Chronic obstructive pulmonary disease in acute coronary syndromes

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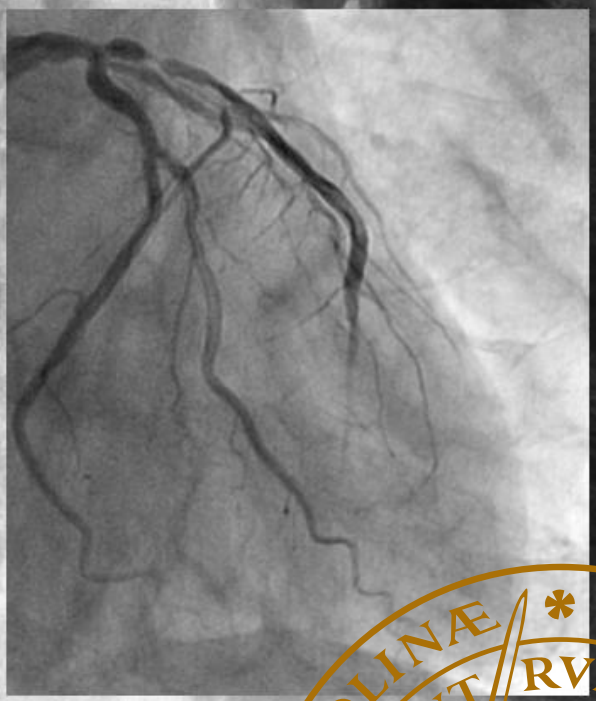

Chronic obstructive pulmonary disease in acute coronary syndromes

Pontus Andell

LUND
UNIVERSITY

DOCTORAL DISSERTATION

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Abstract

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The thesis includes four papers. The first paper characterized the ACS population with concomitant COPD and ascertained the impact of COPD on long-term mortality and cardiovascular morbidity in a large contemporary study population utilizing national registries. The second paper investigated the effect of beta-blocker treatment as secondary prevention on long-term mortality when prescribed at discharge in ACS patients with COPD, also with the use of national registries. The third paper was a post-hoc subgroup study from a randomized clinical trial that explored if the new and more potent antiplatelet agent ticagrelor was more beneficial than clopidogrel in ACS patients with COPD. Finally, the fourth paper investigated the effect of COPD on in-hospital complications and long-term mortality following coronary artery bypass grafting (CABG), in a nationwide concurrent ACS population with severe coronary artery disease, again utilizing national registries.

ACS patients with concomitant COPD were found to be a high-risk population, with a heavy burden of comorbidity and a doubled unadjusted overall mortality. At discharge, ACS patients with COPD were less often treated with guideline-recommended secondary prevention, especially beta-blockers. In this group, beta-blocker treatment at discharge was associated with lower long-term mortality. Ticagrelor reduced the risk of ischemic event in ACS patients with COPD, without an increase in overall major bleeding. ACS patients with COPD and severe coronary artery disease treated with CABG had higher long-term mortality and more in-hospital infections than patients without COPD.

In conclusion, improved guideline-recommended secondary prevention may improve outcome in ACS patients with COPD. Beta-blocker treatment should not be routinely withheld from ACS patients with COPD and the benefit-risk profile supports the use of ticagrelor. After CABG in ACS patients with COPD, preventive measures including careful monitoring of infection signs and prompt antibiotic treatment should be considered.

Key words: chronic obstructive pulmonary disease, acute coronary syndrome, myocardial infarction, epidemiology

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“Never memorize something that you can look up.”

Albert Einstein (1879-1955)

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To mom and dad

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List of papers

I. Andell P, Koul S, Martinsson A, Sundström J, Jernberg T, Smith JG, James S, Lindahl B, Erlinge D. Impact of chronic obstructive pulmonary disease on morbidity and mortality after myocardial infarction. Open Heart 2014;1(1):e000002.

II. Andell P, Erlinge D, Smith JG, Sundström J, Lindahl B, James S, Koul S. β-blocker use and mortality in COPD patients after myocardial infarction: a Swedish nationwide observational study. J Am Heart Assoc 2015;4:e001611

III. Andell P, James SK, Cannon CP, Cyr DD, Himmelmann A, Husted S, Keltai M, Koul S, Santoso A, Steg PG, Storey RF, Wallentin L, Erlinge D; on behalf of the PLATO Investigators. Ticagrelor Versus Clopidogrel in Patients With Acute Coronary Syndromes and Chronic Obstructive Pulmonary Disease: An Analysis From the Platelet Inhibition and Patient Outcomes (PLATO) Trial. J Am Heart Assoc 2015;4:e002490

IV. Andell P, Erlinge D, Koul S. Chronic obstructive pulmonary disease and outcomes in coronary artery bypass grafted treated patients. Manuscript.

In addition to the above papers, the author has published seven other articles in international peer-reviewed journals.

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The thesis includes four papers. The first paper characterized the ACS population with concomitant COPD and ascertained the impact of COPD on long-term mortality and cardiovascular morbidity in a large contemporary study population utilizing national registries. The second paper investigated the effect of beta-blocker treatment as secondary prevention on long-term mortality when prescribed at discharge in ACS patients with COPD, also with the use of national registries. The third paper was a post-hoc subgroup study from a randomized clinical trial that explored if the new and more potent antiplatelet agent ticagrelor was more beneficial than clopidogrel in ACS patients with COPD. Finally, the fourth paper investigated the effect of COPD on in-hospital complications and long-term mortality following coronary artery bypass grafting (CABG), in a nationwide concurrent ACS population with severe coronary artery disease, again utilizing national registries.

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Sammanfattning (in Swedish)

Kranskärlsjukdomar och kronisk obstruktiv lungsjukdom (KOL) utgör idag två av de vanligaste sjukdomarna orsakande död och lidande i världen. I denna avhandling undersöktes KOL i relation till hjärtinfarkt med hjälp av främst svenska kvalitetsregister. Olika aspekter av KOL-diagnosens påverkan på hjärtinfarkt-patienters karaktäristika, behandling och prognos utvärderades i fyra arbeten. Förutom svenska kvalitetsregister användes också studiematerialet från en randomiserad klinisk prövning för att undersöka en specifik behandling i förhållande till KOL. I studierna som använde kvalitetsregister var det främst det kardiovaskulära registret SWEDEHEART som bidrog med data. SWEDEHEART är ett nationsomfattande kvalitetsregister länkat till alla hjärtintensivvårds-avdelningar, center för kranskärlsintervention (PCI) samt thoraxkirurgiska kliniker i hela Sverige.

Det första arbetet tillämpade data från SWEDEHEART och studerade över 80000 hjärtinfarktpatienter inlagda för hjärtinfarkt mellan år 2005 och 2010. Först undersöktes prevalensen av KOL bland hjärtinfarktpatienterna, och den befanns vara 6%. Hjärtinfarktpatienter med samtidig KOL var äldre och hade mer samsjuklighet än hjärtinfarktpatienter utan KOL. Avseende utredning och behandling genomgick KOL-patienter med hjärtinfarkt i lägre utsträckning kranskärlsröntgen och PCI, och de behandlades i lägre omfattning med evidensbaserade sekundärpreventiva läkemedel vid utskrivning. Prognosen efter hjärtinfarkt var betydligt sämre för patienterna med samtidig KOL som hade en dubblerad överdödlighet, vilket dock visade sig till stor del bero på högre ålder och samsjuklighet. Studiens viktigaste fynd var att en viss underbehandling av KOL-patienter förekom, i synnerhet med beta-blockerare - en vanlig typ av hjärtmedicin efter hjärtinfarkt. Detta påverkade prognosen negativt och därför drogs slutsatsen att en mer evidensbaserad behandling enligt internationella riktlinjer möjligen kan förbättra prognosen.

Studie två följde upp fyndet från första arbetet i närmare detalj och undersökte om beta-blockerare var associerade med bättre prognos för hjärtinfarktpatienter med samtidig KOL. Beta-blockerare har historiskt sett undanhållits från KOL-patienter eftersom de tidigare ospecifika beta-blockerarna var förenade med biverkningar i luftvägarna, vilket inte längre anses vara fallet med de nyare hjärtspecifika beta-blockerarna. Med hjälp av SWEDEHEART jämfördes hjärtinfarktpatienter med

KOL som skrevs ut med beta-blockerare mot hjärtinfarktpatienter med KOL som inte skrevs ut med medicinen. Studien fann att beta-blockerare var associerade med bättre prognos och lägre dödlighet och konkluderade att KOL-patienter med hjärtinfarkt bör behandlas med beta-blockerare efter hjärtinfarkt och inte rutinmässigt undanhållas den.

I det tredje arbetet användes materialet från en stor randomiserad klinisk behandlingsprövning för att undersöka om den nya trombocythämmaren (blodförtunnande läkemedel som ges efter hjärtinfarkt) ticagrelor, som visat sig bättre än äldre preparat, även var av värde för hjärtinfarktpatienter med samtidig KOL. Läkemedlet är mer potent än äldre preparat i att förhindra framtida hjärtinfarkter och andra kardiovaskulära händelser, men det kan orsaka kortvarig subjektiv andnöd, en känd biverkan som kan leda till att KOL-patienter inte behandlas med preparatet, varför det var viktigt att studera detta närmre. Studien fann att ticagrelor hade en mycket god effekt i hjärtinfarktpopulationen med samtidig KOL genom en betydande riskminskning av framtida kardiovaskulära händelser som hjärtinfarkt samt hjärt- och kärlrelaterad död. Den allmänna blödningsrisken var inte förhöjd, och risken för andnöd associerad med läkemedlet var inte relativt högre än den som tidigare påvisats. Slutsatsen blev att ticagrelor hade en övervägande god klinisk nytta hos hjärtinfarktpatienter med KOL och att dessa patienter bör behandlas med läkemedlet efter hjärtinfarkt.

