)	With or without objective findings in favor of AHF
planned to be admitted for the treatment of HF as the primary diagnosis	With or without hospital admission
must be able to be randomized within 16 hours of presenting to the ED	must be consented within 24 hours of presenting to the ED
Exclusion criteria	**Exclusion criteria**
Patients on home oxygen	Unwilling or unable to consent for HiLo-HF registry
known prior hypercapnic failure ($PaCO_2$>50 mmHg)	
Asthma	
primary pulmonary hypertension	
requiring urgent positive pressure ventilation or intubation	
on >10 L/min oxygen	
Unwilling or unable to consent for HiLo-HF pilot	

Note: AHF: acute heart failure; BNP: brain natriuretic peptide; ED: emergency department; HiLo: high-dose oxygen/low-dose oxygen; L/min: litres/min; mmHg: millimetres of mercury; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; RCT: randomized controlled trial.

Supplementary Table 5.2. Guideline recommendations regarding oxygen therapy in hypoxemic and normoxemic patients with heart failure

Guideline	Year	Recommendation on O_2 Therapy in hypoxemic patients	Recommendation Class	Level of evidence *	Recommendation on O_2 Therapy in normoxemic patients	Recommendation Class	Level of evidence *
ACCF/AHA [2]	2013	Not mentioned	N/A	N/A	Not mentioned	N/A	N/A
ACCF/AHA [3]	2009	Oxygen therapy should be administered to relieve symptoms related to hypoxemia	Class I	C	Not mentioned	N/A	N/A
HFSA [4]	2010	Routine administration of supplemental oxygen in the presence of hypoxia is recommended.	Class I	C	Routine administration of supplemental oxygen in the absence of hypoxia is not recommended.	Class III	C
ESC [5]	2016	Oxygen may be given to treat hypoxaemia (SpO_2<90%% or PaO_2 <60 mmHg (8.0 kPa)).	Class I	C	Oxygen should not be used routinely in non-hypoxaemic patients.	Class III	C
CCS [6]	2017	Supplemental oxygen therapy should be considered for patients who are hypoxemic (SaO_2<90%)	Strong	Moderate	Oxygen should be used cautiously in normoxic patients	N/A	N/A
ACCP consensus [7]	2010	Supplemental oxygen can provide relief of dyspnea for patients who are	Class I	Clear consensus (~75% agreement)	Use of supplemental oxygen for non-hypoxemic patients with	Class III	47% agreement

		hypoxemic at rest or during minimal activity			advanced lung and heart disease		
NICE [8, 9]	2014	Not mentioned	N/A	N/A	Not mentioned	N/A	N/A
NHFA/ CSANZ [10]	2011	No clear recommendation statement, however suggested oxygenation for hypoxemic patients	N/A	N/A	Not mentioned	N/A	N/A

Note: ACCF/AHA: American College of Cardiology Foundation/American Heart Association; ACCP: American College of Chest Physicians; C: consensus of the opinion of the experts and/or small studies, retrospective studies, registries; CCS: Canadian Cardiovascular Society; ESC: European Society of Cardiology; HFSA: Heart Failure Society of America; N/A: not available; NHFA/CSANZ: National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand; NICE: National Institute for Health and Care Excellence; * The level of evidence and the class of the recommendations are graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale.[11] Table reproduced and updated from Sepehrvand *et al*.[12]

Supplementary Table 5.3. Baseline medications in the study populations of HiLo-HF trial and registry

	HiLo Registry	HiLo pilot RCT			
		All (n=50)	High SpO_2 target (n=25)	Low SpO_2 target (n=25)	p-value
ACEi	24 (40)	20 (40)	11 (44)	9 (36)	0.56
ARBs	16 (26.7)	5 (10)	4 (16)	1 (4)	0.35
Betablockers	38 (36.3)	30 (60)	15 (60)	15 (60)	1.0
CCB	19 (31.7)	12 (24)	7 (28)	5 (20)	0.50
Diuretics	44 (73.3)	36 (72)	16 (64)	20 (80)	0.20
Furosemide	37 (61.7)	33 (66)	16 (64)	17 (68)	0.76
MRAs	10 (16.7)	6 (12)	4 (16)	2 (8)	0.66
Metolazone	4 (6.7)	1 (2)	1 (4)	0 (0)	1.0
Thiazides	8 (13.3)	3 (6)	0 (0)	3 (12)	0.23
Anticoagulants	27 (45)	24 (48)	12 (48)	12 (48)	1.0
NOACs	15 (25)	13 (26)	7 (28)	6 (24)	0.74
Warfarin	12 (20)	11 (22)	5 (20)	6 (24)	0.73
Antiplatelet	20 (33.3)	14 (28)	7 (28)	7 (28)	1.0
ASA	15 (25)	13 (26)	7 (28)	6 (24)	0.74
P2Y12 inhibitors	8 (13.3)	5 (10)	2 (8)	3 (12)	1.0
Amiodarone	4 (6.7)	4 (8)	2 (8)	2 (8)	1.0
Digoxin	3 (5)	3 (6)	1 (4)	2 (8)	1.0
Bronchodilators	17 (28.3)	9 (18)	7 (28)	2 (8)	0.13

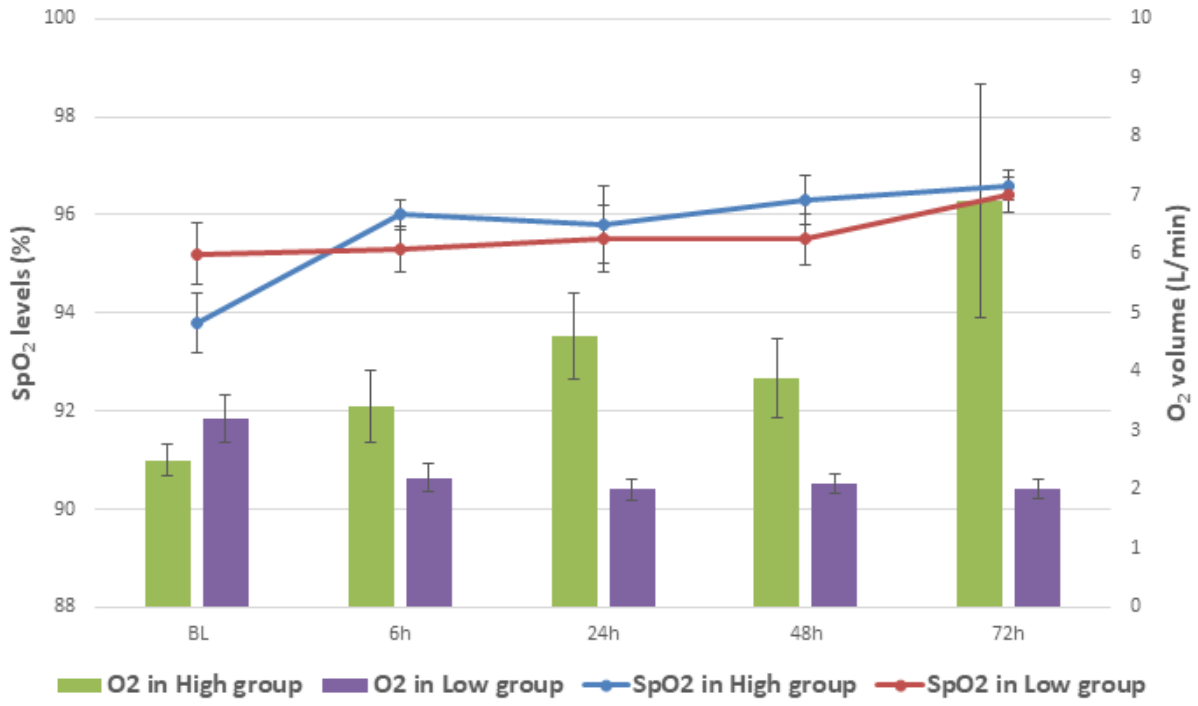
Note: ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers; ASA: acetylsalicylic acid; CCB: calcium channel blockers; HiLo: High-dose oxygen /Low-dose oxygen cohort; MRA: mineralocorticoid receptor antagonists; NOAC: novel oral anticoagulant; RCT: randomized controlled trial; SpO_2: peripheral oxygen saturation level.

Supplementary Table 5.4. Total Furosemide dose at home, during the first 72 hours in hospital and on discharge

	HiLo Registry	HiLo pilot RCT			
		All (n=50)	High SpO_2 target (n=25)	Low SpO_2 target (n=25)	p-value
Home	40 (30, 80)	40 (0, 80)	20 (0, 70)	40 (0, 80)	0.59
Day 1	80 (40, 160)	120 (80, 160)	160 (40, 160)	120 (80, 160)	0.77
Day 2	160 (80, 160)	120 (80, 160)	100 (50, 160)	120 (80, 160)	0.82
Day 3	90 (50, 160)	120 (40, 240)	80 (40, 200)	160 (80, 240)	0.40
Discharge	60 (40, 80)	80 (40, 80)	80 (40, 80)	70 (40, 120)	0.71

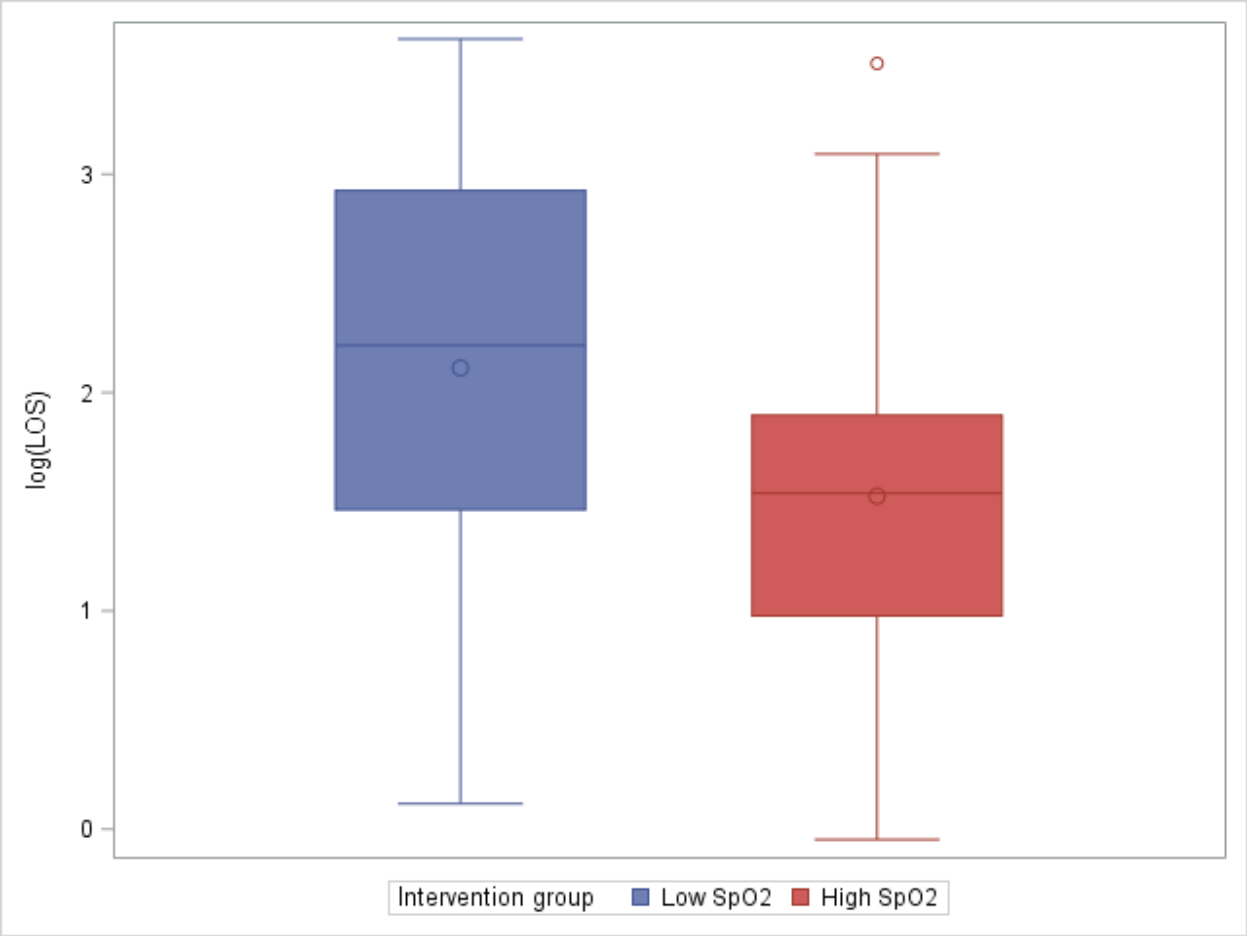
Note: HiLo: High-dose oxygen /Low-dose oxygen; RCT: randomized controlled trial; SpO_2: peripheral oxygen saturation level.

Supplementary Figure 5.1. SpO_2 levels and O_2 volumes in two study groups in different study timepoints



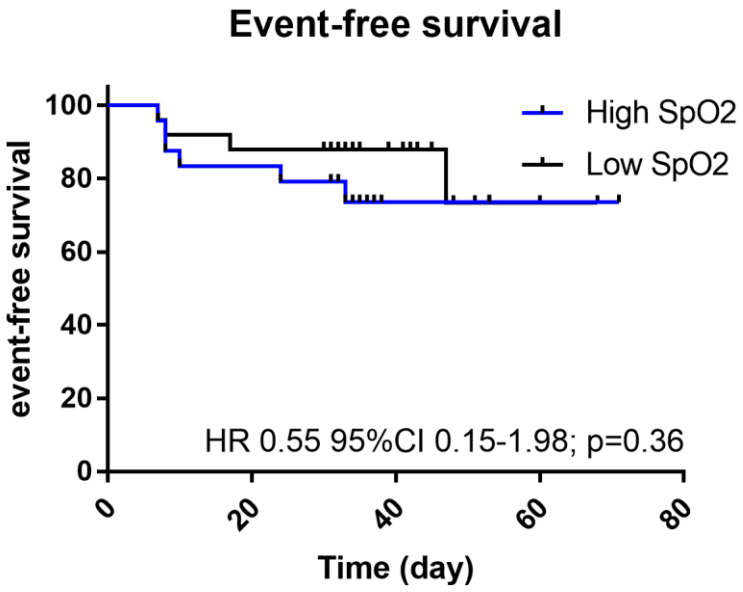
Note: h: hours; L/min: litres per minute; O_2: oxygen; SpO_2: peripheral oxygen saturation level.

Supplementary Figure 5.2. Comparison of the distribution of length of hospital stay (in days & log-scale) between the intervention groups



Note: LOS: length of stay as time duration from admission to discharge, regardless of survival status at discharge; SpO_2: peripheral oxygen saturation level.

Supplementary Figure 5.3. Kaplan-Meier curves of clinical events consisted of in-hospital mortality and death/ re-hospitalization at 30-day following hospital discharge



Note: CI: confidence interval; HR: hazard ratio; SpO_2: peripheral oxygen saturation level.