Det fjärde och avslutande arbetet studerade KOL i relation till kranskärlskirurgi, så kallad bypassoperation, ett ingrepp som likt PCI syftar till att återställa blodflödet i hjärtats kranskärl. Ingreppet är relativt omfattande och används idag mest efter hjärtinfarkter med avancerad kranskärlssjukdom som involverar flera kranskärl. I studien fann man att KOL påverkar prognosen negativt även efter bypasskirurgi, och att förekomsten av infektioner efter kirurgin var högre. Författarna konkluderar att läkare bör vara vaksamma på infektionstecken efter bypasskirurgi hos KOL-patienter, och tidigt sätta in rätt behandling om en infektion skulle uppkomma.

Abbreviations

ACS	Acute coronary syndrome
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
COPD	Chronic obstructive pulmonary disease
CI	Confidence interval
euroSCORE	European System for Cardiac Operative Risk Evaluation
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GOLD	Global Initiative for Obstructive Lung Disease
HR	Hazard ratio
ICD	International Classification of Disease
MI	Myocardial infarction
NPR	National Patient Registry
NSTEMI	Non-ST-elevation myocardial infarction
OR	Odds ratio
PLATO	PLATelet inhibition and Outcomes Trial
PCI	Percutaneous coronary intervention
STEMI	ST-elevation myocardial infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

Introduction

Historical perspective

Coronary artery disease

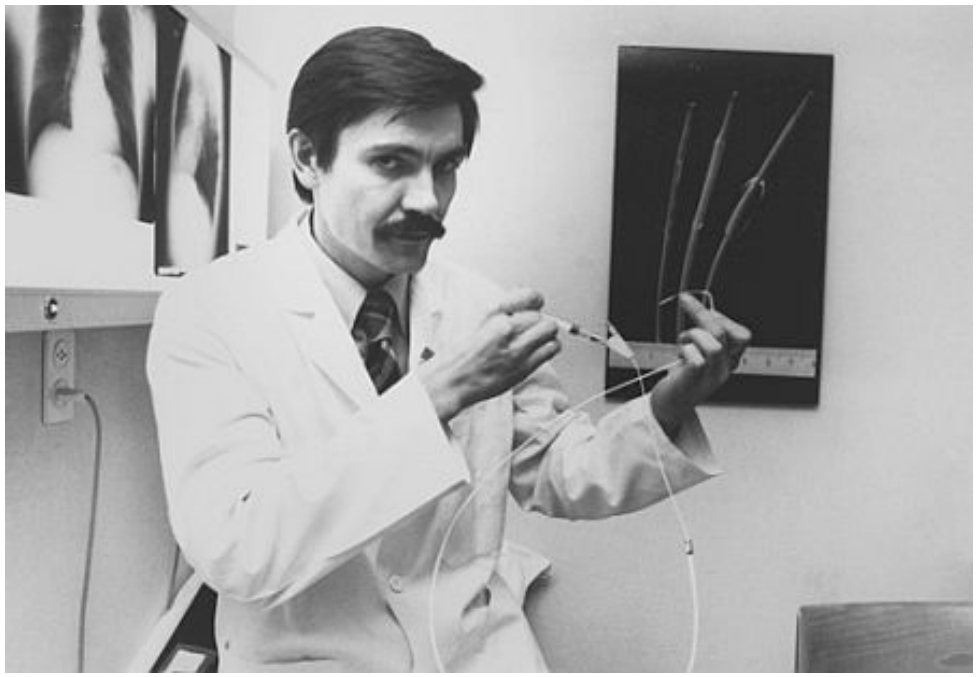
The main symptom of coronary artery disease (CAD), central chest pain termed angina pectoris, was first clinically described in the late 18th century.[1] Nearly a century later, pathologists identified what they called thrombotic occlusions and ossifications in the coronary arteries, though initially these findings were not coupled to the symptoms of CAD.[2] Animal studies in dogs in the late 19th century lead to the finding that occluded coronary arteries caused the ventricles of the heart to tremble, an early depiction of ventricular fibrillation, which ultimately lead to rapid death.[3,4] In the early 20th century, a number of cases of acute myocardial infarction (MI) were described and by 1919 electrocardiography was able to diagnose the disease.[5] Treatment options were scarce and initially the recommended therapy was plain bed rest, which remained the gold standard of MI treatment up until fifty years ago.[6] By this time, in-hospital mortality was close to 40%, and many victims likely succumbed to early malignant arrhythmias.[2]

In 1929, Werner Forssmann performed the first ever human heart catheterization and around thirty years later coronary arteriography was developed.[7,8] With these invasive diagnostic procedures, clinicians were able to adequately measure pump function and visualize the coronary anatomy, both of paramount importance to the development of the first revascularization strategy, coronary artery bypass grafting (CABG).[9,10] However, prior to CABG and long before the advent of percutaneous coronary intervention (PCI), the first major advance in the treatment of MI came in the early 1960s with the development of dedicated coronary intensive care units.[11] This provided new features such as continuous electrocardiographic monitoring with prompt options for chest compressions and external defibrillation if a malignant arrhythmia would strike. The in-hospital mortality for MI patients was halved with the addition of coronary intensive care units. In parallel, the prospective Framingham Heart Study lead to new insights into the development of CAD, and identified high blood pressure and elevated cholesterol levels as definite risk factors.[12] Later, evidence also pointed at smoking being another major risk factor

for the development of CAD.[13,14] The education of both clinicians and patients to treat and control risk factors was, and still remains, a fundamental strategy in battling CAD.

The next seminal discovery happened in 1976 when fibrinolysis with streptokinase for the first time opened up a previously occluded coronary vessel.[15] Soon thereafter, one of the first large modern cardiac trials, which randomized more than 10000 patients to either streptokinase or placebo, showed that fibrinolysis reduced mortality in patients with acute MI.[16] Another paramount and equally successful study showed that long-term treatment with aspirin, added on top of streptokinase, also reduced mortality.[17] The platelet has been a pharmacological target ever since, with many subsequent trials and agents replacing one another, including glycoprotein IIb/IIIa blockers and $P2Y_{12}$ inhibitors such as ticlopidine, clopidogrel, prasugrel and ticagrelor.[18–20] After aspirin, more drugs continued to be developed as researchers found new pharmacological targets in the dysregulated neuro-hormonal pathways signature to post-MI remodeling. Both angiotensin-converting-enzyme inhibitors and beta-blockers were shown to reduce mortality by limiting the detrimental remodeling processes of the heart following MI.[21–24] Meanwhile, the increasing body of evidence for the lipid hypothesis,[25] i.e. that high cholesterol levels lead to MI, directed researchers to target cholesterol and in particular low-density lipoprotein cholesterol. The results of cholesterol lowering were substantial and introduced the statin era.[26,27] In comparison to the 1960s, clinicians now had an arsenal of pharmacological agents for the treatment of MI, with a consequent large reduction in mortality.

In 1979 Andreas Grüntzig, hailed as the father of percutaneous invasive cardiology, invented the first PCI technique, balloon angioplasty, utilizing a catheter with a dilating balloon to open up a stenosed coronary vessel.[28,29] More than a decade later, randomized clinical trials showed it to be more effective than thrombolytic therapy and paved the way for the primary PCI era.[30,31] Since then, the technique has become more refined with the use of expandable stents, first by bare metal and later coated with anti-proliferative drugs, to combat the problem of restenosis.[32] Today, PCI is the main revascularization strategy in patients presenting with MI, and CABG is reserved for cases with more complex coronary artery disease.[33]



Andreas Grüntzig showcasing an early PCI catheter.

Chronic obstructive pulmonary disease

The clinical knowledge of chronic obstructive pulmonary disease (COPD) and its components of emphysema and chronic bronchitis, begun as early as in the late 17th century when Theophile Bonet found a number of cases in which the lungs were "turgid" from air, perhaps an early account of emphysematous lungs.[34,35] In 1814, Charles Badham coined the term "bronchitis", referring to chronic productive cough with yellow colorful sputum, and just seven years later René Laënnec, inventor of the stethoscope, described emphysema.[36,37] In these days smoking was rare, but it was understood that the disease could be caused by environmental factors.

In 1846, the spirometer was invented by John Hutchinson, still today the most important instrument in diagnosis and severity characterization of COPD.[38] The early versions of the spirometer only measured vital capacity, i.e. the maximum amount of air a person can expel from the lungs after a maximum inhalation, and it was not until 100 years later that measurement of airflow was added. In the mid 20th century, more sophisticated measurements became available with forced vital capacity (FVC), i.e. the volume changes of the lungs between a full inspiration and a forced maximal expiration, and forced expiratory volume in one second (FEV_1), i.e. the volume exhaled during the first second of a forced maximal expiration

starting from a full inspiration. Guidelines still use these spirometric measurements for diagnosis and severity characterization.[39,40] In 1962, the American Thoracic Society defined the clinical components of COPD, chronic bronchitis and emphysema, but by this time without known causes.[41] Just a few years later, by somewhat serendipitous events, Gross et al stumbled upon the pathophysiology of emphysema, when he introduced pancreatic extracts into the airways of guinea pigs.[42] He discovered that proteolytic damage by proteases caused emphysema, an important component in the inflammatory activity principal to COPD. Around 10 years later, Charles Fletcher identified that smoking accelerated the rate of pulmonary function decline and that quitting smoking halted it.[43]

Unfortunately, the treatment of COPD has not been quite the same success story compared to the treatment of CAD. Around 50 years ago, treatment options for COPD were mostly limited to antibiotics for pneumonias and combination agents containing ephedrine and theophylline and a sedative to deal with the side effects of these substances. Both oxygen therapy and exercise were deemed contraindicated.[35] Patients were initially saved from respiratory failure by being put in mechanical ventilators. A breakthrough was reached in the 1980s when, after a number of clinical trials, long-term oxygen therapy was shown to improve outcome in patients with severe COPD.[35,44,45] Around the same time, the use of bronchodilators and corticosteroids increased and the importance of smoking cessation became further apparent. In 2003, a randomized clinical trial showed lung volume reduction surgery to improve quality of life, albeit not mortality, a story shared by other promising treatment options for COPD.[46,47] Lung transplantation became another surgical treatment option, though extremely limited due to lack of donor organs.[48]

The important Lung Health study published in 1994 randomized almost 6000 heavy smokers with mild COPD to special smoking cessation interventions or ipratropium bromide, an inhaled bronchodilator, or standard care. While the bronchodilator only showed transient effects on pulmonary function, the aggressive smoking intervention program significantly reduced the rate of FEV_1 decline.[49] In a 14.5 years follow-up study, it was also shown that lung cancer was the most common cause of death in patients with COPD, followed by cardiovascular deaths, mainly due to CAD, providing the first evidence of the interplay between these disorders.[50]

Epidemiology

CAD and COPD are two of the most burdensome diseases globally. In the latest global burden of disease report by the World Health Organization in 2013, CAD, also known as ischemic heart disease, is the number one cause of disability-adjusted life years (the sum of years of healthy life lost to premature death and years lived with disability), with COPD trailing behind at rank six.[51]

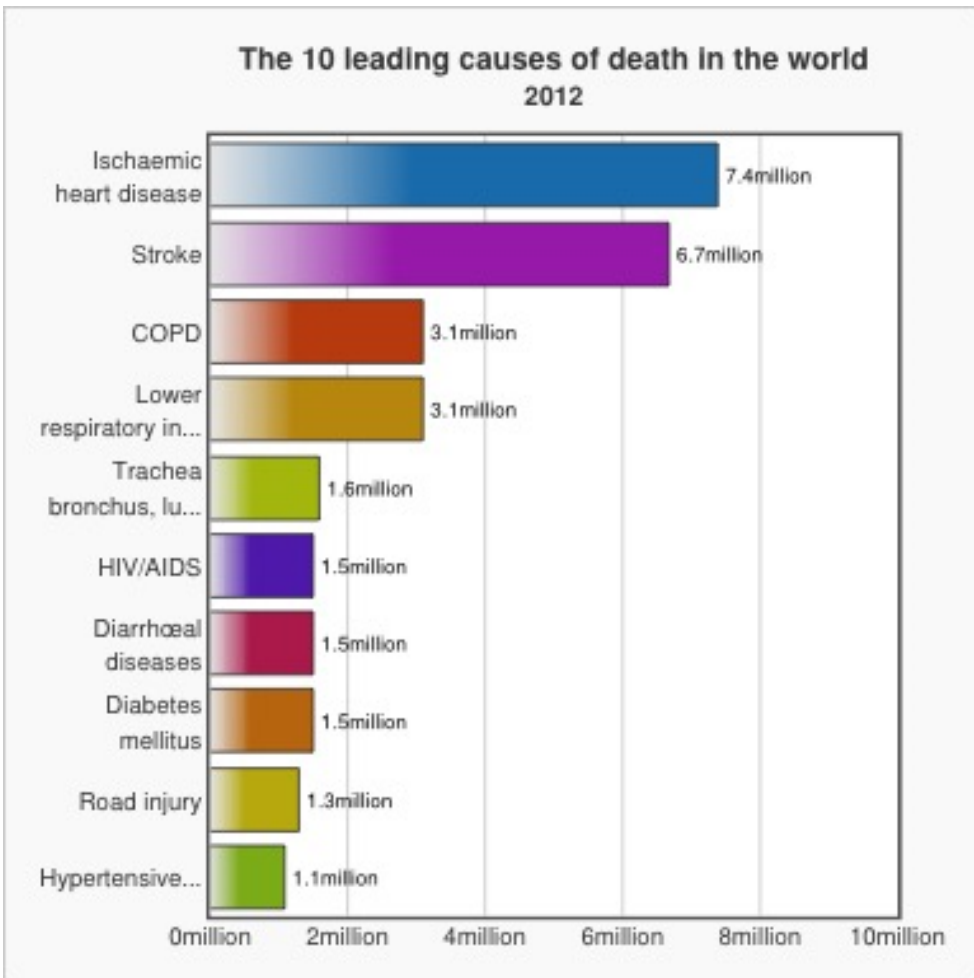


Figure 1.
Top ten leading causes of death in the world by 2012, according to the World Health Organization's Global Burden of Disease Study.

Coronary artery disease

Although there have been substantial improvements in both prevention and treatment of CAD today, it still remains the dominating cause of death in the world.[52] Globally, the age-standardized incidence of MI decreased in all age-groups between 1990 to 2010 from 223 to 195 per 100000 person-years in males and from 136 to 115 per 100000 person-years in females. In most high-income countries the incidence declined during this time, while the biggest increase was seen in Eastern Europe, where the highest incidence rates are found together with Central Asia and Russia.[53] With regard to type of MI, ST-elevation myocardial infarction (STEMI) incidence declined in the previous decades, whereas non-ST-elevation myocardial infarction (NSTEMI) incidence concomitantly increased.[54] Age-standardized case fatality in both STEMI and NSTEMI decreased substantially in the past decades, explained by improved primary prevention due to better risk factor control, more effective treatment options and improved secondary prevention.[55–57] Although age-standardized incidence and case fatality decreased, the global burden of CAD still increased between 1990 to 2010 attributable to population growth and increased life expectancy.[53,58] In Sweden, CAD is also the leading cause of death, despite a 49% decrease in years of life lost to premature death caused by CAD from 1990 to 2013. CAD ranks second in leading causes of disability-adjusted life years in Sweden.[59]

Chronic obstructive pulmonary disease

COPD is currently the third leading cause of death globally.[52] Like CAD, it generates significant healthcare costs and imposes great burdens on quality of life, especially in the later stages of the disease.[60,61] The epidemiology of COPD is less well known compared to CAD. The prevalence varies greatly depending on region, age groups and due to lack of consensus on diagnostic methods and definitions.[62] In a recent systematic literature review, the prevalence ranged from <1% in Japan to 37% in the US, illustrating the problem of dissimilar diagnostic criteria applied in heterogeneous studies and populations.[62] Spirometric prevalence estimates are generally higher than methods based on asking for symptoms, underscoring the silent subclinical nature of the disease in the early stages with subsequent underdiagnosing.[63–67] The prevalence of COPD has increased over time but may have stagnated in men in recent years, likely due to declining prevalence of smoking in men.[62,68] However, not only smokers are affected, as the prevalence of modest to severe COPD may be as high as 3-11% among never smokers.[69] Like in CAD, the age-standardized death rate of COPD has fallen between 1990 to 2010, but not as dramatically.[70] In Sweden, COPD prevalence is believed to be around 15% among individuals aged 40 or older, similar to comparable high-income countries.[71] The

mortality for COPD increases with disease severity but was doubled compared to non-COPD controls in a Swedish study.[72]

COPD in myocardial infarction

Cardiovascular disease is a very common and important comorbidity in COPD, accounting for around 30% of all deaths in this group.[47,73–77] Previously diagnosed COPD in patients presenting with MI has been estimated to around 10-17%,[78–81] although the true number is likely higher due to substantial underdiagnosis.[64–67] Reduced pulmonary function, irrespective of underlying cause, is associated with both all-cause and cardiovascular mortality as well as MI incidence.[82–84]