Supplementary Table 5.5. Patient characteristics in the HiLo patients with available NT-proBNP data for primary endpoint (N=36)

	All (n=36)	**High SpO_2 target (n=18)**	**Low SpO_2 target (n=18)**	**p-value**
Age, yr	73.0 (65.0, 80.5)	73.5 (71.0, 81.0)	70.0 (59.0, 80.0)	0.33
Women, n(%)	17 (47.2)	9 (50.0)	8 (44.4)	0.73
Race				
Aboriginal	1 (2.8)	0 (0.0)	1 (5.6)	0.31
Caucasian	26 (72.2)	14 (77.8)	12 (66.7)	0.45
Other	9 (25.0)	4 (22.2)	5 (27.8)	0.70
Medical History				
Heart failure	27 (75.0)	13 (72.2)	14 (77.8)	0.70
Ischemic	17 (47.2)	8 (44.4)	9 (50.0)	0.73
Non-ischemic	10 (27.8)	5 (27.8)	5 (27.8)	
AF/Flutter	19 (52.8)	10 (55.6)	9 (50.0)	0.73
Cardiac devices*	8 (22.2)	5 (27.8)	3 (16.7)	0.42
CAD	22 (61.1)	12 (66.7)	10 (55.6)	0.49
MI	11 (30.6)	8 (44.4)	3 (16.7)	0.07
PCI	6 (16.7)	3 (16.7)	3 (16.7)	1
CABG	9 (25.0)	5 (27.8)	4 (22.2)	0.70
Prior Stroke	6 (17.1)	4 (23.5)	2 (11.1)	0.32
Diabetes	17 (47.2)	5 (27.8)	12 (66.7)	0.02
HTN	25 (69.4)	11 (61.1)	14 (77.8)	0.27
COPD	6 (16.7)	4 (22.2)	2 (11.1)	0.37
Asthma	0 (0.0)	0 (0.0)	0 (0.0)	n/a
Smoking	22 (61.1)	12 (66.7)	10 (55.6)	0.49
Current	6 (27.3)	3 (25.0)	3 (30.0)	0.79
Pack/year	25.0 (6.3, 36.0)	25.0 (5.0, 40.0)	27.5 (6.3, 31.0)	0.77
Cancer within past 5 years	2 (5.6)	1 (5.6)	1 (5.6)	1
Charlson Index	12.0 (10.0, 13.0)	11.0 (11.0, 13.0)	12.0 (9.0, 14.0)	0.66
Mode of ED arrival				0.51
Direct admission	0 (0.0)	1 (5.6)	1 (2.8)	
Self-presentation	10 (55.6)	11 (61.1)	21 (58.3)	
EMS	14 (38.9)	8 (44.4)	6 (33.3)	
O_2 on EMS, n (%)	8 (57.1)	5 (62.5)	3 (50.0)	0.64
Time				
From triage to admission order, hour	6.9 (4.9, 11.6)	7.5 (4.7, 11.8)	6.6 (5.0, 8.8)	0.83
From triage to enrollment, hour	11.2 (7.2, 13.4)	11.5 (6.3, 13.5)	10.2 (7.3, 13.4)	0.98
From triage to first NT-proBNP test, hour	13.2 (7.5, 15.4)	13.2 (8.1, 15.5)	13.2 (7.5, 16.3)	0.61
From triage to disposition from ED, hour	12.3 (9.1, 15.6)	12.8 (9.2, 13.6)	11.3 (9.0, 16.8)	0.75

From triage to discharge from hospital, days	8.1 (5.2, 17.3)	6.3 (4.5, 9.0)	11.1 (8.1, 21.1)	0.01

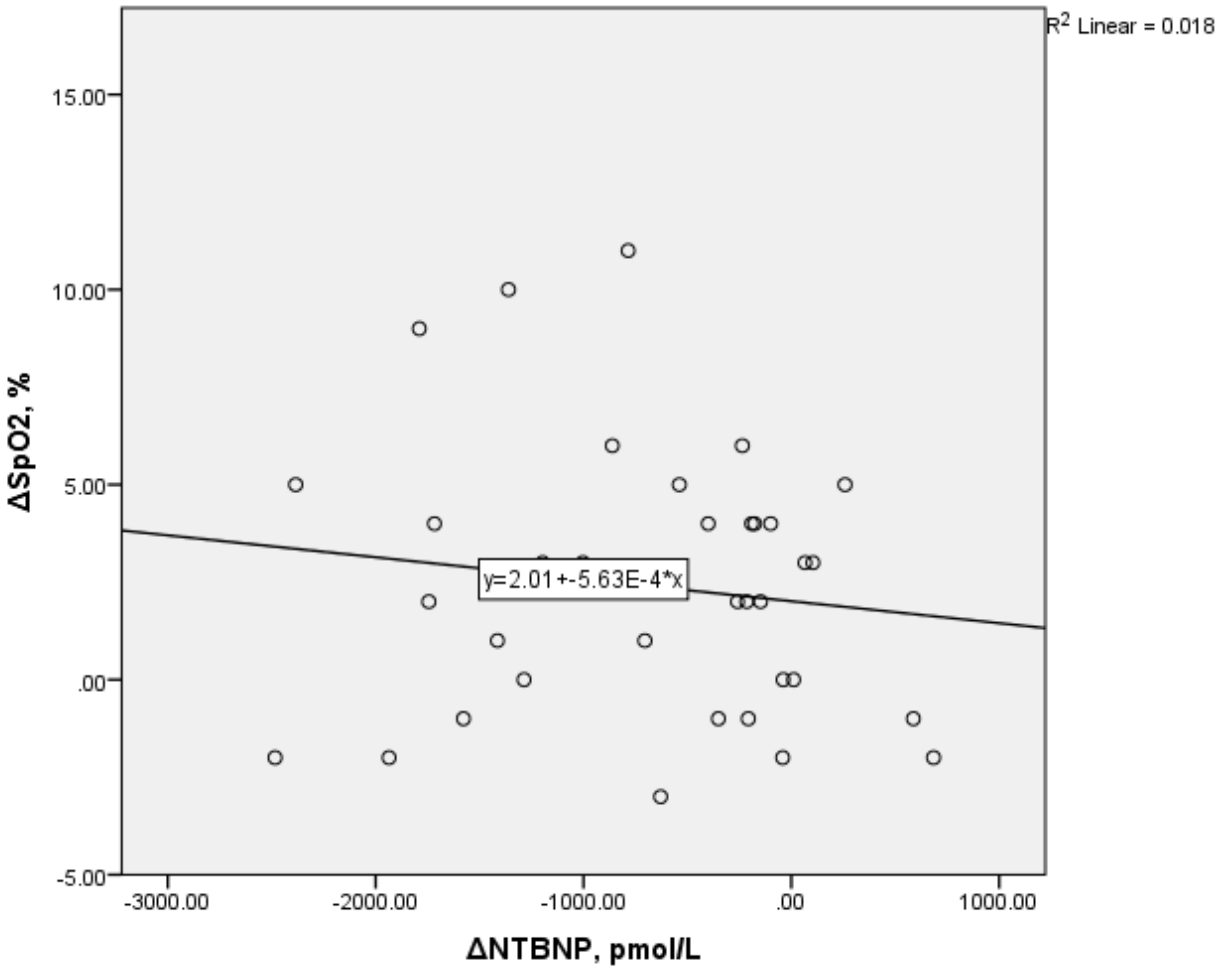
Note: AF: atrial fibrillation; CABG: coronary artery bypass grafting; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; ED: emergency department; EMS: emergency medical services; HiLo: High-dose oxygen /Low-dose oxygen; MI: myocardial infarction; NT-proBNP: N-terminal pro brain-type natriuretic peptide; PCI: percutaneous coronary intervention; For cases of mortality, the length of hospital stay was calculated from hospital admission to the time of death.

Supplementary Table 5.6. Correlation between natriuretic peptide levels and patient's saturation level and symptoms at baseline and follow-up

	BL SpO_2	**BL VAS**	**BL PGA**	**BL PEF**
BL BNP	r=-0.001, p=0.99	r=-0.006, p=0.95	r=0.027, p=0.78	r=0.148, p=0.13
	BL SpO_2	**BL VAS**	**BL PGA**	**BL PEF**
BL NT-proBNP	r=-0.268, p=0.06	r=-0.005, p=0.97	r=0.245, p=0.09	r=0.139, p=0.34
	72h SpO_2	**72h VAS**	**72h PGA**	**72h PEF**
72h NT-proBNP	r=0.004, p=0.98	r=-0.170, p=0.32	r=0.131, p=0.45	r=0.136, p=0.43

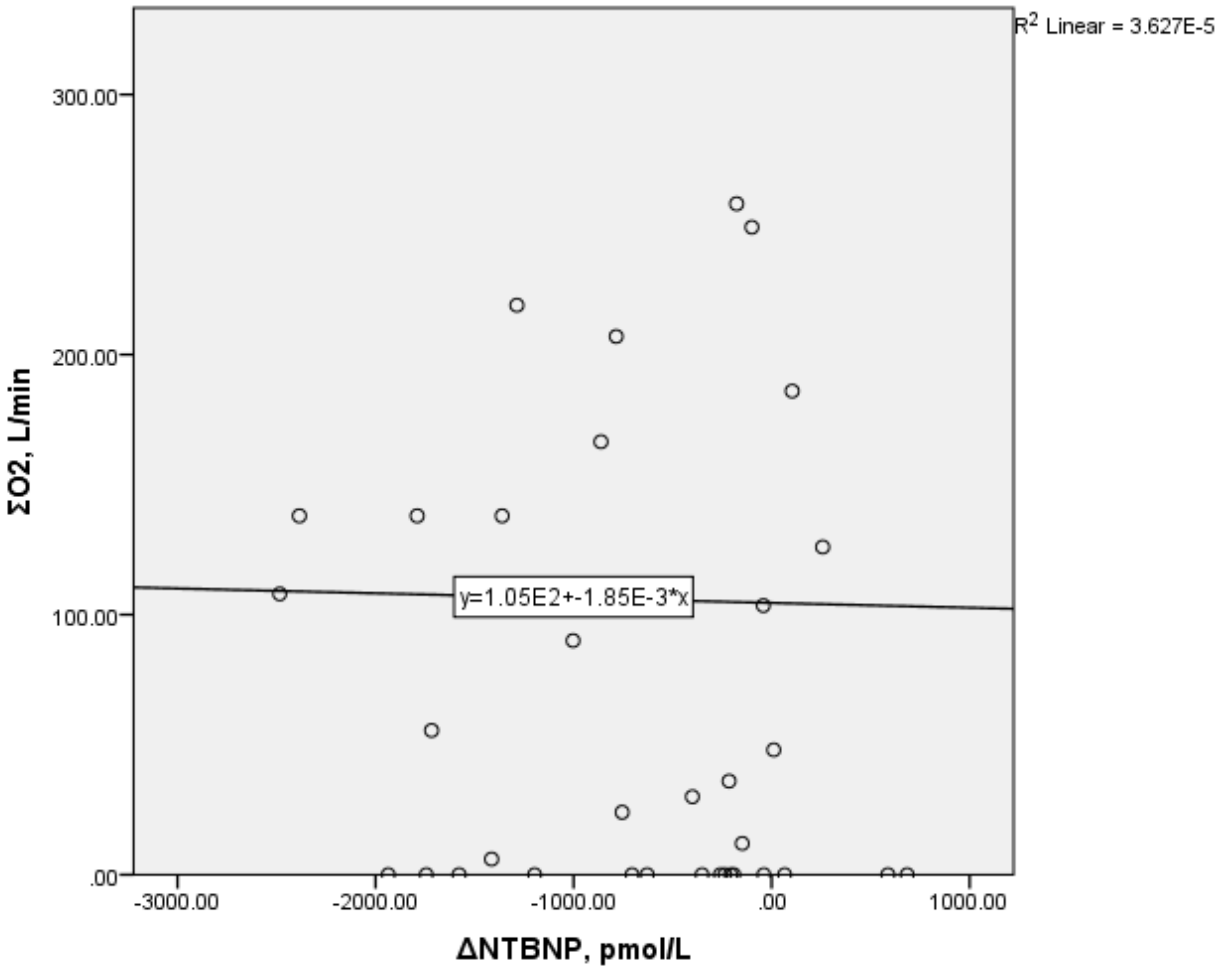
Note: BL: baseline; NT-proBNP: N-terminal pro brain-type natriuretic peptide; h: hours; PEF: peak expiratory flow; PGA: patient global assessment; SpO_2: peripheral blood oxygen saturation; VAS: dyspnea visual analogue scale;

Supplementary Figure 5.4. The relationship between ΔSpO_2 and ΔNT-BNP in HiLo-HF cohort (N=50)



Note: HiLo: High-dose oxygen /Low-dose oxygen; HF: heart failure; NT-proBNP: N-terminal pro brain-type natriuretic peptide; SpO_2: peripheral oxygen saturation level.

Supplementary Figure 5.5. The relationship between O_2 from baseline to 72 hours and ΔNT-BNP in HiLo-HF cohort (N=50)



Note: HiLo: High-dose oxygen /Low-dose oxygen; L/min: litres per minute; NT-proBNP: N-terminal pro brain-type natriuretic peptide;

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Chapter 6 : Effects of supplemental oxygen therapy in patients with suspected acute myocardial infarction: A meta-analysis of randomized clinical trials

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6.1 Abstract

Background: Although oxygen therapy has been used for over a century in the management of patients with suspected acute myocardial infarction (AMI), recent studies have raised concerns around the efficacy and safety of supplemental oxygen in normoxemic patients.

Objective: To synthesize the evidence from randomized clinical trials (RCT) that investigated the effects of supplemental oxygen therapy as compared to room air in patients with suspected or confirmed AMI.

Methods: For this aggregate data meta-analysis, multiple databases were searched from inception to September 30th 2017. RCTs with any length of follow-up and any outcome measure were included if they studied the use of supplemental O_2 therapy administered by any device at normal pressure as compared to room air. Following PRISMA guidelines, an investigator assessed all the included studies and extracted the data. Outcomes of interests included mortality, troponin levels, infarct size, pain and hypoxemia.

Results: Eight RCTs with a total of 7,998 participants (3,982 and 4,002 patients in O_2 and Air groups, respectively) were identified and pooled. In-hospital and 30-day death occurred in 135 and 149 patients, respectively. Oxygen therapy did not reduce the risk of in-hospital (OR, 1.11 [95%CI, 0.69 to 1.77]) or 30-day mortality (OR, 1.09 [95%CI, 0.80 to 1.50]) in patients with suspected AMI and the results remained similar in the subgroup of patients with confirmed AMI. The infarct size (based on cardiac MRI) in a subgroup of patients was not different between groups with and without O_2 therapy. O_2 therapy reduced the risk of hypoxemia (OR, 0.29 [95%CI, 0.17 to 0.47]).

Conclusion: Although supplemental O_2 therapy is commonly used, it was not associated with important clinical benefits. These findings from 8 RCTs support departing from the usual practice of administering oxygen in normoxemic patients.