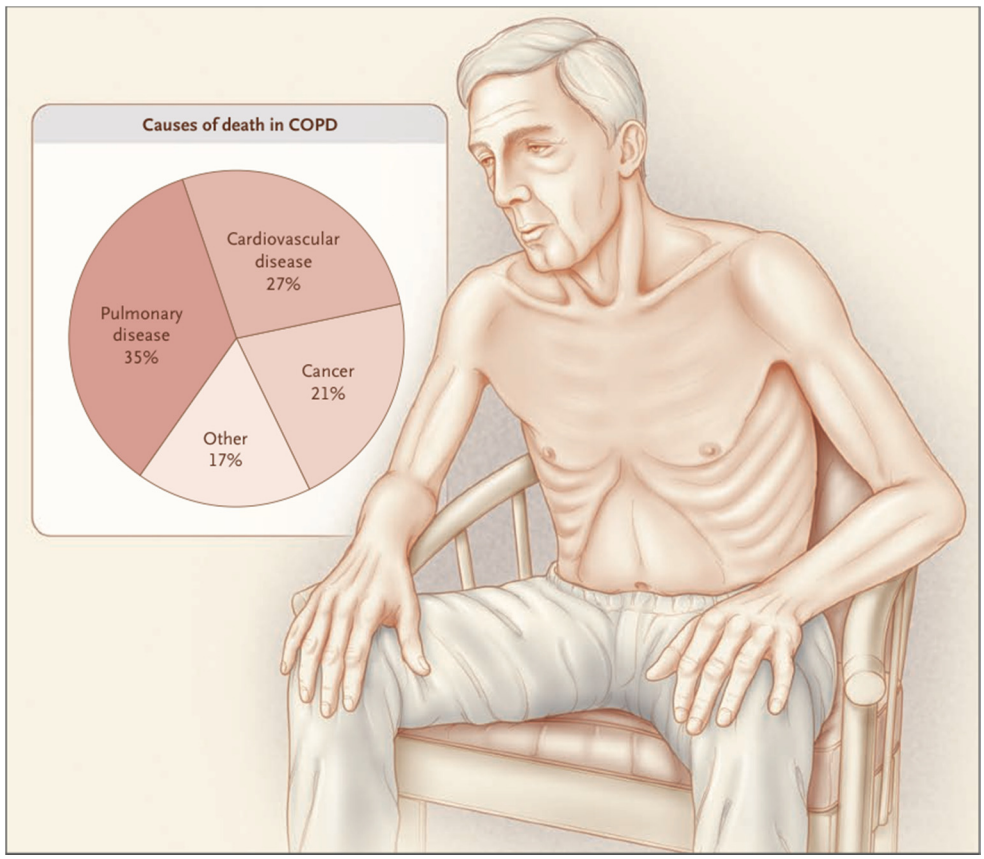


Figure 2.
Major causes of death in COPD. From adjudicated deaths in the Towards a Revolution in COPD Health (TORCH) trial. Reproduced with permission from the New England Journal of Medicine, Copyright Massachusetts Medical Society.

Studies looking into the impact of COPD on outcomes following MI report varying results depending on studied endpoints,[78–80,85,86] but the impact on mortality was recently investigated in a systematic review and meta-analysis, which concluded that there was only weak evidence that COPD influences in-hospital mortality (odds ratio 1.13, 95% CI 0.97-1.31) but strong evidence that long-term mortality is detrimentally affected (hazard ratio 1.26, 95% CI 1.13-1.40).[74] In terms of other outcomes, heart failure incidence after MI may also be increased.[78,79,85,87] However, dyspnea is a cardinal symptom of both COPD and heart failure, which could lead to misclassifications and possible overdiagnosis of heart failure. Despite numerous clues that COPD patients are a high-risk group in regard to MI, this population has arguably received less attention than other high-risk groups, such as patients with diabetes. The latter are often a pre-specified subgroup in large trials and the guidelines on MI management and treatment dedicate sections that detail how they should be specifically managed.[33,88–91]

Definitions

Coronary artery disease

Coronary artery disease comprises stable angina pectoris and the working diagnosis of acute coronary syndrome (ACS), the latter includes definite diagnoses of unstable angina pectoris, non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI).[92] This thesis focuses on ACS including both NSTEMI or STEMI. The guidelines of the 3rd universal MI definition state that for an acute MI to be diagnosed, the following criteria must be fulfilled: Detection of specific cardiac biomarkers with at least one additional criteria: ischemic chest pain, new significant electrocardiographic ST-segment–T wave changes or new left bundle branch block, other imaging evidence of loss of myocardial function, or identification of an intracoronary thrombus by angiography. Additional definitions for special cases and situations are found in the guidelines.[92] MIs are further divided into different types, type 1-5, where type 1 is the classical spontaneous myocardial infarction caused by the rupture, fissure, erosion or dissection of a vulnerable atherosclerotic plaque that results in an intraluminal thrombus with impaired or completely blocked blood flow. This thesis will only discuss type 1 MI.

Chronic obstructive pulmonary disease

The Global initiative for chronic Obstructive Lung Disease (GOLD) was formed in 1998 to promote education and help set universal standards for the definition, diagnosis and evidence-based treatment of COPD. In their latest guidelines, they state that a clinical diagnosis of COPD should be considered in patients with progressive dyspnea, characteristically worse with exercise, and chronic cough, often productive, and lastly a history of exposure to risk factors such as tobacco smoke or occupational dusts.[40] A family history also adds to the likelihood. However, for the diagnosis to be made, the presence of persistent airflow limitation must be objectively quantified with spirometry.[40] The spirometric criteria for airflow limitation is a quota of $FEV_1/FVC < 0.70$ after bronchodilators have been applied. Previously, the degree of reversibility caused by bronchodilation was also measured but this is no longer considered recommended, as it does not differentiate well enough between asthma and COPD, nor predict treatment response with corticosteroids or bronchodilators, thus not adding anything to the diagnosis.

The result of applying a fixed FEV_1/FVC ratio in the whole population is controversial, as it will lead to overdiagnosis in asymptomatic elderly.[93] To counter this difficulty, some clinicians argue for the application of a stricter diagnostic quota in subjects aged 65 and older, e.g. $FEV_1/FVC < 0.65$.[94] Spirometry is also used to characterize the severity of the disease, i.e. how advanced the airflow limitation is. $FEV_1 \geq 80\%$ (of expected) indicates mild COPD, 50-80% moderate, 30-50% severe and <30% very severe COPD.

Pathophysiology

Acute coronary syndrome

The most common mechanism underlying ACS is the gradual buildup and increasing severity of coronary artery atherosclerosis, ultimately culminating in the rupture of a vulnerable plaque.[95] The atherosclerotic processes leading up to this event are complex and multifactorial, driven by the interplay of lipids, lipoproteins and inflammation.[96,97] The first developments of lipid accumulation and formation of fatty streaks in the arterial intimal layer begin early in life.[98] Here, lipids aggregate and become modified by oxidation, a process that stimulates the innate and adaptive immune system, leading to induction of endothelial and smooth muscle cells to express adhesion molecules and chemo-attractants that attracts the migration of monocytes into the early atherosclerotic plaque.[99] The monocytes differentiate into macrophages that scavenge oxidized lipids and further develop into larger foam

cells that secrete additional cytokines and oxidative substances, perpetuating the atherosclerotic plaque development.[100,101] With time some atherosclerotic lesions develop into vulnerable plaques, composed of large inner necrotic cores consisting of lipids and debris, coated by a thin layer of endothelial cells and fibrous tissue in the case of a thin cap fibroatheroma.

The rupture of a thin cap fibroatheroma is the most common cause of ACS and occur in 60-80% of the cases.[102,103] The mechanisms influencing the rupture of a vulnerable plaque are not fully understood, but both local and systemic inflammation are believed to be key components. Matrix metalloproteases degrade connective tissue in the cap, making it thinner and more prone to rupture, while increasing systemic levels of circulating C-reactive protein have been associated with occurrence of cardiovascular events.[99,104,105] After a vulnerable plaque ruptures, cap collagen and the very thrombogenic lipid core become exposed to the blood and initiates platelet activation. Activated platelets release granules that in turn activates other nearby platelets. These express receptors that cross-link with fibrinogen and von Willebrand factor to bind other platelets in close formation, forming a platelet clot that subsequently activates the coagulation cascade completing the thrombus formation.[106,107] Depending on Virchow's triad: a) thrombogenicity of the exposed plaque material, b) local blood flow disturbances and c) systemic hypercoagulability, the magnitude of the outcome following the plaque rupture is determined, either leading to a clinical event in the form of an ACS, or passing by in silence with plaque healing.[99,108,109]

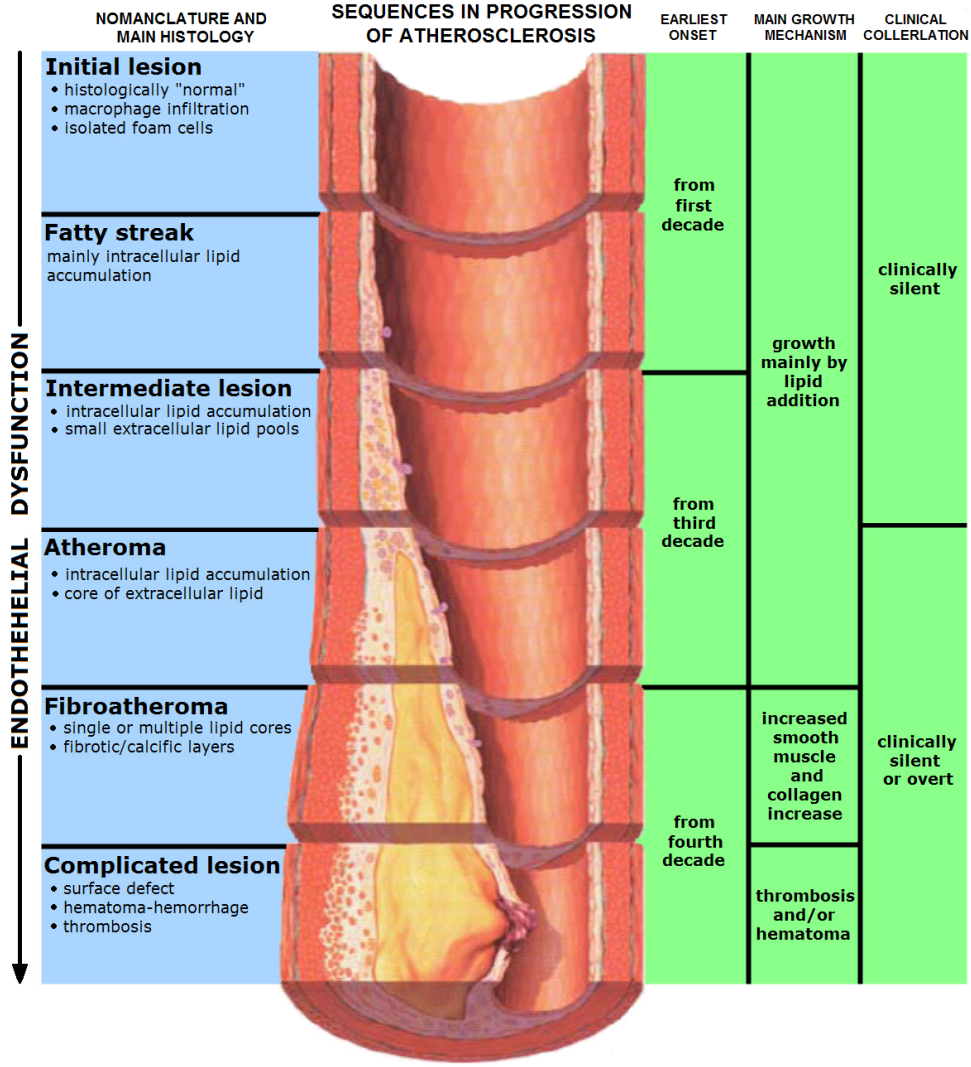


Figure 3.
Atherosclerotic plaque development during life.

If a plaque rupture leads to obstruction of a coronary artery and impairs blood flow, ischemia of the myocardium ensues. The time from ischemia to necrosis normally takes 20-30 minutes but highly depends on various other factors, including presence of collaterals, pre-conditioning, intermittent spontaneous revascularization and body temperature.[110,111] Final infarct size also depends on myocardium at risk, essentially a product of where and in which vessel the lesion occurs, as different loci in the coronary tree supply different amounts of myocardium.[112] More proximal

lesions, in particular of the left anterior descending coronary artery that supply a large proportion of the left ventricle, lead to larger infarctions with more detrimental sequelae, such as heart failure and ventricular arrhythmias.[113]

Chronic obstructive pulmonary disease

COPD is characterized by pathological changes in the large and small airways, alveoli and pulmonary vascularization.[114] These effects are caused by chronic inflammation that perpetuate repeated injury and defective repair as the disease progresses. Chronic inflammation results from exposure to chronic irritants, such as tobacco smoke, which remains the major cause of COPD worldwide.[115] Tobacco smoke contains more than a thousand hazardous compounds, some of the more famous include nicotine, heavy metals, carcinogens and oxidants.[116] Inhaled tobacco smoke cause a rapid inflammatory reaction that initially manifests as a breach in the barrier function of the epithelial and endothelial cells lining the alveoli, eliciting an inflammatory response that recruits circulating immune cells into the alveoli.[117]

The acute inflammatory response is transient, but if the exposure to the irritant is continuous, the inflammatory response causes extracellular matrix degradation and alveolar destruction. Matrix metalloproteases and elastases of the immune system degrade elastins, a highly elastic protein integral in allowing lung tissue to resume shape after stretching, causing emphysema. Elastases also play a key role in the autosomal dominant hereditary disorder of alpha1-antitrypsin-deficiency, another etiology of COPD.[118] Furthermore, pro-apoptotic agents in cigarette smoke induce apoptosis of alveolar cells, triggering autophagy by alveolar macrophages, normally there to clear bacteria from the alveolar surface.[115] As the disease progresses, the chronic inflammatory milieu continues to degrade the lung parenchyma, and the alveolar macrophages exhibit changes making them less effective at clearing microbes, leading to chronic colonization and an increased propensity to respiratory tract infections, a common cause of COPD exacerbations.[119]

With increasing emphysema, the total surface of the alveoli becomes much smaller, effectively decreasing the area normally responsible of gas exchange, leading to hypoxemia and hypercapnia central to COPD. Emphysematous destruction also leads to increased compliance in the lungs, prolonging and making lung emptying harder causing hyperinflation, clinically visible as the "barrel chest". In addition to emphysema, large and small airways undergo significant changes. Large airways become chronically inflamed and epithelial cells secrete excessive mucus that obstruct the small airways due to interference with mucociliar clearance. This leads to accumulation of inflammatory mucus in the lumen of small airways which can become blocked causing air trapping that affects the distribution of ventilation detrimentally, aggravating the poor gas exchange. Inflammation in the small

airways is believed to produce growth factors that influence lung fibroblasts to deposit connective tissue in the airway wall, causing fibrosis, remodeling and thickening of the small airway walls, increasing airway resistance and contributing to prolonged lung emptying.[114,115,120,121] With increasing severity of the disease, it becomes more and more debilitating and difficult to breath, eventually leading to hypercapnic coma and respiratory failure.[122]

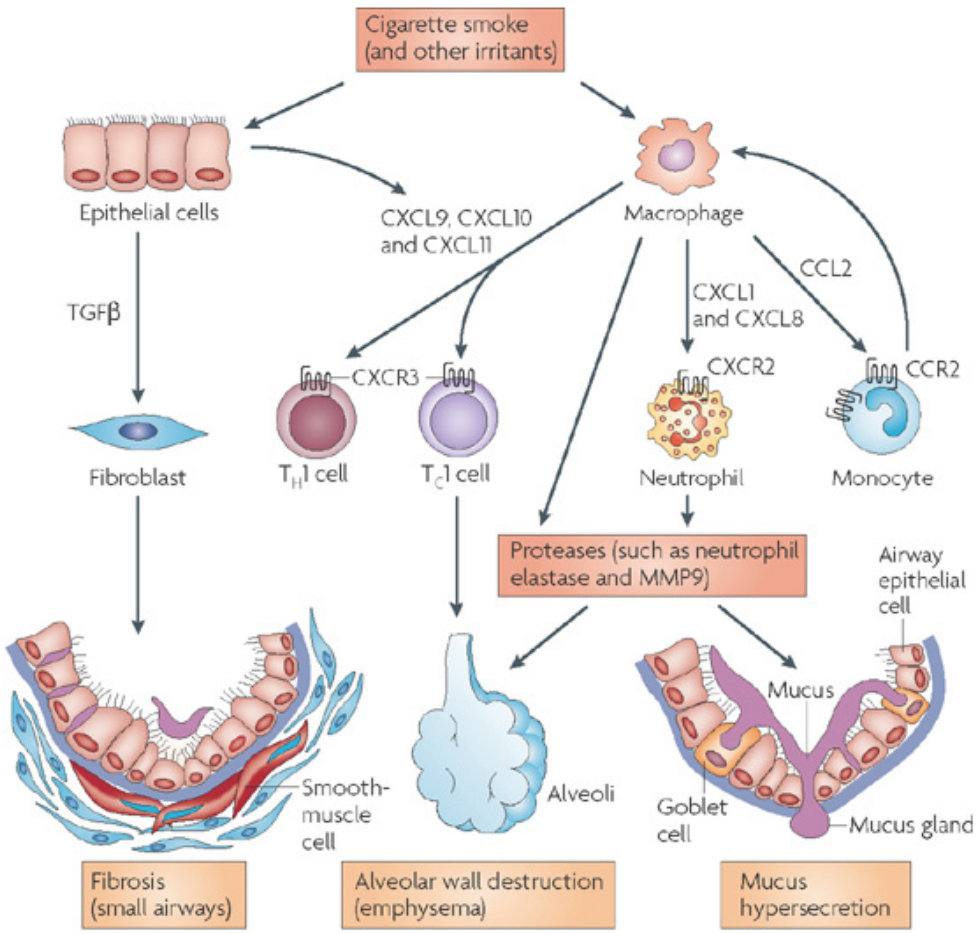


Figure 4.
Inhaled cigarette smoke and downstream inflammatory effects on the small airways, alveoli and large airways. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology. Immunology of asthma and chronic obstructive pulmonary disease, 2008.