Keywords: Oxygen, acute myocardial infarction, meta-analysis

6.2 Introduction

For over a century, oxygen therapy has been one of the cornerstones of the acute management of patients presenting with chest pain and those diagnosed with acute myocardial infarction (AMI).[1, 2] The rationale behind using oxygen in this specific patient population was that it increased the oxygen delivery to the areas of myocardium that are at risk of infarction due to ischemia, thus potentially decreasing the infarct size and the risk of lethal arrhythmias.[3, 4] Although there is no controversy around the benefit of supplemental oxygen in patients with an acute coronary syndrome (ACS) who have hypoxemia, several preclinical and small clinical studies have suggested the deleterious effects of the extra oxygen on cardiac function in those who are not hypoxemic ($SpO_2 \geq 90\%$).[5-8] The main postulated mechanisms for the detrimental effects of extra oxygen include reduced coronary blood flow from the hyperoxia-induced vasoconstriction, and the production of reactive oxygen species (ROS) stimulated by hyperoxia and its related oxidative stress.[9-18]

The results of the Air Versus Oxygen In myocarDial infarction (AVOID) trial refreshed the concerns around the routine use of oxygen in normoxemic patients.[19] The study showed no additional benefit and evidence of increased myocardial injury with supplemental oxygen therapy in normoxemic patients with ST elevation Myocardial Infarction (STEMI). A sub-study of the AVOID trial reported a 17-21% increase in the myocardial infarct size (measured by the creatine kinase and cardiac troponin levels) with exposure to 6 L/min of oxygen via face mask.[20] A prior meta-analysis (5 trials, 1173 participants) showed a lack of mortality benefit for using supplemental O_2 in patients with ACS who were not hypoxic at presentation, although the evidence was of very low quality, and could not rule out potential harmful effects.[21] Since then, several clinical trials addressing the same question[22-24] have been completed. The most prominent study is the DETermination of the role of OXygen in suspected Acute Myocardial Infarction (DETO2X-AMI) trial, enrolling 6,629 patients into a registry-based RCT[22, 25] in which supplemental O_2 therapy was not associated with reduced mortality or re-hospitalization within one year.[22]

In this study, our objective was to synthesize the evidence from randomized clinical trials to investigate the effects of supplemental oxygen therapy in patients with suspected or confirmed AMI.

6.3 Material and Methods

6.3.1 Inclusion criteria and study selection

Randomized controlled trials (RCT) in any language, with any length of follow-up and any outcome measure used were included if they studied the use of supplemental oxygen therapy administered by any device at normal pressure (excluding hyperbaric O_2) as compared to room air, regardless of the concomitant therapies (e.g. the choice of reperfusion therapy).

The studies featured in the following databases from June 1st 2016 to September 30th 2017 were screened: Cochrane Central Register for Controlled Trials in the Cochrane Library, MEDLINE Ovid, Embase Ovid, PubMed, CINAHL Plus and Web of Science Core Collection. This was supplemented by the authors knowledge, and hand-search of bibliographies of relevant articles. We adopted the same search strategy that was applied in a prior Cochrane review [21] (details in supplementary material). No language restriction was applied for the search. The study titles / abstracts were reviewed by an experienced reviewer (NS) to identify the eligible studies. In case of ambiguity regarding the eligibility of an individual study based on title and abstract, the full-text article was reviewed. If the uncertainty persisted despite reviewing the full article, the eligibility was discussed and a decision was made among all co-authors. The eligible studies were added to the five studies,[8, 19, 26-28] pooled by the previous Cochrane review.[21] Supplementary Figure 6.1 depicts the study inclusion / exclusion process for this aggregate data meta-analysis.

6.3.2 Data extraction

Following PRISMA guidelines, an author assessed all the included studies and extracted the data. Any uncertainty was resolved by discussion among all the co-authors. In case of missing data, we contacted the authors of the individual studies to access any potential unpublished data. Clinical outcomes including in-hospital and 30-day mortality were included as outcome measures for all individual studies. The incidence of hypoxemia, pain as assessed by the opiate use, the infarct size as measured by the cardiac enzymes (including creatinine kinase CK, CK-MB, and cardiac troponins), and the left ventricular ejection fraction (LVEF) at follow-up were also explored.

6.3.3 Quality assessment

The Cochrane risk of bias tool was used to assess the risk of bias in individual included studies. To assess the quality of evidence, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method exploring the five different GRADE domains including study limitations, consistency of effect, imprecision, indirectness and publication bias.[29] Study quality assessment was also done by a single adjudicator.

6.3.4 Subgroup analysis

The aggregate nature of this meta-analysis and the inadequate information reported in the individual studies prevented an extensive subgroup analysis, with the exception of a pre-specified sub-group analysis between suspected versus confirmed AMI.

6.3.5 Sensitivity analysis

For missing data on outcome measures such as mortality, we performed sensitivity analysis, exploring different best-case and worst-case scenarios in the pooled analysis.

6.3.6 Statistical analysis

We used a random-effects model with Mantel-Haenszel test to pool data on dichotomous outcomes such as in-hospital or 30-day mortality. Corresponding forest plots were constructed using the statistical software Review Manager v.5.0. Odds ratio (OR) and respective 95% confidence intervals (CI) were calculated for all categorical outcomes. For continuous variables, mean difference (MD) and respective 95%CI were reported. Heterogeneity across the studies were sought using the I^2 statistics (I^2>50% suggested substantial heterogeneity).[30] Publication bias was evaluated through the construction of funnel plot for all included studies.

6.4 Results

6.4.1 Study selection and evaluation

The primary literature search for the timeline between June 1st, 2016 and September 30, 2017 yielded 286 records (Supplementary Figure 6.1). Of these, 3 studies (4 records) [22-24, 31] met the inclusion criteria and were added to the 5 trials [8, 19, 26-28] from the previous systematic review.[21] In total, 7,998 participants were pooled for this meta-analysis. All the included trials are published and all were parallel-designed randomized controlled trials. The majority of the trials

were conducted in the PCI era, however the study of Wilson *et al*. was from the thrombolysis era [28] and the study of Rawles and Kenmure was from pre-thrombolysis era.[8] Five studies were open-label,[19, 22, 26-28] and there was also one single-blind,[24] a double-blind [8] and a triple-blind study.[31] Table 6.1 summarizes the characteristics of the included trials. The findings of the quality assessment are provided in Supplementary Table 6.1.

Supplementary Table 6.2 shows the patient characteristics of the 7,998 participants (3,982 patients in the intervention arm and 4,002 patients in the control arm) in the included 8 trials. The mean age ranged from 55.1 to 67.8 years, and the trials included predominantly male patients. The rate of comorbidities varied among the studies, ranging from 36.8 to 56.6% for hypertension, 8.0-40.5% for diabetes mellitus, and 27.3-38.3% for hyperlipidemia. In seven trials,[8, 19, 22, 24, 27, 28, 31] the oxygen therapy was compared with the room air, and in Ranchord *et al*., patients in the control group received oxygen with SpO_2 titration at the range of 93-96%.[26] The SpO_2 at presentation was not reported in 4 trials,[8, 26-28] but the median baseline SpO_2 level ranged between 97.0% and 98.2% in the remaining studies.[19, 22, 24, 31]

6.4.2 In-hospital all-cause mortality

Data regarding in-hospital mortality outcome was available from all included studies. Among the 7,732 patients who were analyzed in this pooled analysis, in-hospital death occurred in 135 patients (72 patients (1.8%) in the O_2 group and 63 patients (1.6%) in the Air group). Oxygen therapy did not reduce the risk of in-hospital mortality (OR, 1.11 [95%CI, 0.69 to 1.77]) (Figure 6.1-A). There was low level of statistical heterogeneity among the included studies for the endpoint of in-hospital mortality (p-value for $Chi^2 = 0.33$; $I^2=13\%$).

We repeated the pooled analysis in the confirmed AMI subgroup and O_2 therapy was not associated with decreased in-hospital mortality (OR, 0.97 [95%CI, 0.60 to 1.58]) (Figure 6.1-B).

In the study by Wilson *et al*.,[28] there was a lack of clarity on whether the only in-hospital death occurred in the intervention or the control group. In the study of Ranchord *et al*.,[26] 2 patients were excluded after randomization because of cardiogenic shock. We did a sensitivity analysis to account for those three cases, considering them as in-hospital death. We considered two case-scenarios (best and worst for oxygen): once considering the three cases to occur in the intervention arm and next assigning those to the control group. The sensitivity analysis showed minimal effect on the point estimate (Supplementary Figure 6.2 and 6.3).

6.4.3 30-day all-cause mortality

Only two studies reported the 30-day mortality rates in their participants.[22, 24] Among the 6,762 patients analyzed in these two individual studies, death within 30-days occurred in 149 patients (78 patients in the O_2 group and 71 patients in the Air group). In the pooled analysis, oxygen therapy did not reduce the risk of 30-day mortality (OR, 1.09 [95%CI, 0.80 to 1.50]) with no evidence of statistical heterogeneity (I^2=0%) (Figure 6.2). This analysis was dominated by the DETO2X-AMI trial, since it carried most of the weight (~94%). The results remained consistent in the confirmed AMI subgroup of study (OR, 1.09 [95%CI, 0.72 to 1.66]) (Supplementary Figure 6.4).

6.4.4 Cardiac biomarker

Five RCTs reported cardiac troponin levels as the marker of myocardial necrosis in AMI.[19, 22, 24, 26, 31] In the pooled analysis (n=5,957), O_2 therapy was not associated with any significant effect on troponin levels (Mean difference, - 0.13; 95%CI -0.66 to 0.44; p=0.64; Figure 6.3). In the confirmed AMI subgroup (n=3,070), O_2 was not associated with any difference between groups in terms of serum troponin levels (Mean difference, -0.06; 95%CI -0.70 to 0.59; p=0.86; Supplementary Figure 6.5). Rawles *et al.*[8] used serum aspartate aminotransferase (AST) levels to confirm the diagnosis of acute MI and the reported the AST level to be significantly higher in the O_2 versus Air group (99.9 ± 7.1 vs 80.7 ± 6.6; $p<0.05$). Ukholkina *et al*. reported creatine kinase and CK-MB and the levels of CK-MB was lower in the O_2 group as compared to room air (224.5 ± 49.7 vs 385.5 ± 36.2; $p<0.05$).[27]

6.4.5 Infarct size

Cardiac MRI (CMR) was reported from a subgroup of patients in three studies (n=370).[19, 24, 26] The infarct size, when presented as a proportion of the left ventricular mass, was not statistically different between groups with and without O_2 therapy (Mean difference, 0.91; 95%CI -1.39 to 3.20; p=0.44; Figure 6.4).

6.4.6 Pain

Opiate use, as a surrogate marker of angina, was lower with O_2 therapy ($p<0.01$) in the study of Wilson *et al*,[28] however, the frequency of angina pectoris, pain scores and the number of patients treated with opiates were not different between groups in the Rawles *et al*.,[8] and Heidari *et al*.[31] studies. The AVOID trial reported no difference in chest pain scores or the opiate use between

the study groups.[19] Considering the different approaches of reporting the opiate use across the included studies, we were not able to pool the patients for this specific outcome (Table 6.2).

6.4.7 Hypoxemia

Two studies reported the rate of hypoxemia in both study groups.[22, 28] AVOID trial only reported hypoxemia in the Room Air group of study (7.7%) but not in the oxygen arm.[19] For the study by Ukholkina *et al.*, no patient met the criteria for hypoxemia defined by the trial (SpO_2<94%) at the end of the first day, however no further details provided regarding the rate of hypoxemia within the first 24 hours.[27] Among the 6,679 patients in the pooled analysis, hypoxemia was reported in 336 patients (68 patients in the O_2 group and 268 patients in the Air group). Oxygen therapy significantly reduced the risk of hypoxemia (OR, 0.29 [95%CI, 0.17 to 0.47]) in total cohort (Figure 6.5) and in the confirmed AMI subgroup of study (OR, 0.27 [95%CI, 0.18 to 0.41]) (Supplementary Figure 6.6).

6.4.8 Assessment of publication bias

There was no publication bias using Funnel Plot for all-cause mortality (Supplementary Figure 6.7).

6.5 Discussion

Our meta-analysis failed to find evidence supporting the use of oxygen therapy in normoxemic patients with AMI. Based on the existing evidence, O_2 therapy seems to have no additional benefit in patients with normal baseline oxygen levels. We additionally noted that there was no additional benefit of supplemental oxygen therapy on infarct size or in-hospital mortality with the caveat that the quality of evidence is at best moderate and a harmful effect cannot be ruled out. Nevertheless, and in line with the updated ESC practice guidelines,[32] clinical pathways should be updated to reflect this contemporary evidence.

Several studies in the latter part of the 20th century suggested possible harm with O_2 therapy in the AMI setting,[5, 7, 8, 10, 33, 34] but research in this field remained dormant until the AVOID trial made headlines and refreshed the concerns of the scientific community about the possible detrimental effects of oxygen therapy in this patient population.[19] A widespread belief that the oxygen therapy, if not helpful, is safe and harmless was a main reason for the above-mentioned delay in addressing this research question. This belief is reflected in the results of a survey in which 55% of respondents (emergency department, cardiology and ambulance staff) believed

that oxygen reduces the risk of death in AMI and most (98.3%) reported a routine use of oxygen in this setting.[35]

Several practice guidelines have recently taken a more cautious approach[32, 36, 37] and have diverged from the position of previous guidelines that favored "routine O_2 therapy for all". Nevertheless, the latest ACCF/AHA guidelines for the management of ST elevation myocardial infarction (STEMI) suggested the supplemental O_2 to have "salutary placebo effects" in normoxemic patients[38] and 2013 ACCF/AHA guidelines for the acute management of unstable angina / non-STEMI recommended the use of supplemental O_2 in all patients, at least during the first 6 hours after presentation[39] (Table 6.3). In the latest version of the European Society of Cardiology's STEMI guideline which was published simultaneously with the results of DETO2X-AMI trial, they alluded to routine oxygen therapy as "not-recommended in normoxemic patients".[32]

The addition of DETO2X-AMI trial was an important step to invigorate the quality of existing evidence, as some of previous trials were implemented in advance of the recent advancements in the management of AMI such as reperfusion techniques and other co-therapies. Although incorporating three new RCTs to this meta-analysis, one of which is the largest trial in the field, the results of this study are in consistence with the results of the latest Cochrane review which showed no effect of O_2 therapy in AMI patients.[21] With the results of the DETO2X-AMI trial and this meta-analysis, we can expect the practice guidelines to take an evidence-based position and recommend against the routine use of supplemental O_2 in patients with normal oxygen saturation levels at presentation.

It should be noted that considering the low rate of mortality in the included studies (1.7% overall mortality), both the studies and the meta-analysis were underpowered for this clinical outcome. Hence, further adequately powered and designed studies are required to fully answer this question. A large, pragmatic, non-inferiority RCT using composite endpoint consisted of all-cause mortality, cardiac arrest and cardiogenic shock and elevated troponin levels within 24-48 hours might be a of interest. An ongoing RCT in New Zealand has the goal of recruiting 21,000 patients with suspected ACS in a cross-over-designed registry-based study (ACTRN12616000461493). This study has the potential to provide sufficient evidence and address this issue.

Several limitations are noteworthy. Clinical heterogeneity among the included studies is common in meta-analysis and the studies might have differences in terms of patient characteristics, study design, etc. For example, the duration of supplemental oxygen therapy varied among the included studies. Nevertheless, for the outcome of in-hospital and 30-day mortality, there was negligible levels of statistical heterogeneity among included studies. The evidence around the troponin data should be considered of low quality, due to significant heterogeneity of troponin assays and different sampling timepoints and clinical processes used in the included studies. Considering the different definitions that were used for normoxemia in the included studies (e.g. $SpO_2 \geq 90\%$ in DETO2X-AMI and $SpO_2 \geq 94\%$ in AVOID trial), it should be noted that this study cannot rule out a benefit in the SpO_2 range between 90-94%, and it cannot rule out potential deleterious effects of oxygen in SpO_2 levels closer to 100%.

In conclusion, this meta-analysis showed that supplemental O_2 therapy is not associated with clinical benefits such as reduced mortality. Oxygen therapy in patients with ACS who have normal oxygen levels at presentation may face the same fate as did the O_2 therapy in neonates, which is becoming a part of medical history.