Mechanisms connecting COPD and ACS

ACS and COPD have shared risk factors that may contribute substantially to the relationship between the diseases, the most important are smoking and high age.[50,123] Even passive smoking increases the risks of both ACS and COPD.[124] Components of the metabolic syndrome may also be overrepresented in COPD, including abdominal obesity, dyslipidemia, insulin resistance, hypertension and physical inactivity.[125–128]

Besides shared exposures, the most established hypothesis explaining the interaction of COPD and ACS is the inflammation model.[125,129] There is substantial evidence that inflammation plays a key role in the development of both COPD and CAD, and that inflammation increases proportionally to the severity of COPD.[129–135] A number of important inflammatory biomarkers, including C-reactive protein and tumor necrosis factor alpha are elevated in patient with COPD compared to healthy controls, and C-reactive protein has been shown to inversely correlate with pulmonary function, not explained by smoking.[133,136,137] The inflammation model hypothesize that the local airway inflammation in COPD "spills over" into the systemic circulation and the coronary arteries, promoting coronary plaque development, perhaps explaining why CAD is highly prevalent in COPD.[129,138]

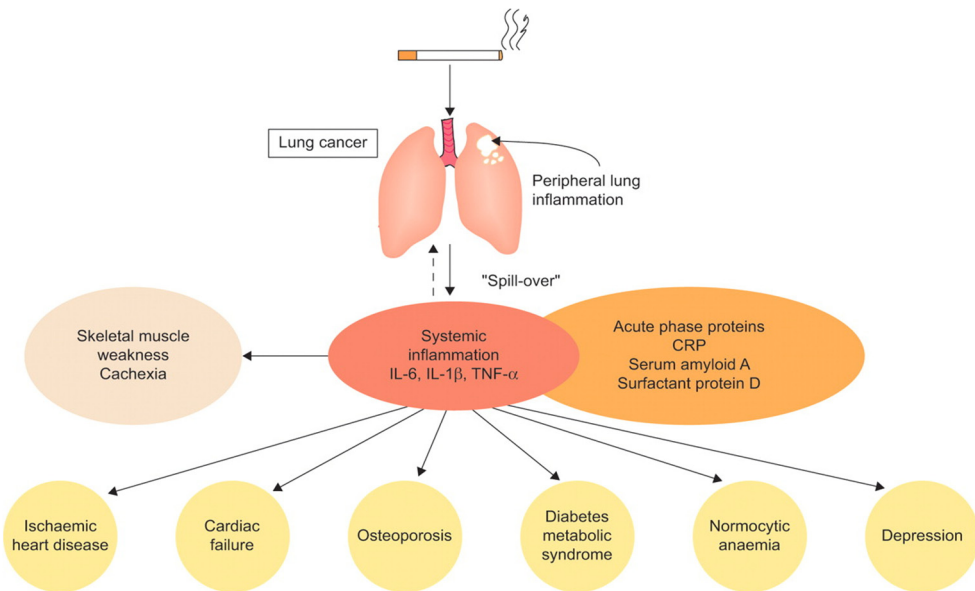


Figure 5.
Systemic effects and comorbidities of COPD. Reproduced with permission of the European Respiratory Society ©. European Respiratory Journal May 2009, 33 (5) 1165-1185; DOI: 10.1183/09031936.00128008.

Another potential contributor to the association between COPD and ACS is the dysregulation and overactivation of the sympathetic nervous system. COPD patients exhibit reduced heart rate variability, increased norepinephrine turnover and increased plasma levels of renin, all signs of increased sympathetic nervous system activity, also known to be harmful in CAD.[123,139,140] In addition, there may be similarities in genetic predispositions to develop CAD and COPD. For example, matrix metalloproteases are proteolytic enzymes influential in both COPD and CAD pathophysiology, and polymorphisms of these have been shown to be associated with both emphysema and MI, respectively.[141,142]

Certain treatment and management aspects in ACS

This thesis investigated treatment patterns in ACS relative to COPD status, it is therefore important to briefly introduce the reader to certain aspects of contemporary ACS treatment and management. For full comprehensive details, please refer to respective guidelines.[90,91]

Reperfusion therapy

In patients with a clinical presentation of STEMI, it is of utmost importance to restore coronary blood flow as soon as possible. Primary PCI, without prior fibrinolytic therapy, is the recommended reperfusion strategy in the setting of STEMI, provided it can be achieved rapidly, preferably within 90 minutes after the first medical contact.[91,143,144] There are a number of randomized clinical trials showing primary PCI to be more effective than fibrinolytic therapy.[145,146] If primary PCI cannot be achieved within two hours after first medical contact, fibrinolysis should be considered. If the coronary anatomy is unfavorable for PCI, emergency CABG may be indicated. More than half of STEMI patients present with significant multivessel disease on the angiogram. Although some recent studies have shown multivessel PCI to be beneficial,[147–149] the current version of the European Society of Cardiology's STEMI guidelines do not recommend multivessel PCI in the acute setting, provided the non-infarct related stenosis is <90% and the patient is not in cardiogenic shock. Instead, two approaches are mentioned, either a conservative approach that aims to revascularize non-infarct related arteries only if symptoms arise, or a staged revascularization approach with PCI or CABG in several days to weeks after the initial event.[91]

In patients presenting with NSTEMI, a coronary angiogram should be performed.[90] The timing and choice of reperfusion therapy are more complex and depend on a number of factors, including the patient's general condition, presence of

comorbidities, and the extent and severity of lesions identified by the angiogram. NSTEMI patients are a heterogeneous patient population with regard to both risk and prognosis, therefore it is important with risk stratification for the selection of the optimal management strategy. If mechanical reperfusion is indicated, the choice between ad hoc culprit lesion PCI, multivessel PCI, or CABG should be based on the clinical status and the disease severity, i.e. distribution and angiographic lesion characteristics, e.g. SYNTAX score, according to the local "Heart Team" protocol.[90] The SYNTAX score was developed in the *Synergy Between PCI With Taxus and Cardiac Surgery* (SYNTAX) *trial*, and it is based on 11 angiographic variables that consider lesion locations and characteristics.[150,151] A higher score indicates more complex coronary artery disease. Partly based on the SYNTAX trial, CABG is the preferred revascularization strategy in patients with three-vessel disease or left main coronary artery disease with a SYNTAX score of ≥32.

In patients with severe comorbidities such as dementia, severe chronic renal dysfunction, advanced cancer, high bleeding risk, or otherwise very frail and elderly, an invasive revascularization strategy might be deemed unfeasible and withheld as the perceived risk of the procedure outweighs the potential benefits. These patient categories are usually excluded from randomized clinical trials, therefore there is limited evidence on how to best treat this group.[90]

Dual anti-platelet therapy

Aspirin and $P2Y_{12}$ inhibitors are cornerstones in modern ACS treatment. Aspirin irreversibly inhibits cyclooxygenase activity and thereby suppresses pro-thrombotic thromboxane production. $P2Y_{12}$ inhibitors block adenosine diphosphate-stimulated activation of the glycoprotein IIb/IIIa receptor, thereby decreasing platelet degranulation and thromboxane production.[152] In STEMI, patients undergoing primary PCI should be treated with dual anti-platelet therapy, including aspirin and a $P2Y_{12}$ receptor inhibitor as early as possible before angiography.[91] In NSTEMI, both patients scheduled for an invasive strategy or a non-invasive strategy should also be treated with dual anti-platelet therapy, as soon as the diagnosis is confirmed.[90] The exact timings when dual anti-platelet therapy should commence, whether or not patients should be pretreated, remains a highly debated controversial topic in both STEMI and NSTEMI, without conclusive evidence.[153–155]

The recommended $P2Y_{12}$ receptor inhibitors are prasugrel or ticagrelor, as they have been proven to have a more rapid onset, greater potency and superior clinical benefit compared to the older agent clopidogrel.[20,156] In patients scheduled for PCI, prasugrel significantly decreased ischemic events but significantly increased major bleeding with a neutral effect on overall mortality compared to clopidogrel.[157] Prasugrel is contraindicated in patients with prior ischemic stroke or transient

ischemic attack and generally not recommended in patients aged ≥75 or in patients weighing <60kg due to lack of net clinical benefit in these patient categories. Ticagrelor reduced the primary composite endpoint of cardiovascular, death, non-fatal MI, or stroke in the *PLATelet inhibition and patient Outcomes* (PLATO) *trial*.[20] Cardiovascular mortality and overall mortality was also significantly decreased, respectively. There was no significant increase in PLATO-defined major bleeding, but there was a significant increase in major bleeding not related to CABG. There was also an increase in dyspnea following onset of treatment with ticagrelor, which has been characterized as mild to moderate in severity, of transient nature, and without any detrimental effects on cardiac or pulmonary function measurements.[158–160] If prasugrel or ticagrelor are contraindicated, clopidogrel should be administered instead. It is recommended to continue dual anti-platelet therapy for 12 months.

Beta-blockers

Beta-blockers inhibit the effect of circulating catecholamines on the myocardium, reducing myocardial oxygen demand by lowering the heart rate, blood pressure and contractility. Most of the studies that established the positive effect of beta-blockers in ACS pre-date the modern reperfusion era,[21,22,24] but they are still widely used today. In STEMI, the role of intravenous beta-blockers is controversial and current guidelines advice that patients should be stabilized before initiation, and the oral administration route is preferred.[91] Moreover, continued oral treatment with beta-blockers should be considered in all STEMI patients, with special emphasis on patients with heart failure or left ventricular dysfunction.

In NSTEMI, it is recommended to initiate beta-blocker treatment early in patients with ongoing ischemia and without contraindications.[90] The major contraindications for beta-blockers in the setting of ACS are bradycardia, atrioventricular block, hypotension and cardiogenic shock. Like in the STEMI guidelines, long-term therapy is primarily recommended in patients with reduced systolic function (left ventricular ejection ≤40%), where it has been proved to reduce mortality, recurrent MI and hospitalization for heart failure.[161–163] There is a lack of randomized clinical trials in the modern reperfusion era investigating the role of beta-blockers in post-MI patients without left ventricular dysfunction or heart failure, but a large observational propensity score-matched study did not find a lower risk of cardiovascular events after ACS in these patients.[164]

Aims

The general aim of this thesis was to describe and characterize MI/ACS patients with concomitant COPD, their management, and the impact of COPD on outcome. It also aimed to examine if there are any areas where potential improvements can be made in regard to the clinical care of this patient population. Three of the four articles have employed national registries in pursuit of these aims.