6.6 References

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Figures and Tables:

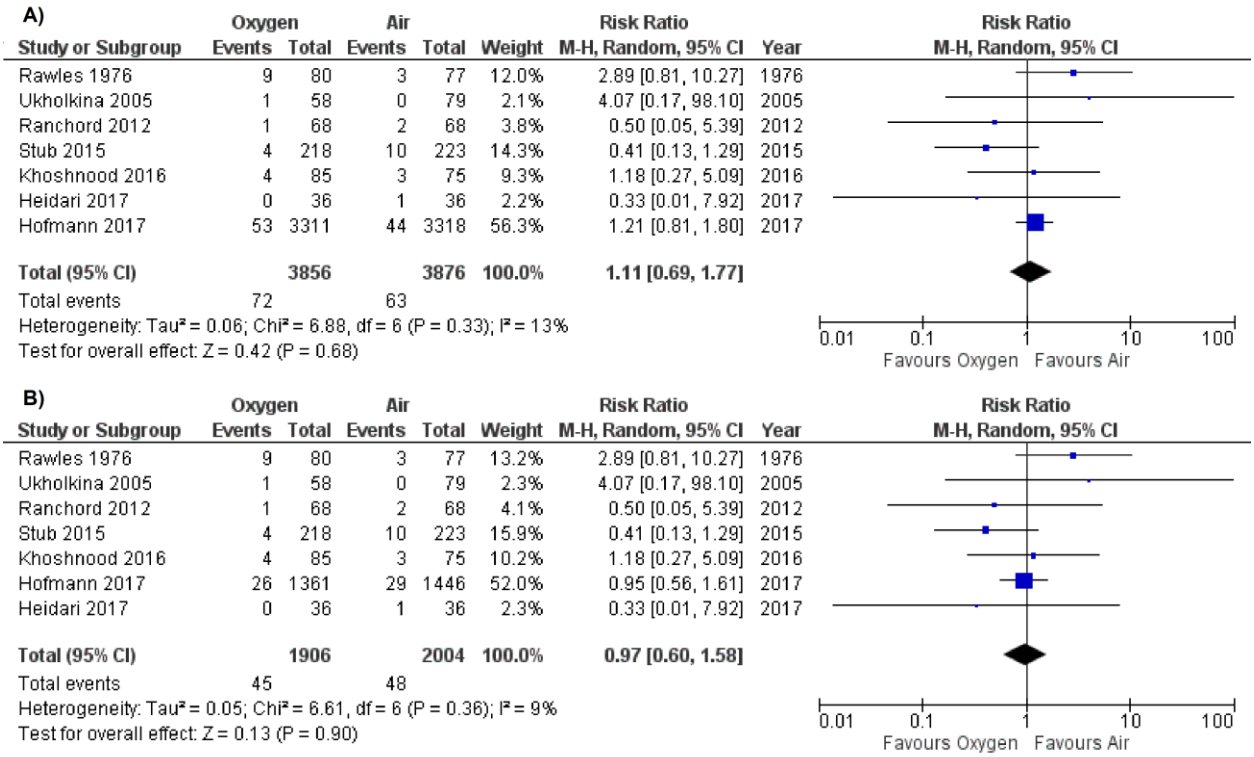


Figure 6.1. Forest plot of Oxygen versus Air comparison for the outcome of in-hospital mortality in patients with A) suspected or B) confirmed AMI (Random effect)

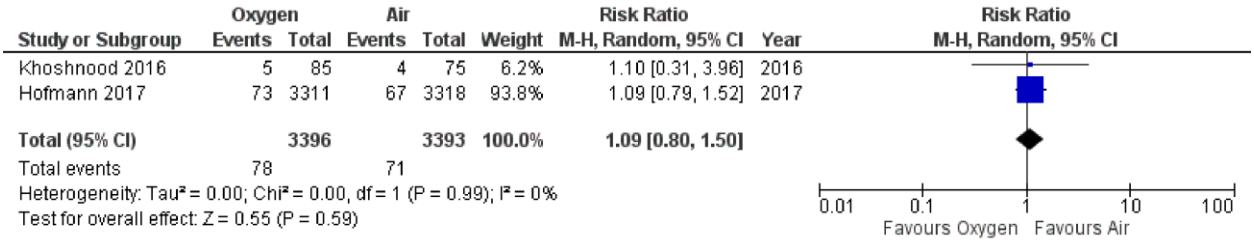


Figure 6.2. Forest plot of Oxygen versus Air comparison for the outcome of 30-day mortality (Random effect)

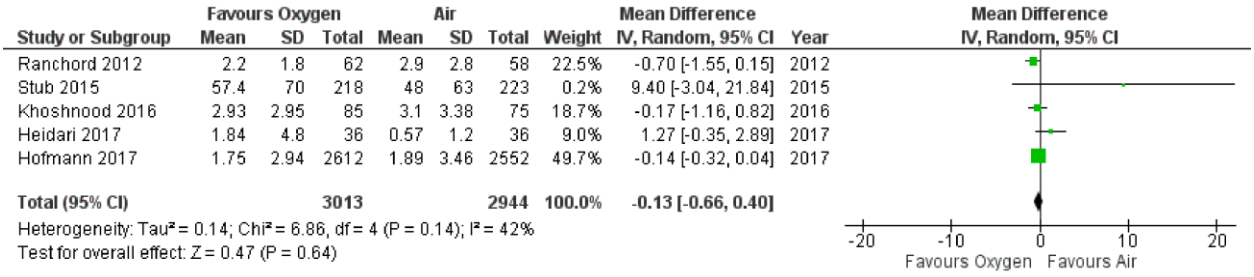


Figure 6.3. Forest plot of Oxygen versus Air comparison for the outcome of cardiac troponin levels in the ITT population (Random effect)

Note: There is significant limitation to this analysis, due to significant heterogeneity around troponin assays and different sampling timepoints and clinical processes used in the included studies.

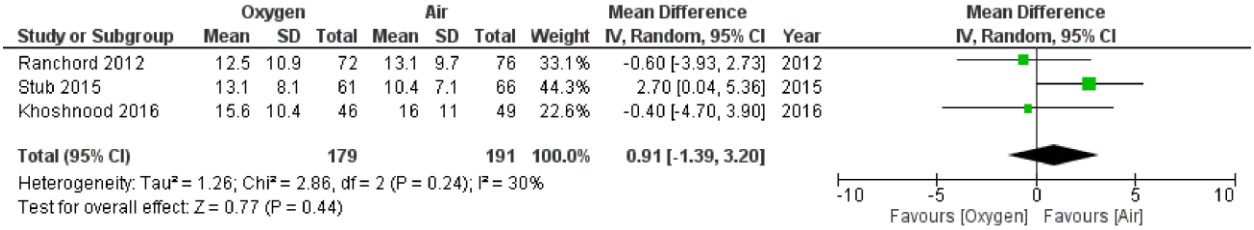


Figure 6.4. Forest plot of Oxygen versus Air comparison for the outcome of infarct size according to CMR in the ITT population (Random effect)

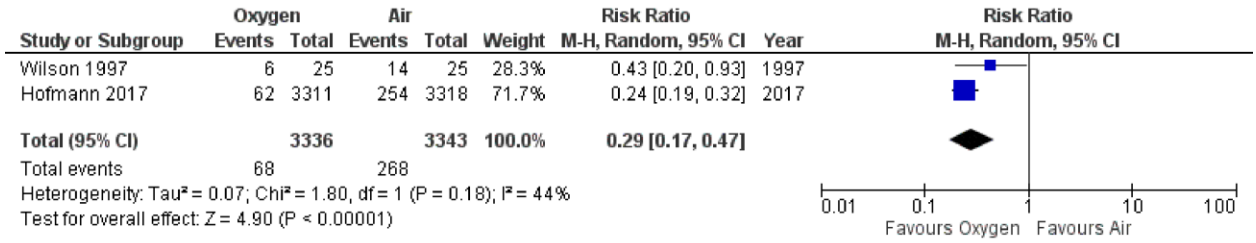


Figure 6.5. Forest plot of Oxygen versus Air comparison for the outcome of hypoxemia in the ITT population (Random effect)

Table 6.1. Characteristics of the included studies

Trial, year and country	Sites	Setting	Study design and sample size	Study era	Participants	Intervention	Comparator	Endpoints	Length of F/U
Rawles and Kenmure, 1976, UK [8]	1	CCU	Double-blind, RCT N=157	Pre-PCI era	Suspected AMI presenting within 24 h of onset of pain	6 L/min Oxygen, MC mask, 24 h	6 L/min Air at normal pressure, MC mask, 24 h	In-hospital mortality, hypoxemia and arrhythmia in 24 h, opiate use, peak AST level, LOS, systolic ejection time	Until discharge
Wilson and Channer, 1997, UK [28]	1	CCU	Open label RCT N=50 randomized, 42 analysed	Thrombolysis era	Confirmed uncomplicated AMI	4 L/min Oxygen, face mask, 24 h	Air breathed normally	Incidence of hypoxemia/ Severe hypoxemia, arrhythmia and ST segment changes in 24 hours	Until discharge
Ukholkina *et al*. 2005, Russia [27]	1	CCU	Open-label RCT N=137	PCI era	Confirmed uncomplicated AMI within 12 h of	3-6 L/min Oxygen (FiO_2 30-40%), nasal cannulae, 3 h	Air breathed normally	Death, arrhythmia within 1 hr or reperfusion, recurrent AMI, post-infarction angina, hypoxemia, cardiac damage	10 days

					symptom onset			measured by ECG mapping and CK-MB	
Ranchord *et al*. 2012, New Zealand [26]	2	Inpatients	Open-label RCT N=148 randomized, 136 analysed	PCI era	Confirmed uncomplicated AMI	6 L/min Oxygen, medium concentration mask, 6 h	Oxygen titrated to SaO_2 of 93-96%, nasal prongs or mask	30-day mortality, 30-day MACE (death, reinfarction, target vessel revascularization), complications, infarct size based on TnT level at 66-78 hr post-randomization, infarct mass according to MRI at 4-6 weeks post-AMI, pro-BNP at 24 hr after randomization,	30 days
Stub *et al*. 2015, Australia [19]	9	EMS	Open-label RCT N=638 randomized, 441 analysed	PCI era	Normoxemic (≥94%) patients with confirmed uncomplicated AMI	8 L/min Oxygen, Hudson mask, until the end of acute PCI (Median 3.6 h)	Room air	Infact size estimated by cTnI and CK at 72 h of reperfusion, Pain score, In-hospital mortality, MACE (death, recurrent MI, repeat revascularization at 6 months, infarct size measured by CMR at 6 months	6 months
Khoshnood *et al*. 2016, Sweden [24]	2	EMS	Single-blind RCT N=160 randomized, 95 analysed	PCI era	Normoxemic (≥94%) patients with confirmed STEMI and	10 L/min Oxygen, oxymask TM, until the end of acute PCI (Median 1.4 h)	Room air	Primary: Myocardial Salvage Index in CMR Secondary: Infarct size, myocardium at risk, peak TnT, WMSI and LVEF on Echo	6 months

					symptoms <12 h				
Hofmann *et al*. 2017, Sweden [22]	34	EMS, ED, CCU, Cath Lab	Open label RCT N=6629 randomized with suspected AMI; N=5010 with confirmed AMI. All analysed	PCI era	Normoxemic (≥90%) patients with suspected AMI	6 L/min Oxygen, Open face mask for 6-12 h (median 11.6 h)	Room air	1-year all-cause death, 30-day all-cause death, rehospitalization with MI, rehospitalization with HF, cardiovascular death, composites of these endpoints	1 year
Heidari *et al*. 2017, Iran [31]	1	Inpatients	Triple-blind RCT, N=79 randomized, 72 analysed	PCI-era	Normoxemic (>90%) patients with non-STE ACS	4-6 L/min Oxygen (FiO_2 45%), Nasal Cannula for 6 hours post-admission	Room Air	Incidence of arrhythmia, hypoxia, angina and analgesic consumption within first 24 h, Infarct size using CTnI (baseline to 4-8 h)	24 h

Table 6.2. Outcomes in studies included in the meta-analysis

Trial, year and country	Study group, (n)	Hypoxemia	Opiate use as a proxy for pain	Cardiac enzymes			Infarct size	LVEF	In-hospital mortality	30-day mortality
				Troponin; µg/L	CK	CK-MB				
Rawles and Kenmure, 1976, UK [8]	Oxygen therapy (80)	NR	57 (71.2), 2.1±0.2	NR	NR	NR	NR	NR	9 (11.2)	NR
	Room air (77)	NR	52 (67.5), 2.0±0.2	NR	NR	NR	NR	NR	3 (3.9)	NR
Wilson and Channer, 1997, UK [28]	Oxygen therapy (25)	6 (27.0%)*	16 (72.7)*	NR	NR	NR	NR	NR	0 ‡	NR
	Room air (25)	14 (70.0%)*	18 (90.0)*	NR	NR	NR	NR	NR	0 ‡	NR
Ukholkina *et al*. 2005, Russia [27]	Oxygen therapy (58)	0 (0.0)	NR	NR	1469.3 ± 346.6	224.5 ± 49.7	2.49 ± 0.19, ECG	42.2 ± 2.3	1 (1.7)	NR
	Room air (79)	0 (0.0)	NR	NR	2430.4 ± 291.8	385.5 ± 36.2	3.10 ± 0.14, ECG	54.1 ± 1.8	0 (0.0)	NR
Ranchord *et al*. 2012, New Zealand [26]	Oxygen therapy (72)	NR	NR	2.2 ± 1.8 (62)*	NR	NR	12.5 ± 10.9 %, MRI*	55.9 ± 11.0*	1 (1.4)	NR
	Room air (76)	NR	NR	2.9 ± 2.8 (58)*	NR	NR	13.1 ± 9.7%, MRI*	56.0 ± 10.6*	2 (2.6)	NR
Stub *et al*. 2015,	Oxygen thera	NR	192 (89.3)	52.9 ± 52.3 *	1948 (17	NR	13.1 ±	54.4 ± 9.5*	5 (1.6)	NR

Australia [19]	py (312)				21-2205)*		8.1%; MRI*			
	Room air (312)	7.7%*	204 (91.5)	51.5 ± 62.5*	1543 (1341-1776)*	NR	10.4 ± 7.1%; MRI*	54.9 ± 10.0*	11 (3.5)	NR
Khoshnood *et al*. 2016, Sweden [24]	Oxygen therapy (85)	NR	NR	2.93 ± 2.95	NR	NR	15.6 ± 10.4 %; MRI*	47.0 ± 8.5 (46)§*	4 (4.7)	5 (5.9)
	Room air (75)	NR	NR	3.10 ± 3.38	NR	NR	16.0 ± 11.0 %; MRI*	49.2 ± 8.1 (41)§*	3 (4.0)	4 (5.3)
Hofmann *et al*. 2017, Sweden [22]	Oxygen therapy (3311)	62 (1.9)	NR	1.75 ± 2.94 (2612)	NR	NR	NR	<40%: 428 (13.0)	53 (1.6)	73 (2.2)
	Room air (3318)	254 (7.7)	NR	1.89 ± 3.46 (2552)	NR	NR	NR	<40%: 428 (12.9)	44 (1.3)	67 (2.0)
Heidari *et al*. 2017, Iran [31]	Oxygen therapy (39)	NR	4.6 ± 2.3*	1.84 ± 4.8*	NR	NR	NR	49.5 ± 1.4*	0 (0.0)	NR
	Room Air (40)	NR	6.4 ± 2.4*	0.57 ± 1.2*	NR	NR	NR	47.9 ± 1.5*	1 (2.5)	NR

CK: creatine kinase; LVEF: left ventricular ejection fraction; NR: not reported. * data from the analysed/confirmed AMI subgroup of study rather than the randomized group. ‡ According to the Wilson *et al*, one patient died in hospital among those who were randomized, not clear in which study group. §LVEF data from SOCCER trial were collected from a SOCCER sub-study [23]

Table 6.3. Guideline recommendations regarding oxygen therapy in hypoxemic and normoxemic patients with myocardial infarction

Guideline	Year	Recommendation on O_2 Therapy in hypoxemic patients	Recommendation Class	Level of evidence	Recommendation on O_2 Therapy in normoxemic patients	Recommendation Class	Level of evidence
ACCF/AHA [38, 39]	2013	Appropriate for patients who are hypoxemic (SpO_2<90%)	Class I	B	May have salutary placebo effect. Reasonable to administer supplemental O_2 to all patients during the first 6h after presentation	Class IIa	C
AHA/ACC [36]	2014	Supplemental oxygen should be administered to patients with SaO_2<90%, respiratory distress, cyanosis or other high risk features of hypoxemia	Class I	C	Routine use of O_2 in normoxemic patients may have untoward effects	N/A	N/A
ESC [32]	2017	Oxygen is indicated in hypoxic patients with SaO_2 <90% or PaO_2 < 60 mmHg	Class I	C	Routine oxygen is not recommended when SaO_2 is ≥ 90%	III	B
CCS [40]	2011	Supplemental oxygen is recommended, when hypoxic or dyspneic	N/A	N/A	Not mentioned	N/A	N/A

ACCP consensus [41]	2010	Supplemental oxygen can provide relief of dyspnea for patients who are hypoxemic at rest or during minimal activity	Class I	Clear consensus (~75% agreement)	Use of supplemental oxygen for non-hypoxemic patients with advanced lung and heart disease	Class III	47% agreement
NICE [42]	2013	Not mentioned	N/A	N/A	Not mentioned	N/A	N/A
NHFA/CSANZ [37]	2016	O_2 use advocated if SaO2 is <93%	N/A	N/A	Routine use in patients with SaO_2>93% is not recommended.	N/A	N/A

ACC: American College of Cardiology; ACCF/AHA: American College of Cardiology Foundation/American Heart Association; HFSA: Heart Failure Society of America; ESC: European Society of Cardiology; CCS: Canadian Cardiovascular Society; ACCP: American College of Chest Physicians; NICE: National Institute for Health and Care Excellence; NHFA/CSANZ: National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand

6.7 Supplementary Materials

6.7.1 Search strategy

CENTRAL
#1 MeSH descriptor: [Myocardial Infarction] explode all trees
#2 myocardial infarct*
#3 heart attack*
#4 heart infarct*
#5 (coronary near/3 syndrome*)
#6 ”acute coronary“
#7 MeSH descriptor: [Coronary Thrombosis] this term only
#8 ”coronary thrombosis“
#9 ami
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11 MeSH descriptor: [Oxygen Inhalation Therapy] this term only
#12 (oxygen near/3 (therapy or treat* or effect* or admin* or inhal*))
#13 oxygen:ti
#14 oxygenotherapy
#15 #11 or #12 or #13 or #14
#16 #10 and #15 Publication Year from 2016 to 2017

MEDLINE OVID
1 exp Myocardial Infarction/
2 myocardial infarct$.tw.
3 heart attack$.tw.
4 heart infarct$.tw.
5 (coronary adj3 syndrome$).tw.
6 acute coronary.tw.
7 Coronary Thrombosis/
8 coronary thrombosis.tw.
9 ami.tw.
10 or/1-9
11 Oxygen Inhalation Therapy/
12 (oxygen adj3 (therapy or treat$ or effect$ or admin$ or inhal$)).tw.
13 oxygen.ti. or Oxygenotherapy.tw.
14 or/11-13
15 10 and 14
16 randomized controlled trial.pt.
17 controlled clinical trial.pt.
18 randomized.ab.
19 placebo.ab.

MEDLINE OVID
1 exp Myocardial Infarction/
2 myocardial infarct$.tw.
3 heart attack$.tw.
4 heart infarct$.tw.
5 (coronary adj3 syndrome$).tw.
6 acute coronary.tw.

7 Coronary Thrombosis/
8 coronary thrombosis.tw.
9 ami.tw.
10 or/1-9
11 Oxygen Inhalation Therapy/
12 (oxygen adj3 (therapy or treat$ or effect$ or admin$ or inhal$)).tw.
13 oxygen.ti. or Oxygenotherapy.tw.
14 or/11-13
15 10 and 14
16 randomized controlled trial.pt.
17 controlled clinical trial.pt.
18 randomized.ab.
19 placebo.ab.

20 drug therapy.fs.

21 randomly.ab.
22 trial.ab.
23 groups.ab.
24 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25 exp animals/ not humans.sh.
26 24 not 25
27 15 and 26
28 limit 27 to yr="2016 -Current"

EMBASE OVID
1 exp Myocardial Infarction/
2 myocardial infarct$.tw.
3 heart attack$.tw.
4 heart infarct$.tw.
5 (coronary adj3 syndrome$).tw.
6 acute coronary.tw.
7 Coronary Thrombosis/
8 coronary thrombosis.tw.
9 ami.tw.
10 or/1-9
11 Oxygen Inhalation Therapy/
12 (oxygen adj3 (therapy or treat$ or effect$ or admin$ or inhal$)).tw.
13 oxygen.ti. or Oxygenotherapy.tw.
14 or/11-13
15 10 and 14
16 random$.tw.
17 factorial$.tw.
18 crossover$.tw.
19 cross over$.tw.
20 cross-over$.tw.
21 placebo$.tw.
22 (doubl$ adj blind$).tw.
23 (singl$ adj blind$).tw.
24 assign$.tw.
25 allocat$. tw.

26 volunteer$.tw.
27 crossover procedure/
28 double blind procedure/
29 randomized controlled trial/
30 single blind procedure/
31 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 (animal/ or nonhuman/) not human/
33 31 not 32
34 15 and 33
35 limit 34 to yr="2016 - 2017"

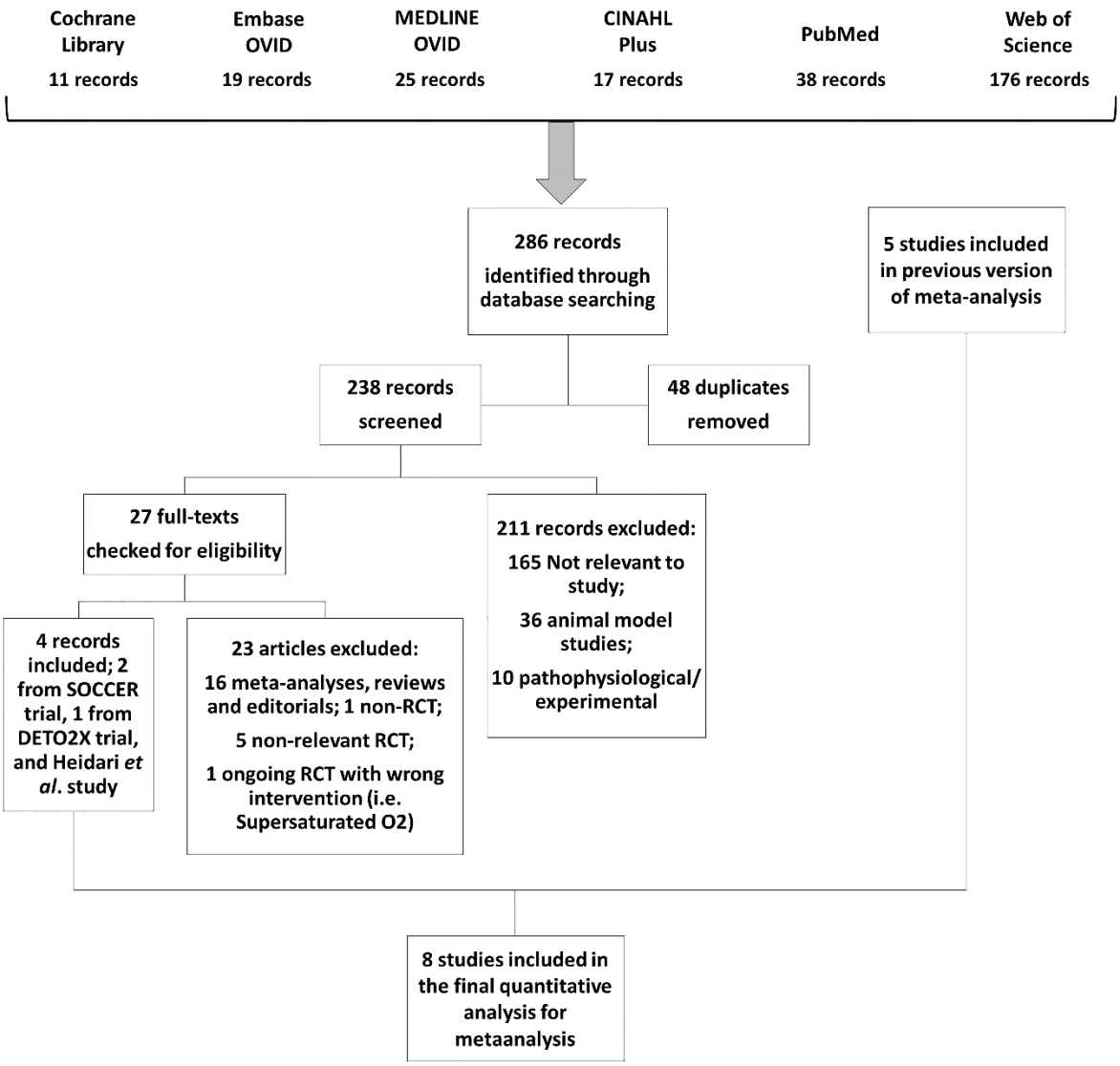
Cinahl Plus (EBSCO)
S19 S14 and S17 Limiters - Published Date from: 20160601-20171231
S18 S14 and S17
S17 S15 or S16
S16 (MH "Randomized Controlled Trials")
S15 random* or blind* or allocat* or trial* or placebo* or crossover* or cross-over*
S14 S10 and S13
S13 S11 or S12

S12 oxygen or oxygenotherapy
S11 (MH "Oxygen Therapy+")
S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S9 ami
S8 coronary N3 thrombosis
S7 (MH "Coronary Thrombosis")
S6 (heart attack*)
S5 (coronary N3 syndrome*)
S4 (acute N3 coronary)
S3 (heart infarct*)
S2 (myocardial infarct*)
S1 (MH "Myocardial Infarction+")

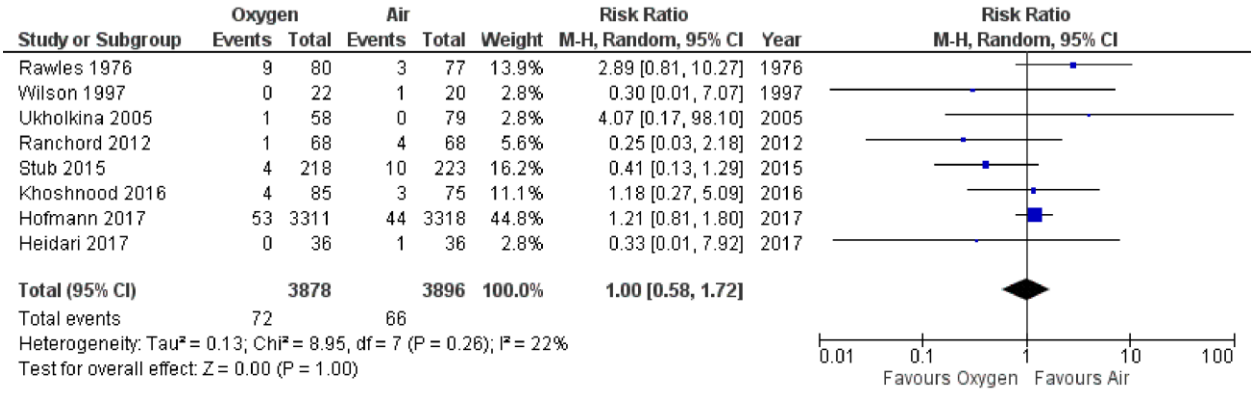
Web of Science (ISI)
#14 #13 AND #12 AND #8
#13 TS =((random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*))
#12 #11 OR #10 OR #9
#11 TS =(oxygenotherapy)
#10 TS =((oxygen near/3 (therapy or treat* or effect* or admin* or inhal*)))
#9 TS=(oxygen)
#8 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#7 TS=(ami)
#6 TS=(coronary near/3 thrombosis)
#5 TS=((heart attack*))
#4 TS=((coronary near/3 syndrome*))
#3 TS=((acute near/3 coronary))
#2 TS=((heart infarct*))
#1 TS=((myocardial infarct*))

PubMed

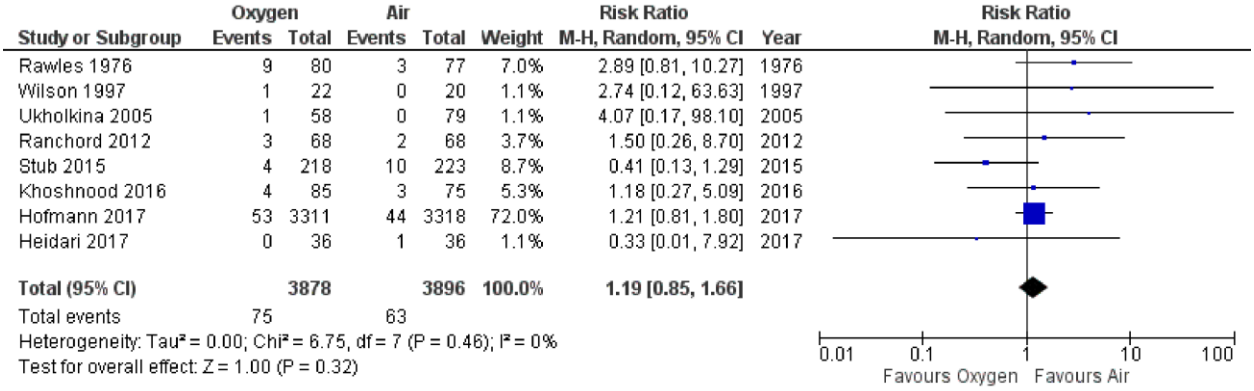
(publisher[sb] NOT pubstatusnihms) AND (”2016/06/01“[PDat] : ”2017/12/31“[PDat]) AND (Oxygen Inhalation Therapy[MeSH Major Topic]) OR (oxygen n3 (therapy or treat* or effect* or admin* or inhal*)) OR (oxygen[Title])
OR oxygenotherapy) AND (myocardial infarct* or heart attack* or heart infarct* or (coronary n3 syndrome) or ”acute coronary“ or ”coronary thrombosis“ or ami)
OR Coronary Thrombosis[MeSH Major Topic]) AND (((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type]) OR randomized[Title/Abstract] OR placebo[Title/Abstract] OR drug therapy[MeSH Subheading] OR randomly[Title/Abstract] OR trial[Title/Abstract] OR groups[Title/Abstract]) NOT ((animals[MeSH Terms]) NOT humans[MeSH Terms])) AND (”2016/06/01“[PDat] : ”2017/12/31“[PDat])