I. To characterize the MI population with concomitant COPD and to ascertain the impact of COPD on the long-term mortality and cardiovascular morbidity after MI in a contemporary nationwide MI population utilizing the SWEDEHEART registry.

II. To investigate the effect of beta-blockers as secondary prevention, currently often withheld from COPD patients, on long-term mortality when prescribed at discharge after MI in COPD patients, using the SWEDEHEART registry.

III. To investigate if the new and more potent P2Y12 inhibitor ticagrelor, proven to be superior to the older agent clopidogrel in broad ACS populations, is also beneficial in ACS patients with concomitant COPD. This is a post-hoc subgroup study of the large international PLATO trial.

IV. To investigate the effect of COPD on in-hospital complications and long-term mortality following CABG, in a nationwide concurrent ACS population presenting with severe coronary artery disease, again utilizing the SWEDEHEART registry.

Methods

This is a summary of the materials and methods used in the different papers. For more detailed information, please refer to each individual paper.

Patient populations

National healthcare registries

The SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) registry is the largest quality-of-care registry in Sweden. It started in 2009 when four nationwide cardiac registries were merged into one. The Register of Information and Knowledge about Swedish Heart Intensive-Care Admissions (RIKS-HIA), the longest running of the four since 1991, includes patients admitted to any coronary intensive care unit in Sweden. The Swedish Coronary Angiography & Angioplasty Registry (SCAAR) includes patients that undergo a procedure in any of the 29 cardiac catheterization labs in Sweden. The Swedish National Registry of Secondary Prevention (SEPHIA) includes patients under the age of 75 from the specialized cardiac outpatient care post-MI. Lastly, the Swedish Heart Surgery Registry includes patients undergoing any heart surgery procedure in one of the eight thoracic surgery centers in Sweden. Recently, the trans-aortic valve replacement registry and the registry for cardiogenetics have also been added to SWEDEHEART. Upon enrollment in SWEDEHEART, information on patient characteristics, including demographics, risk factors, comorbidities, presenting symptoms and previous medications are gathered. During the hospitalization many more variables are entered prospectively, such as angiographic findings, number of implanted stents, complications following surgery, type of MI, discharge medications, and much more. The primary aim of the SWEDEHEART registry is to support the continuous development of evidence-based cardiac care in Sweden, and to measure quality-of-care outcome parameters across the country in order to improve the cardiac health of the Swedish citizens. It has also increasingly become a platform for research of CAD.[165]

Sweden has several other important quality-of-care registries that have been used for this thesis. First, the National Cause of Death registry has been used to ascertain vital status and date of death or last date of follow-up. Second, the National Patient Registry[166] (NPR) was used to enrich data on comorbidities and determine COPD status. Like SWEDEHEART, the registry is nationwide and connected to all hospitals in Sweden and collects ICD (International Classification of Disease) diagnosis codes linked to all inpatient hospitalizations and specialized outpatient visits. Reporting to the NPR is mandatory and departmental reimbursements from the Swedish tax-financed healthcare system are wholly based on flat rates from the ICD diagnosis codes. In addition to comorbidities, the NPR was also used for cardiovascular endpoints in paper I, for reinfarction, new-onset heart failure, stroke and bleeding. The national drug dispensary registry[167] was also used to gather data on previously dispensed prescriptions of COPD medications in paper II and IV. Data from the components of SWEDEHEART and other national registries were merged into a single database when each of the studies were conducted, with the use of the personal identification number unique to each Swedish citizen. Anonymity was protected by replacing the personal identification number with a serial number. In Sweden, quality-of-care registries are parts of the continuing development of improved routine healthcare, written consent for patient inclusion in the registries is therefore not needed. Patients are informed of quality-of-care registries and have the right to opt out, although very few exercise this right. The ethics committee at Lund University approved the studies.

Study samples

As outlined in table 1, paper I and II included patients from SWEDEHEART if they were diagnosed with an acute MI, regardless of STEMI or NSTEMI and irrespective of reperfusion strategy. COPD status was ascertained using the NPR, as described above. Paper IV also included patients from SWEDEHEART, but only patients who presented with ACS and severe coronary artery disease, defined as three-vessel disease or left main coronary artery lesions, who underwent CABG within 30 days of the initial event. In paper IV, COPD status was ascertained using the NPR as described above and also with the use of the national drug dispensary registry, defining patients who collected a prescription of a COPD specific medication within the past six months as having COPD. Unfortunately, there was no access to information on pulmonary function tests underlying these diagnoses, as neither SWEDEHEART nor the NPR records it. However, a COPD diagnosis in the NPR has previously been validated by Inghammar et al where they found less than 10% misclassifications.[168]

Paper III did not utilize Swedish quality-of-care registries, instead it was a post-hoc subgroup analysis from the PLATO trial. Details about and results from the PLATO

trial have been published previously.[20,169] In brief, PLATO was an international randomized double-blind placebo-controlled trial investigating ticagrelor vs. clopidogrel on top of aspirin in patients presenting with ACS. COPD status was ascertained by the treating clinicians at time of inclusion.

Table 1.
Brief summary of study samples, sample sizes and purposes.

Paper	Study sample	Sample size	Study purpose
I	MI patients 2005 to 2010 From SWEDEHEART	81191	Characterize MI patients with COPD. Investigate the prognostic impact.
II	MI patients who survived hospitalization 2005 to 2010 From SWEDEHEART	62855	Investigate the effect of beta-blockers as secondary prevention on long-term mortality in MI patients with COPD.
III	ACS patients October 2006 to July 2008 From the PLATO trial	18624	Study the efficacy and safety of ticagrelor vs. clopidogrel in ACS patients with COPD.
IV	ACS patients with three-vessel disease or left main coronary artery stenosis undergoing CABG 2006 to 2014 From SWEDEHEART	6985	Characterize COPD patients undergoing CABG due to ACS. Investigate the prognostic impact.

Endpoints

In paper I patients were followed for up to one year after the initial event and the endpoints were all-cause mortality, reinfarction, new-onset stroke, new-onset bleeding and new-onset heart failure. In paper II patients were followed for the maximum available follow-up time (median follow-up time 2.8 years) and the endpoint was all-cause mortality. Paper III had one year of follow-up and several different endpoints, the primary efficacy endpoint was a composite of death from vascular causes, MI, or stroke and the primary safety endpoint was PLATO-defined major bleeding. In paper IV, the endpoints were 5-year mortality and in-hospital complications post-CABG, such as infections and prolonged ventilator time.

Medical interventions

Paper II

Paper II compared MI patients with COPD discharged with vs. without a beta-blocker. Although information was lacking on which specific beta-blocker and at what dose it was prescribed, the most often used agent in Sweden post-MI is metoprolol, generally starting one or two days after the event during hospitalization with initial doses of 25-50mg once daily with gradual uptitration. Information on whether patients stayed on treatment or if they discontinued it during follow-up was also not available.

Paper III

Paper III compared ticagrelor vs. clopidogrel in ACS patients with concomitant COPD. The study protocol for the main trial has previously been published.[169] Treatment with ticagrelor started with a 180mg loading dose followed by 90mg twice daily, or in the case of clopidogrel a loading dose of 300mg followed by 75mg once daily. Treatment started within 24 hours of the event. The median treatment duration was 9.1 months.

Statistical analyses

In baseline characteristics tables, continuous variables are expressed as means with standard deviation or medians with interquartile range. Categorical variables are expressed as counts and percentages. Differences in parametric continuous variables were assessed with Student's t-test. Differences in nonparametric continuous variables were assessed with the Mann-Whitney U test. Differences between categorical variables were assessed with Pearson's chi-squared test when the cell frequencies were sufficient, otherwise an exact test was used. Endpoint rates were calculated with the Kaplan-Meier estimator and significance testing between groups were assessed with the log-rank test. Unadjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were computed using univariable Cox proportional hazard models and adjusted HRs with 95% CI were computed using multivariable Cox proportional hazard models. Unadjusted odds ratios (ORs) with 95% CI were computed using univariable logistic regression and adjusted ORs with 95% CI were computed using multivariable logistic regression. In paper III and IV, continuous variables were assessed for linearity and linear splines were used to account for

nonlinear relationships when appropriate. In a sensitivity analysis in paper II, we calculated propensity scores with fixed effects logistic regression and after that adjusting for the propensity score entering it as a continuous variable in a multivariable Cox proportional hazards model. In paper III and paper IV, subgroup analyses with p-values for interactions were calculated. Outcome analyses were restricted to complete case only; no imputations were performed. Statistical analyses were performed in SPSS (version 20, IBM, Armonk, NY), SAS (version 9.2, SAS institute Inc., Cary, NC) or STATA (version 14.1, StataCorp, College Station, TX).