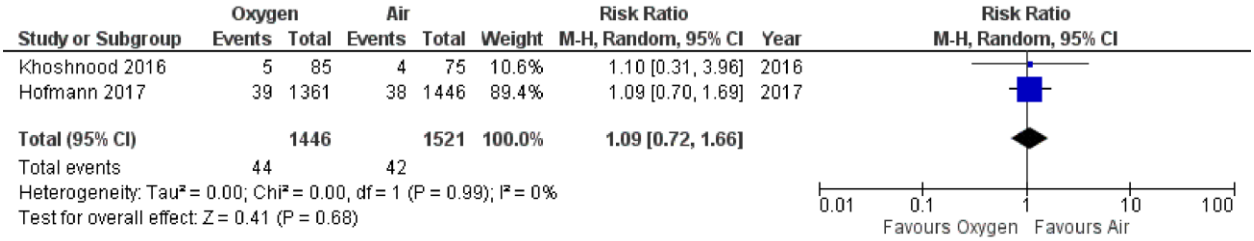
Supplementary Figure 6.1. Study flow diagram with the results of the updated literature search from June 2016 until present incorporated with the studies included in the previous Cochrane review



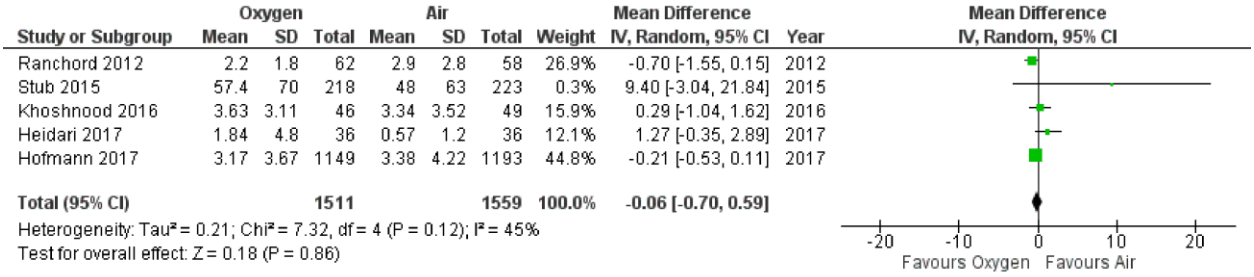
Supplementary Figure 6.2. Forest plot of Oxygen versus Air comparison for the outcome of in-hospital mortality (Random effect / Best case scenario)



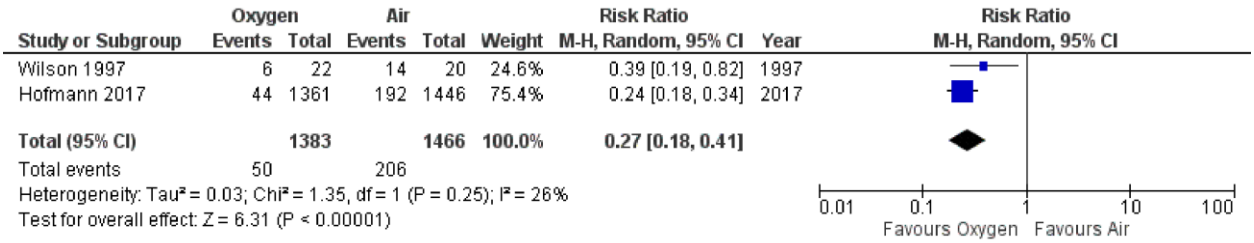
Supplementary Figure 6.3. Forest plot of Oxygen versus Air comparison for the outcome of in-hospital mortality (Random effect / Worst case scenario)



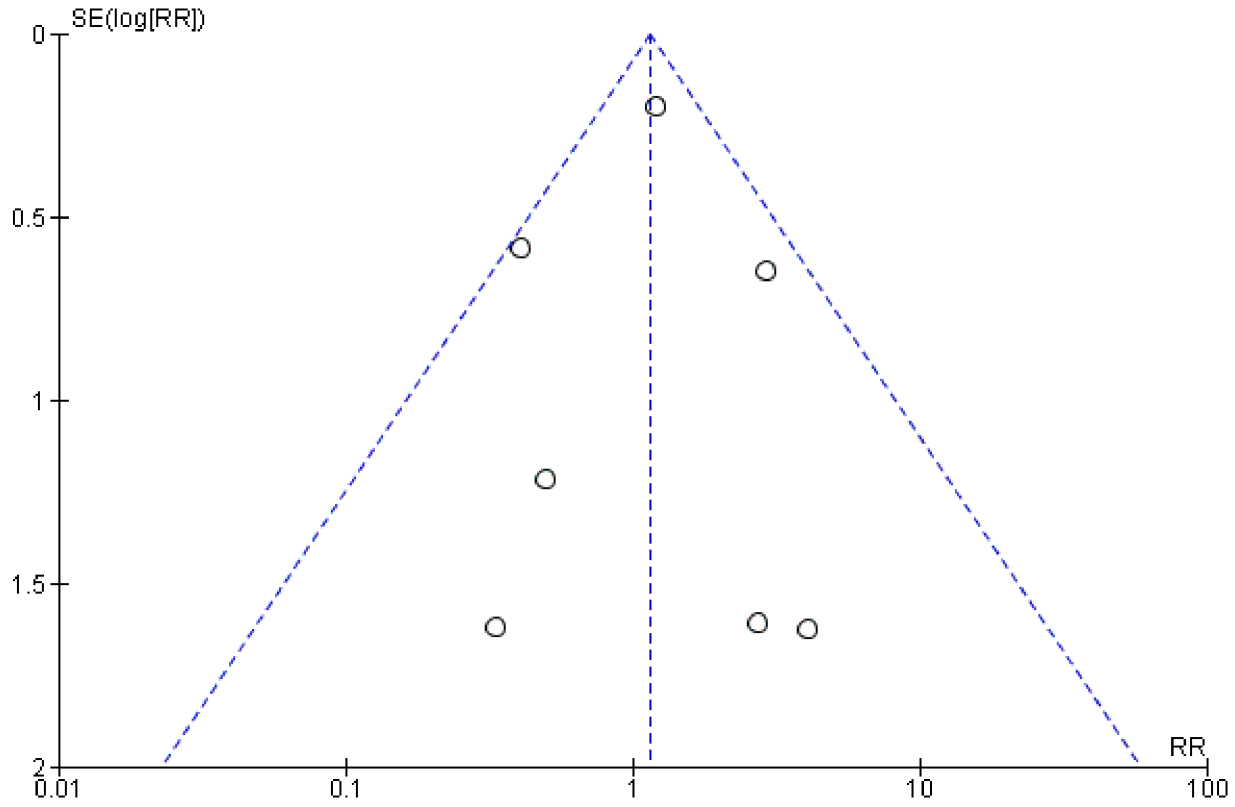
Supplementary Figure 6.4. Forest plot of Oxygen versus Air comparison for the outcome of 30-day mortality in patients with confirmed AMI (Random Effect)



Supplementary Figure 6.5. Forest plot of Oxygen versus Air comparison for the outcome of cardiac troponin levels in patients with confirmed AMI (Random effect)



Supplementary Figure 6.6. Forest plot of Oxygen versus Air comparison for the outcome of hypoxemia in patients with confirmed AMI (Random effect)



Supplementary Figure 6.7. Funnel plot of comparison between Oxygen versus Air for the outcome of in-hospital mortality

Supplementary Table 6.1. Quality of evidence for evaluated outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oxygen**	**Room Air**	**Relative (95% CI)**	**Absolute (95% CI)**		
In-hospital mortality in patients with suspected AMI (follow up: median 1 weeks)												
7	randomised trials	serious[a]	not serious	not serious	not serious	none	72/3878 (1.9%)	63/3896 (1.6%)	**RR 1.15** (0.79 to 1.66)	**2 more per 1,000** (from 3 fewer to 11 more)	⊕⊕⊕◯ MODERATE	CRITICAL
In-hospital mortality in patients with confirmed AMI (follow up: median 1 weeks)												
7	randomised trials	serious[b]	not serious	not serious	not serious	none	45/1928 (2.3%)	48/2024 (2.4%)	**RR 0.94** (0.62 to 1.44)	**1 fewer per 1,000** (from 9 fewer to 10 more)	⊕⊕⊕◯ MODERATE	CRITICAL
30-day mortality in patients with suspected AMI (follow up: median 1 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oxygen**	**Room Air**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	not serious	not serious	not serious	not serious	none	78/3396 (2.3%)	71/3393 (2.1%)	**RR 1.09** (0.80 to 1.50)	**2 more per 1,000** (from 4 fewer to 10 more)	⊕⊕⊕⊕ HIGH	CRITICAL
30-day mortality in patients confirmed AMI (follow up: median 1 months)												
2	randomised trials	serious[c]	not serious	not serious	not serious	none	44/1446 (3.0%)	42/1521 (2.8%)	**RR 1.09** (0.72 to 1.66)	**2 more per 1,000** (from 8 fewer to 18 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Hypoxemia in patients with suspected AMI (follow up: median 1 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oxygen**	**Room Air**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	not serious	serious	not serious	not serious	none	68/3336 (2.0%)	268/3343 (8.0%)	**RR 0.29** (0.17 to 0.47)	**57 fewer per 1,000** (from 42 fewer to 67 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Hypoxemia in patients with confirmed AMI (follow up: median 1 weeks)												
2	randomised trials	serious[c]	not serious	not serious	not serious	none	50/1383 (3.6%)	206/1466 (14.1%)	**RR 0.27** (0.18 to 0.41)	**103 fewer per 1,000** (from 83 fewer to 115 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT
Infarct size based on CTn levels in patients with suspected AMI (follow up: median 1 weeks)												

Certainty assessment							№ of patients		Effect			
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oxygen**	**Room Air**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
5	randomised trials	serious[d]	serious	not serious	not serious	publication bias strongly suspected	3013	2944	-	MD **0.13 lower** (0.66 lower to 0.4 higher)	⊕⊕◯◯ LOW	CRITICAL
Infarct size based on CTn levels in patients with confirmed AMI (follow up: median 1 weeks)												
5	randomised trials	serious[e]	serious	not serious	not serious	publication bias strongly suspected	1511	1559	-	MD **0.06 lower** (0.7 lower to 0.59 higher)	⊕◯◯◯ VERY LOW	CRITICAL
Infarct size based on CMR (% of the LV mass) (follow up: median 6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxygen	Room Air	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	very serious [f]	not serious	not serious	serious [h]	publication bias strongly suspected	179	191	-	MD **0.91 higher** (1.39 lower to 3.2 higher)	⊕◯◯◯ VERY LOW	CRITICAL

AMI: Acute myocardial infarction; **CI:** Confidence interval; **CMR:** Cardiac MRI; **CTn:** Cardiac Troponin; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Incomplete outcome data in 2 of the 7 included studies (Ranchord 2012, Ukholkina 2005), but will downgraded only one level, as these two studies carry only 5.9% of the weight of meta-analysis

b. Downgraded 2 levels: In 2 trials (Rawles 1976, Hofmann 2017), the evidence comes from a selected subgroup of patients which was not randomised for this comparison. Incomplete outcome data in 2 of the 7 included studies (Ranchord 2012, Ukholkina 2005).

c. Evidence comes from a selected subgroup of patients which was not randomised for this comparison

d. Incomplete outcome data. Three studies reported troponin T levels, but Stub *et al* and Heidari *et al*. reported troponin I

e. Incomplete outcome data. The evidence comes from a selected subgroup of patients which was not randomised for this comparison. Three studies reported troponin T levels, but two reported troponin I

f. Incomplete outcome data. Also, the evidence comes from a selected subgroup of patients which was not randomised for this comparison

h. Level of imprecision was considered serious, because of the wide confidence interval which encompasses both benefit and clinically-significant risk

Supplementary Table 6.2. Patient characteristics for the ITT analysis (randomized patients)

Trial, year and country	Study group, (n)	Age, mean ± SD	Male %	HTN, %	DM, %	HLP, %	Smoker, %	Previous PCI or CABG, %
Rawles and Kenmure, 1976, UK [8]	Oxygen therapy (80)	55.1 ± 0.9	63 (78.7)	NR	NR	NR	NR	NR
	Room air (77)	56.4 ± 0.8	61 (79.2)	NR	NR	NR	NR	NR
Wilson and Channer, 1997, UK [28]	Oxygen therapy (25)	64*	NR	NR	2 (9.0)*	NR	5 (22.7)*	NR
	Room air (25)	65*	NR	NR	2 (10.0)*	NR	7 (35.0)*	NR
Ukholkina *et al*. 2005, Russia [27]	Oxygen therapy (58)	55.6±1.33	45 (77.5)	39 (67.2)	NR	NR	39 (67.2)	NR
	Room air (79)	53.5±1.06	70 (88.6)	51 (64.5)	NR	NR	56 (70.8)	NR
Ranchord *et al*. 2012, New Zealand [26]	Oxygen therapy (72)	60.0±12.5*	53 (77.9)*	23 (33.8)*	7 (10.3)*	19 (27.9)*	32 (47.1)*	3 (4.4)*
	Room air (76)	60.0±12.8*	48 (70.6)*	28 (41.2)*	8 (11.8)*	25 (36.8)*	21 (30.9)*	5 (7.4)*
Stub *et al*. 2015, Australia [19]	Oxygen therapy (312)	63.5 (54.0, 73.0)	240 (76.9)	130 (59.6)*	37 (17.0)*	121 (55.5)*	141 (65.3)*	28 (12.8)*
	Room air (312)	62.0 (53.0, 71.0)	242 (77.6)	123 (55.2)*	41 (18.4)*	118 (52.9)*	165 (74.3)*	29 (13.0)*
Khoshnood *et al*. 2016, Sweden [24]	Oxygen therapy (85)	64.4 ± 12.3	54 (63.5)	27 (31.8)	11 (12.9)	NR	30 (35.3)	NR
	Room air (75)	67.6 ± 12.0	51 (68.0)	32 (42.7)	12 (16.0)	NR	24 (32.0)	NR
	Oxygen therapy (3311)	67.8 ± 12.0	2264 (68.4)	1575 (47.6)	589 (17.8)	903 (27.3)	704 (21.3)	733 (22.2)

Hofmann *et al*. 2017, Sweden [22]	Room air (3318)	67.5 ± 12.0	2342 (70.6)	1559 (47.0)	644 (19.4)	912 (27.5)	721 (21.7)	755 (22.7)
Heidari *et al*. 2017, Iran [31]	Oxygen therapy (39)	58.6 ± 12.7*	27 (67.5)*	22 (56.4)*	14 (35.9)*	15 (38.2)*	15 (38.5)*	NR
	Room Air (40)	60.3 ± 11.4*	18 (46.2)*	22 (56.4)*	18 (46.2)*	17 (43.6)*	13 (33.3)*	NR

NR: not reported. * data from the analysed/confirmed AMI subgroup of study rather than the randomized group

Supplementary Table 6.2, continued:

Trial, year and country	Study group, (n)	Medications at presentation				SpO2 at presentation	Culprit artery			Coronary Artery disease		
		ASA	BB	ACEi/ ARB	Statin		LAD	LCX	RCA	SVD	Multi-vessel	LMCA
Rawles and Kenmure, 1976, UK [8]	Oxygen therapy (80)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Room air (77)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wilson and Channer, 1997, UK [28]	Oxygen therapy (25)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Room air (25)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ukholkina *et al*. 2005, Russia [27]	Oxygen therapy (58)	NR	NR	NR	NR	NR	32 (55.1)	0 (0.0)	26 (44.8)	NR	NR	NR
	Room air (79)	NR	NR	NR	NR	NR	35 (44.3)	0 (0.0)	44 (55.6)	NR	NR	NR

Ranchord *et al*. 2012, New Zealand [26]	Oxygen therapy (72)	11 (16.2)*	7 (10.3)*	13 (19.1)*	17 (25.0)*	NR	18 (26.5)*	1 (1.5)*	49 (72.0)*	NR	NR	NR
	Room air (76)	11 (16.2)*	7 (10.3)*	18 (26.5)*	14 (20.6)*	NR	31 (45.6)*	0 (0.0)*	37 (54.1)*	NR	NR	NR
Stub *et al*. 2015, Australia [19]	Oxygen therapy (312)	NR	NR	NR	NR	98.0 (97.0-99.0)	82 (38.0)*	21 (9.7)*	100 (46.3)*	95 (43.8)*	122 (56.2)*	9 (4.1)*
	Room air (312)	NR	NR	NR	NR	98.0 (97.0-99.0)	74 (33.8)*	31 (14.2)*	101 (46.1)*	84 (37.7)*	139 (62.3)*	7 (3.1)*
Khoshnood *et al*. 2016, Sweden [24]	Oxygen therapy (85)	9 (10.6)	5 (5.9)	17 (20.0)	5 (5.9)	98.0 ± 1.7	44 (51.8)	6 (7.1)	29 (34.1)	39 (45.9)	39 (45.9)	3 (3.5)
	Room air (75)	11 (14.7)	15 (20.0)	14 (18.7)	8 (10.7)	97.7 ± 1.8	33 (44.0)	6 (8.0)	28 (37.3)	41 (54.7)	27 (36.0)	4 (5.3)
Hofmann *et al*. 2017, Sweden [22]	Oxygen therapy (1361 STEMI)	904 (27.3)	1030 (31.1)	1186 (35.8)	884 (26.7)	97 (95-98)	537 (39.4)*	171 (12.6)*	487 (35.8)*	727 (53.4)*	634 (46.6)*	50 (3.7)*
	Room air (1446 STEMI)	961 (29.0)	1052 (31.7)	1237 (37.3)	895 (27.0)	97 (95-98)	541 (37.4)*	177 (12.2)*	545 (37.7)*	732 (50.6)*	714 (49.4)*	63 (4.4)*
Heidari *et al*.	Oxygen therapy (39)	NR	NR	NR	NR	98.2 ± 0.2	NR	NR	NR	NR	NR	NR

2017, Iran [31]	Room Air (40)	NR	NR	NR	NR	98.1 ± 0.2	NR	NR	NR	NR	NR	NR

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ASA: aspirin; DM: diabetes mellitus; HLP: hyperlipidemia; HTN: hypertension; LAD: left anterior descending artery; LCX: left circumflex artery; LMCA: left main coronary artery; RCA: right coronary artery; SD: standard deviation; SpO2: peripheral oxygen saturation level; STEMI: ST-elevation myocardial infarction; SVD: single vessel disease; NR: not reported. * data from the analysed/confirmed AMI subgroup of study rather than the randomized group

Supplementary Table 6.3. Patient characteristics in patients with confirmed AMI (analyzed group)

Trial, year and country	Study group, (n)	Age, mean ± SD	Male %	HTN, %	DM, %	HLP, %	Smoker, %	Previous PCI or CABG, %
Rawles and Kenmure, 1976, UK [8]	Oxygen therapy (80)	55.1 ± 0.9	63 (78.7)	NR	NR	NR	NR	NR
	Room air (77)	56.4 ± 0.8	61 (79.2)	NR	NR	NR	NR	NR
Wilson and Channer, 1997, UK [28]	Oxygen therapy (22)	64	NR	NR	2 (9.0)	NR	5 (22.7)	NR
	Room air (20)	65	NR	NR	2 (10.0)	NR	7 (35.0)	NR
Ukholkina *et al*. 2005, Russia [27]	Oxygen therapy (58)	55.6±1.33	26 (44.8)	39 (67.2)	NR	NR	39 (67.2)	NR
	Room air (79)	35.5±1.06	55 (69.6)	51 (64.5)	NR	NR	56 (70.8)	NR
Ranchord *et al*. 2012, New Zealand [26]	Oxygen therapy (68)	60.0±12.5	53 (77.9)	23 (33.8)	7 (10.3)	19 (27.9)	32 (47.1)	3 (4.4)
	Room air (68)	60.0±12.8	48 (70.6)	28 (41.2)	8 (11.8)	25 (36.8)	21 (30.9)	5 (7.4)
Stub *et al*. 2015, Australia [19]	Oxygen therapy (218)	63.0±11.9	174 (79.8)	130 (59.6)	37 (17.0)	121 (55.5)	141 (65.3)	28 (12.8)
	Room air (223)	62.6±13.0	174 (78.0)	123 (55.2)	41 (18.4)	118 (52.9)	165 (74.3)	29 (13.0)
Khoshnood *et al*. 2016, Sweden [24]	Oxygen therapy (46)	62.5±12.1	29 (63.0)	11 (24.0)	3 (6.5)	NR	15 (32.6)	NR
	Room air (49)	65.5±11.6	34 (69.3)	21 (43.0)	9 (18.4)	NR	16 (32.7)	NR

Hofmann *et al*. 2017, Sweden [22]	Oxygen therapy (1361 STEM)	66.6 ± 11.5	696 (71.2)	570 (41.9)	209 (15.4)	265 (19.5)	381 (28.0)	177 (13.0)
	Room air (1446 STEM)	66.9 ± 11.5	1067 (73.8)	630 (43.6)	238 (16.5)	287 (19.8)	418 (28.9)	190 (13.1)
Heidari *et al*. 2017, Iran [31]	Oxygen therapy (36)	58.6 ± 12.7	27 (67.5)	22 (56.4)	14 (35.9)	15 (38.2)	15 (38.5)	NR
	Room Air (36)	60.3 ± 11.4	18 (46.2)	22 (56.4)	18 (46.2)	17 (43.6)	13 (33.3)	NR

Supplementary Table 6.3, continued:

Trial, year and country	Study group, (n)	Medications at presentation				SpO2 at presentation	Culprit artery			Coronary Artery disease		
		ASA	BB	ACEi/ARB	Statin		LAD	LCX	RCA	SVD	Multi-vessel	LMCA
Rawles and Kenmure, 1976, UK [8]	Oxygen therapy (80)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Room air (77)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wilson and Channer, 1997, UK [28]	Oxygen therapy (22)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Room air (20)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ukholkina *et al*. 2005, Russia [27]	Oxygen therapy (58)	NR	NR	NR	NR	NR	32 (55.1)	0 (0.0)	26 (44.8)	NR	NR	NR
	Room air (79)	NR	NR	NR	NR	NR	35 (44.3)	0 (0.0)	44 (55.6)	NR	NR	NR

Ranchord *et al*. 2012, New Zealand [26]	Oxygen therapy (68)	11 (16.2)	7 (10.3)	13 (19.1)	17 (25.0)	NR	18 (26.5)	1 (1.5)	49 (72.0)	NR	NR	NR
	Room air (68)	11 (16.2)	7 (10.3)	18 (26.5)	14 (20.6)	NR	31 (45.6)	0 (0.0)	37 (54.1)	NR	NR	NR
Stub *et al*. 2015, Australia [19]	Oxygen therapy (218)	NR	NR	NR	NR	98.0 (97.0 - 99.0)	82 (38.0)	21 (9.7)	100 (46.3)	95 (43.8)	122 (56.2)	9 (4.1)
	Room air (223)	NR	NR	NR	NR	98.0 (97.0 - 99.0)	74 (33.8)	31 (14.2)	101 (46.1)	84 (37.7)	139 (62.3)	7 (3.1)
Khoshnood *et al*. 2016, Sweden [24]	Oxygen therapy (46)	6 (13.0)	0 (0.0)	10 (21.7)	2 (4.3)	98.0± 1.5	23 (50.0)	4 (8.7)	18 (39.1)	25 (54.3)	20 (43.4)	1 (2.2)
	Room air (49)	3 (6.1)	7 (14.3)	7 (14.3)	5 (10.2)	97.6± 1.7	23 (46.9)	3 (6.1)	20 (40.8)	29 (59.2)	17 (34.7)	3 (6.1)
Hofmann *et al*. 2017, Sweden [22]	Oxygen therapy (1361 STEMI)	241 (17.7)	315 (23.1)	386 (28.4)	259 (19.0)	96.6 ± 2.3	537 (39.4)	171 (12.6)	487 (35.8)	727 (53.4)	634 (46.6)	50 (3.7)
	Room air (1446 STEMI)	276 (19.1)	322 (22.3)	425 (29.4)	281 (19.4)	96.6 ± 2.3	541 (37.4)	177 (12.2)	545 (37.7)	732 (50.6)	714 (49.4)	63 (4.4)
Heidari *et al*. 2017, Iran [31]	Oxygen therapy (36)	NR	NR	NR	NR	98.2 ± 0.2	NR	NR	NR	NR	NR	NR
	Room Air (36)	NR	NR	NR	NR	98.1 ± 0.2	NR	NR	NR	NR	NR	NR

ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ASA: aspirin; DM: diabetes mellitus; HLP: hyperlipidemia; HTN: hypertension; LAD: left anterior

descending artery; LCX: left circumflex artery; LMCA: left main coronary artery; RCA: right coronary artery; SD: standard deviation; SpO2: peripheral oxygen saturation level; STEMI: ST-elevation myocardial infarction; SVD: single vessel disease; NR: not reported.

Supplementary Table 6.4. Outcomes in patients with confirmed AMI (analyzed group)

Trial, year and country	Study group, (n)	Hypoxemia	Opiate use as a proxy for pain	Cardiac enzymes			Infarct size	LVEF	In-hospital mortality	30-day mortality
				Troponin; µg/L	CK	CK-MB				
Rawles and Kenmure, 1976, UK [8]	Oxygen therapy (80)	NR	57 (71.2), 2.1±0.2	NR	NR	NR	NR	NR	9 (11.2)	NR
	Room air (77)	NR	52 (67.5), 2.0±0.2	NR	NR	NR	NR	NR	3 (3.9)	NR
Wilson and Channer, 1997, UK [28]	Oxygen therapy (22)	6 (27.0 %)	16 (72.7)	NR	NR	NR	NR	NR	0 ‡	NR
	Room air (20)	14 (70.0 %)	18 (90.0)	NR	NR	NR	NR	NR	0 ‡	NR
Ukholkina *et al.* 2005, Russia [27]	Oxygen therapy (58)	0 (0.0)	NR	NR	1469.3 ± 346.6	224.5 ± 49.7	2.49 ± 0.19, ECG	42.2 ± 2.3	1 (1.7)	NR
	Room air (79)	0 (0.0)	NR	NR	2430.4 ± 291.8	385.5 ± 36.2	3.10 ± 0.14, ECG	54.1 ± 1.8	0 (0.0)	NR
Ranchord *et al.*	Oxygen therapy (68)	NR	NR	2.2 ± 1.8 (62)	NR	NR	12.5 ± 10.9 %, MRI	55.9 ± 11.0	1 (1.5)	NR

2012, New Zealand [26]	Room air (68)	NR	NR	2.9 ± 2.8 (58)	NR	NR	13.1 ± 9.7 %, MRI	56.0 ± 10.6	2 (2.9)	NR
Stub *et al*. 2015, Australia [19]	Oxygen therapy (218)	NR	192 (89.3)	52.9 ± 52.3	1948 (1721-2205)	NR	13.1 ± 8.1 %; MRI	54.4 ± 9.5	4 (1.8)	NR
	Room air (223)	7.7 %	204 (91.5)	51.5 ± 62.5	1543 (1341-1776)	NR	10.4 ± 7.1 %; MRI	54.9 ± 10.0	10 (4.5)	NR
Khoshnood *et al*. 2016, Sweden [24]	Oxygen therapy (46)	NR	NR	3.63 ± 3.11	NR	NR	15.6 ± 10.4 %	47.0 ± 8.5 (46)§	4/85 (4.7)	5/85 (5.9)
	Room air (49)	NR	NR	3.34 ± 3.52	NR	NR	16.0 ± 11.0	49.2 ± 8.1 (41)§	3/75 (4.0)	4/75 (5.3)
Hofmann *et al*. 2017, Sweden [22]	Oxygen therapy (1361 STEMI)	44 (3.2)	NR	3.17 ± 3.67 (1149)	NR	NR	NR	<40%: 245 (18.0)	26 (1.9)	39 (2.9)
	Room air (1446 STEMI)	192 (13.3)	NR	3.38 ± 4.22 (1193)	NR	NR	NR	<40%: 273 (18.9)	29 (2.0)	38 (2.6)
Heidari *et al*. 2017, Iran [31]	Oxygen therapy (36)	NR	4.6 ± 2.3	1.84 ± 4.8	NR	NR	NR	49.5 ± 1.4	0 (0.0)	NR
	Room Air (36)	NR	6.4 ± 2.4	0.57 ± 1.2	NR	NR	NR	47.9 ± 1.5	1 (2.8)	NR

CK: creatine kinase; LVEF: left ventricular ejection fraction; NR: not reported. ‡ According to the Wilson *et al*, one patient died in hospital among those who were randomized, not clear in which study group. §LVEF data from SOCCER trial were collected from a SOCCER sub-study [23]

6.7.2 Summary of findings

Oxygen compared to Room Air for patients with Acute Myocardial Infarction

Patient or population: patients with Acute Myocardial Infarction

Intervention: Oxygen

Comparison: Room Air

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Room Air	**Risk with Oxygen**				
In-hospital mortality in patients with suspected AMI follow up: median 1 weeks	16 per 1,000	**19 per 1,000** (13 to 27)	**RR 1.15** (0.79 to 1.66)	7774 (7 RCTs)	⊕⊕⊕◯ MODERATE [a]	
In-hospital mortality in patients with confirmed AMI follow up: median 1 weeks	24 per 1,000	**22 per 1,000** (15 to 34)	**RR 0.94** (0.62 to 1.44)	3952 (7 RCTs)	⊕⊕⊕◯ MODERATE [b]	
30-day mortality in patients with suspected AMI follow up: median 1 months	21 per 1,000	**23 per 1,000** (17 to 31)	**RR 1.09** (0.80 to 1.50)	6789 (2 RCTs)	⊕⊕⊕⊕ HIGH	
30-day mortality in patients confirmed AMI follow up: median 1 months	28 per 1,000	**30 per 1,000** (20 to 46)	**RR 1.09** (0.72 to 1.66)	2967 (2 RCTs)	⊕⊕⊕◯ MODERATE [c]	
Hypoxemia in patients with suspected AMI follow up: median 1 weeks	80 per 1,000	**23 per 1,000** (14 to 38)	**RR 0.29** (0.17 to 0.47)	6679 (2 RCTs)	⊕⊕⊕◯ MODERATE	

6.7.2 Summary of findings

Oxygen compared to Room Air for patients with Acute Myocardial Infarction

Patient or population: patients with Acute Myocardial Infarction

Intervention: Oxygen

Comparison: Room Air

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Room Air	**Risk with Oxygen**				
Hypoxemia in patients with confirmed AMI follow up: median 1 weeks	141 per 1,000	**38 per 1,000** (25 to 58)	**RR 0.27** (0.18 to 0.41)	2849 (2 RCTs)	⊕⊕⊕◯ MODERATE [c]	
Infarct size based on CTnT levels in patients with suspected AMI follow up: median 1 weeks	The mean infarct size based on CTnT levels in patients with suspected AMI was **0**	The mean infarct size based on CTnT levels in patients with suspected AMI in the intervention group was 0.13 lower (0.66 lower to 0.4 higher)	-	5957 (5 RCTs)	⊕⊕◯◯ LOW [d]	
Infarct size based on CTnT levels in patients with confirmed AMI follow up: median 1 weeks	The mean infarct size based on CTnT levels in patients with confirmed AMI was **0**	The mean infarct size based on CTnT levels in patients with confirmed AMI in the intervention group was 0.06 lower (0.7 lower to 0.59 higher)	-	3070 (5 RCTs)	⊕◯◯◯ VERY LOW [e]	
Infarct size based on CMR (% of the LV mass) follow up: median 6 months	The mean infarct size based on CMR (% of the LV mass) was **0**	The mean infarct size based on CMR (% of the LV mass) in the intervention group was 0.91 higher (1.39 lower to 3.2 higher)	-	370 (3 RCTs)	⊕◯◯◯ VERY LOW [e,f]	

6.7.2 Summary of findings

Oxygen compared to Room Air for patients with Acute Myocardial Infarction

Patient or population: patients with Acute Myocardial Infarction

Intervention: Oxygen

Comparison: Room Air

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Room Air	**Risk with Oxygen**				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AMI: Acute myocardial infarction; **CI:** Confidence interval; **CMR:** Cardiac MRI; **CTn:** Cardiac Troponin; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Incomplete outcome data in 2 of the 7 included studies (Ranchord 2012, Ukholkina 2005), but will downgraded only one level, as these two studies carry only 5.9% of the weight of meta-analysis

b. Downgraded 2 levels: In 2 trials (Rawles 1976, Hofmann 2017), the evidence comes from a selected subgroup of patients which was not randomised for this comparison. Incomplete outcome data in 2 of the 7 included studies (Ranchord 2012, Ukholkina 2005).

c. The evidence comes from a selected subgroup of patients which was not randomised for this comparison

d. Incomplete outcome data

e. Incomplete outcome data. Three studies reported troponin T levels, but Stub *et al.* and Heidari *et al*. reported troponin I. Also the evidence comes from a selected subgroup of patients which was not randomised for this comparison

f. Level of imprecision was considered serious, because of the wide confidence interval which encompasses both benefit and clinically-significant risk

Chapter 7 : Summary and Future Perspective

Randomized clinical trials (RCT) are the gold standard for assessing causal effects in clinical research.[1] This thesis investigated some aspects of RCT design in the field of cardiovascular (CV) medicine. Although the cardiovascular (CV) field has been one of the most advanced in terms of implementing RCTs, there are many unanswered questions and the knowledge gap is widening every day with the advent of new technologies. Greater focus on more efficient design and delivery of CV trials will be required to fill the knowledge gaps and to present interventions that can be applied in broader populations of patients. We tested several avenues of opportunity for improving the implementation of CV RCTs by using appropriate outcomes of interest in different settings. We tested the change of CV RCTs over the past two decades in terms of their level of pragmatism using the PRagmatic Explanatory Continuum Index Summary-2 (PRECIS-2) tool. Then, as an example, we conducted the HiLo-HF pilot trial which was the first RCT to explore the effects of supplemental O_2 therapy in patients with acute heart failure (HF).[2] Furthermore, we evaluated the effects of supplemental oxygen therapy in patients with acute myocardial infarction, by performing a meta-analysis of RCTs in the literature that compared the effects of normobaric supplemental oxygen therapy with room air in patients with acute myocardial infarction (AMI).[3]

7.1 Trial design in cardiovascular medicine

7.1.1 BNP in Alberta

Biomarkers have a critical role in earlier phase RCTs and can help narrow down the long list of experimental interventions that could progress to later phase trials.[4] A province-wide access to natriuretic peptide (NP) testing was provided by Alberta Health Services (AHS) for all emergency departments (ED) in Alberta in 2012, providing the opportunity for their use in participant identification, intervention and as a study endpoint in RCTs. In Chapter 2, using the data from AHS databases, we identified the factors influencing the natriuretic peptide testing patterns, including comorbidities, geographic location, ED volume, and physician specialty.[5] Despite having a single-payer system and the universal availability of NP testing, there was substantial geographic variation in testing for NPs in Alberta EDs.[5] Patients with HF who were tested for NPs were more often admitted to hospital from ED, had lower short-term or long-term re-ED visit rates and shorter length of stay compared to their counterparts with HF but not tested

for NPs. The study had implications for regions which are planning to introduce, extend or standardize their NP testing program in the ED, both for research and clinical purposes.

7.1.2 Adjudication

In Chapter 3, using the data from PROACT-3 (Providing Rapid Out of Hospital Acute Cardiovascular Treatment 3) trial,[6] we explored the level of agreement between the emergency department and adjudication committee and compared the relationship between the site and adjudication committee diagnoses with subsequent clinical outcomes. Despite the substantial agreement between site and adjudication committee (88%), there was higher short-term and long-term mortality in patients where the site and adjudication committee disagreed on the final diagnosis compared to cases in which those two agreed.[7] The above-mentioned difference in mortality persisted even after adjustment for the baseline risk score, and other characteristics.

When looking at key clinical outcomes, the value of the adjudication committee seems to depend on the disease setting. In our study, in almost 90% of cases with emergency department/adjudication committee disagreement for the diagnosis of the acute coronary syndrome (ACS), the site had a different diagnosis, whilst the adjudication committee assigned the diagnosis of ACS. These cases with disagreement on the diagnosis of ACS were associated with 22.5% one-year mortality rate, which was markedly higher than the rate in cases of agreement (12.5%).[7] This observation potentially undermines the use of site diagnoses in trials that are focused on chest pain, acute coronary syndrome or myocardial infarction. The adjudication committee seems to add value by adjudicating outcomes in that setting.

On the other hand, heterogeneous disease states and presentations such as acute heart failure (AHF) may be suitable settings for using diagnoses assigned by the site. In our study, when the patient was labelled by the site as AHF but adjudication committee disagreed, the 1-year mortality rate (83.3%) was higher compared to when adjudication committee labelled the patient as AHF but site disagreed (40%), or compared to when both site and adjudication committee agreed on the diagnosis of AHF (26.9%).[7] The challenging presentations in AHF may be better judged by site clinicians who have access to the whole clinical tableau, compared to adjudicators who have access only to the documents provided to them by site investigators. As such, trial experts should consider the context of the intervention and outcome validity before deciding on a more complex strategy of adjudication and the trade-off around precision of the outcome estimate should there be ‘noise’ in any definition (adjudicated or not) endpoint.

7.1.3 Pragmatism in clinical trials

Pragmatic RCTs apply broad enrollment criteria, use clinically relevant comparators such as usual care, assess interventions within the framework of the routine clinical practice, test clinically-meaningful outcomes in a real-world setting with the intent of generating generalizable information that can inform decision-makers including patients, clinicians, and health policymakers.[8] They evaluate the effectiveness of an intervention in the way that is going to be ultimately applied in real practice, and have the potential for resolving some of the shortcomings of the traditional RCTs such as high costs, long study durations, and limited generalizability.

In Chapter 4, the aim was to investigate the level of pragmatism in CV RCTs and to study its change over the past 2 decades.[9] We observed an increase in the level of pragmatism in CV trials over 2 decades. The increase in pragmatism occurred mainly in the domains of eligibility, setting, intervention delivery, and primary endpoint.[9] Behavioral or health system interventions had a higher level of pragmatism than medicinal or device/procedural interventions. However, we did not find any difference in the level of pragmatism between RCTs with different sources (public/private) of funding. Knowing about the relatively-slow transformation of CV RCTs towards pragmatism over the past two decades, the trial characteristics, and their association with the level of pragmatism in CV RCTs may help us in designing more efficient RCTs in the future that can generate more relevant and generalizable, but at the same time, high-quality evidence to support our daily clinical decisions or healthcare policies.

7.2 Oxygen therapy in patients with acute CV diseases

7.2.1 O_2 therapy in Acute Heart Failure: HiLo-HF

Although supplemental oxygen therapy has been a usual part of the management of patients with acute CV diseases for over a century, its efficacy and safety is debated in patients with normal oxygen saturation levels.[10-12] In chapter 5, we provided the results of the HiLo-HF pilot trial, which was the first RCT to explore the effects of supplemental O_2 therapy in patients with AHF.[2] In this trial, titrating O_2 therapy to high or low SpO_2 targets did not result in changes in biomarkers, symptoms or clinical outcomes. As this was a preliminary study to explore the feasibility of conducting an RCT in this setting, it was not powered to detect small differences between the two groups. In the HiLo-HF trial we failed to achieve the target SpO_2 ranges using the manual SpO_2 titration method, which minimized the difference between treatment groups.

While the pilot demonstrated feasibility and success in recruitment, the protocol resulted in missing information for a variety of reasons, which showed a need for refinement in protocol and operation for future larger RCT.

7.2.2 O_2 therapy in Acute Myocardial Infarction: Meta-analysis

The aim of the study that is presented in Chapter 6 was to synthesize the results of the available RCTs in the literature that studied the normobaric supplemental oxygen therapy delivered with any device or at any dose as compared to room air in patients with AMI.[3] Our meta-analysis, pooling 7,998 patients with AMI from 8 RCTs, failed to find evidence supporting the use of oxygen therapy in normoxemic patients.[3] Based on the existing evidence, O_2 therapy seems to have no additional benefit in patients with normal baseline oxygen levels.[13] We additionally noted that there was no additional benefit of supplemental oxygen therapy on infarct size or in-hospital mortality with the caveat that the quality of evidence is at best moderate and a harmful effect cannot be ruled out.[3]

7.2.3 Oxygen therapy in other CV settings

Other studies have attempted to understand the effects of supplemental O_2 therapy in other CV clinical settings.[14-16] Although the only two small RCTs in patients with cardiac arrest showed no mortality difference between groups treated with high (FiO_2 = 1.0) versus conservative levels of O_2,[17, 18] large cohort studies and meta-analysis of observational studies suggested decreased survival after resuscitation from cardiac arrest with hyperoxia.[19, 20] Studies from the stroke setting demonstrated no benefit of liberal O_2 therapy in those patients.[21, 22] A total of 11 RCTs including 6,366 patients with acute stroke showed a non-significant increase in mortality at 3, 6, and 12 months with normobaric O_2 as compared to room air.[23] A study in the critical care setting reported an absolute risk reduction of 8.6% for the primary outcome of ICU mortality with conservative O_2 therapy (SpO_2 94-98%) as compared to usual care.[24] A meta-analysis of 25 RCTs (16,037 patients) compared the outcomes of liberal versus conservative O_2 treatment in acutely ill patients, and showed liberal oxygenation to increase mortality by roughly 20% in a dose-dependent way, without improving other patient-important outcomes such as disability or length of stay.[25]

7.3 Future Directions in exploring the effects of O_2 in acute CV diseases

With the results of the DETO2X-AMI trial[26] and the meta-analysis in chapter 6,[3] we expect the practice guidelines to recommend against the routine use of supplemental O_2 in patients with AMI and normal oxygen saturation levels at presentation. Nevertheless, the results are not definitive, and a large, pragmatic, non-inferiority RCT using composite endpoint consisted of all-cause mortality, cardiac arrest and cardiogenic shock and elevated troponin levels within 24-48 hours might be of interest for further exploring the effects of O_2 therapy in AMI setting.

Similarly, further RCTs with larger sample size are warranted to determine the comparative efficacy and safety of treatment with supplemental O_2 in patients with AHF. The HiLo-HF pilot study identified some room for improvement in the design and conduct of the RCT that need to be addressed in future RCTs. Large pragmatic RCTs with cluster-randomized or stepped-wedged cluster-randomized design might provide definitive evidence regarding the safety and efficacy of O_2 therapy in patients with AHF and normal oxygen saturation levels. Considering the cost and the ubiquitous use of O_2 therapy in hospitalized and ED patients,[27, 28] adding a cost-effectiveness analysis component to the future trial may provide the healthcare administrators and policymaker with much-needed evidence to inform their decisions.

The use of manual titration and reliance on the treating team to achieve target levels was one of the limitations and a source of non-adherence in the HiLo-HF pilot trial,[2] although it mimicked the real-world practice. A device approach using automated closed loop systems has the potential to solve that issue with near-constant adjustments and less variability of blood O_2 saturations.[29]

7.4 Future perspectives for CV RCTs

The adoption of novel RCT design elements such as pragmatic designs, can help to resolve some of the shortcomings of the traditional RCTs such as limited generalizability while maintaining the high standards of internal validity, etc. The broad availability and utilization of electronic health records, standardized recording through International Classification of Disease (ICD) codes, standardization of medical and procedural interventions within the scheme of routine clinical care are some of the factors that could help us move in that direction. No matter whether the pragmatism is a result of embedding intervention and data collection in routine clinical care

or using electronic health records for collecting follow-up data, it optimizes trials with reduced costs and more impactful results (i.e. with application in broader population of patients).

On the other hand, the discovery of new biomarkers with a strong correlation with the clinically relevant outcomes that capture the important impacts of the study intervention on those clinically relevant outcomes gives the opportunity to provide information about the treatment effect and potential subgroups of patients that can benefit the most from the intervention. Widespread availability of effective biomarkers can inform the design and implementation of RCTs that use biomarkers to identify eligible patients, as a part of the intervention (similar to the use of natriuretic peptides in the Guiding Evidence-Based Therapy Using Biomarker-Intensified Treatment in Heart Failure or GUIDE-IT trial as mentioned in Chapter 1), or as the primary endpoint and surrogate marker. Identifying suitable biomarkers through omics science and technological advances such as point of care testing, microsamples, or wearable trackers hold the promise of greater use of biomarkers in cardiovascular trials and cardiovascular medicine.[4]

Central endpoint committees (CEC) have become a routine part of CV trials. Avoiding the use of adjudication committees in non-indicated cases and limiting it to settings in which adjudication committee delivers additional benefit in terms of enhancing accuracy through systematic and independent evaluation of outcomes would simplify the design and conduct in many RCTs.

Identifying the research priorities for the patients, clinicians and the health care systems and addressing those through well-designed clinical trials or via other study designs when appropriate is important to guide funding agencies and health systems in the proper allocation of their limited research resources. Collaborative efforts among disease-related foundations, academia, federal agencies, industry and patient advocacy groups have been shown to be vital in the determination of those priorities and sometimes even in the effective implementation of trials. Besides collaborations among different sectors, involving stakeholders from different regions at the trial design phase and including sites from different countries during implementation will improve the generalizability of the trial results and should be encouraged.

The emerge of new communication and data collection technologies have tremendous implications for the design of future RCTs. Although there are few challenges that trialists might have to overcome when planning to incorporate new resources such as big data into their trial

design, the opportunities are prevailing. These technologies can also facilitate and boost the effective distribution of RCT findings to the patients, clinicians and policymakers. The change has already started, and we can expect to see their effect in the near future.

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