Results

Paper I

A total of 81191 MI patients were included in this study, of which 4867 (6.0%) had COPD. Patients with COPD were considerably older (mean age 75 vs. 70) than patients without COPD, and they had a heavy burden of comorbidity, including a threefold increase in heart failure as well as doubled renal failure, peripheral artery disease and cancer. Symptoms at presentation also differed, with COPD patients more often presenting with dyspnea (22.5% vs. 7.1%). Their hemodynamics were slightly more compromised as illustrated by a lower presenting blood pressure, higher heart rate and a higher prevalence of pulmonary edema (3.0% vs. 2.1%). The ECG more often showed atrial fibrillation or flutter and less often ST-elevations (26.7% vs. 35.5%).

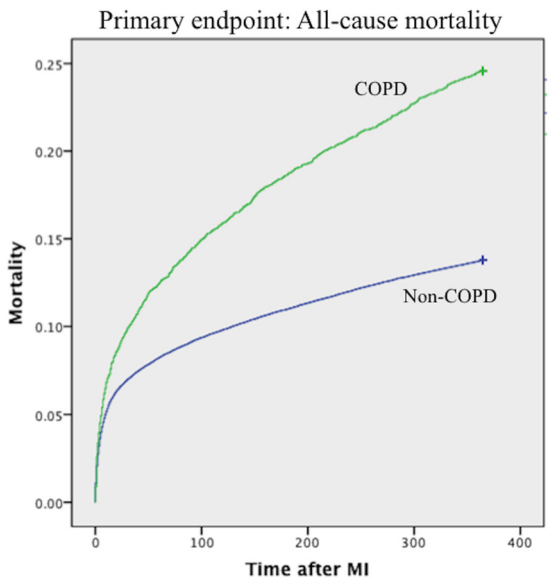


Figure 6.
Kaplan-Meier estimates of the primary endpoint of all-cause mortality at one year in MI patients in between 2005 to 2010 stratified by COPD status.

Furthermore, COPD patients less often underwent invasive investigation (55.4% vs. 72.5%) and subsequent PCI. At discharge, they more often had impaired LV function on echocardiographic assessment and were less often prescribed guideline-recommended secondary prevention, especially beta-blockers (77.7% vs. 86.1%), instead they were more often discharged with digoxin, diuretics and calcium channel blockers.

Table 2.
Clinical endpoints for COPD patients compared to non-COPD patients at one year.

	Crude HR (95% CI)	Adjusted† HR (95% CI)	Adjusted‡ HR (95% CI)
All-cause mortality	1.86 (1.76-1.98)***	1.32 (1.24-1.40)***	1.14 (1.07-1.21)***
Reinfarction	1.17 (1.09-1.26)***	1.00 (0.93-1.08)	0.99 (0.92-1.06)
New-onset stroke	1.14 (0.93-1.40)	0.90 (0.73-1.12)	0.89 (0.72-1.11)
New-onset bleeding	1.45 (1.25-1.69)***	1.13 (0.96-1.32)	1.12 (0.96-1.31)
New-onset heart failure	1.84 (1.70-1.99)***	1.46 (1.34-1.58)***	1.35 (1.24-1.47)***

† Adjustment for age, gender, smoking and comorbidity

‡ Adjustment for age, gender, smoking, comorbidity, treatment during hospitalization and discharge medications. *= p<0.05, **= p<0.01, ***= p<0.001

The crude one-year mortality was doubled in patients with COPD (Kaplan-Meier event rates: 24.6% vs 13.8%, HR 1.86, 95% CI 1.76-1.98), as shown in figure 6. After adjustment for confounders in two steps, the first accounting for age, sex, smoking status and comorbidities, the one-year mortality remained significantly higher in COPD patients (table 2), albeit lowered (HR 1.32, 95% CI 1.24-1.40). The second adjustment step accounted for the above covariates plus treatments during hospitalization and discharge medications. By adjusting for these differences in treatment patterns, potentially modifiable factors, the increased mortality was further lowered (HR 1.14, 95% CI 1.07-1.21). Out of the other endpoints, only new-onset heart failure was significantly higher after one year in patients with COPD (HR 1.35, 95% CI 1.24-1.47)

Paper II

Out of 62855 MI hospital survivors with complete data on beta-blocker treatment at discharge, 4858 (7.7%) COPD patients were identified. Out of these 4858 patients, 4086 (84.1%) were discharged with a beta-blocker while 772 (15.9%) were not. Patients with COPD were more often discharged without beta-blockers (15.9% vs. 9.6%). Those with COPD not receiving beta-blocker treatment at discharge were older and more comorbid, including a higher prevalence of previous stroke and heart failure, but less often had hypertension. They were also less often on beta-blocker treatment prior to the event (14.0% vs. 40.3%). Additionally, they less often presented with STEMI (17.1% vs. 25.4%) and underwent angiography to a lesser extent (42.0% vs. 62.3%). Likewise, these patients were also more often discharged without an echocardiographic assessment during hospitalization (48.7% vs. 30.9%) and guideline-recommended secondary prevention.

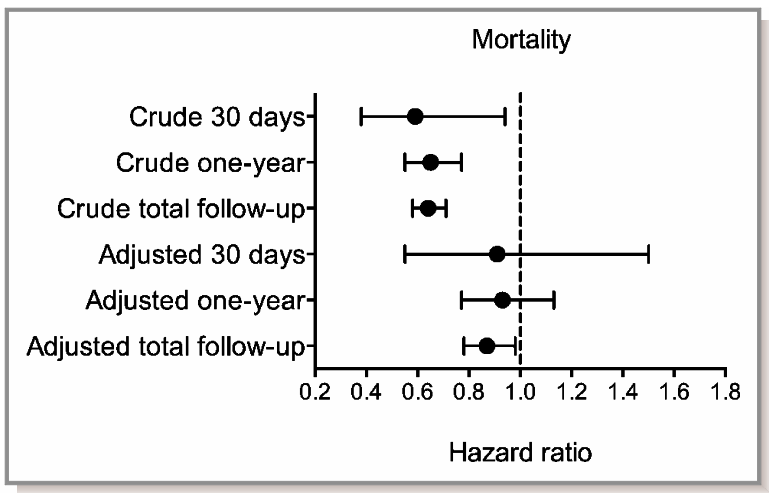


Figure 7.
Forest plot showing HRs and CIs (Cox proportional hazards models) for MI patients with COPD discharged with beta-blocker treatment compared to MI patients with COPD not discharged with beta-blocker treatment. Total follow-up time was up to 7.2 years. Adjusted analyses accounted for age, sex, smoking status, comorbidities, in-hospital characteristics, medications at presentation and discharge.

For MI patients with COPD discharged with a beta-blocker, the crude all-cause mortality was lower at 30 days, one year and during the total follow-up time of up to 7.2 years (HR 0.64, 95% CI 0.58-0.71) (figure 7). After adjustment for known confounders, the mortality was still lower in this group but the difference was attenuated (HR 0.87, 95% CI 0.78-0.98, p=0.017). In the other predefined time intervals, the HRs were similar although with overlapping confidence intervals.

Several sensitivity analyses were conducted. First, the effect of beta-blocker treatment at discharge was tested in the whole MI hospital survivor population (n=62855), which yielded similar results (HR 0.87, 95% CI 0.83-0.91) as in the subset with COPD. Second, a 30-day landmark analysis, starting the time of follow-up 30 days after the initial event, showed similar results as in the primary analysis. Third, a propensity score was calculated with confounders believed to influence the clinician's decision to treat or not to treat with beta-blockers. This propensity score was entered into a multivariable Cox proportional hazards model as a continuous variable, resulting in a slightly lower HR for COPD patients discharged with a beta-blocker (HR 0.84, 95% CI 0.75-0.94).

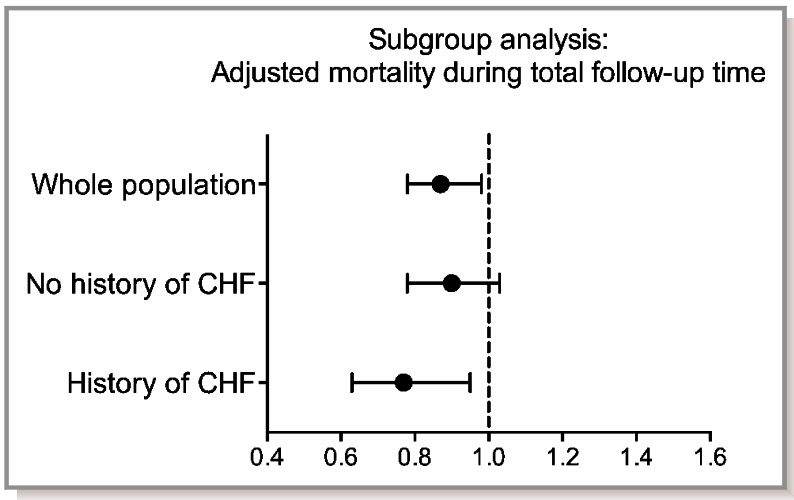


Figure 8.
Forest plot showing HRs and CIs (Cox proportional hazards models) for MI patients with COPD discharged with beta-blocker treatment compared to MI patients with COPD not discharged with beta-blocker treatment in patients with or without a history of congestive heart failure.

Subgroup analyses were performed in patients with or without a history of heart failure, shown in figure 8. MI Patients with COPD plus a history of heart failure discharged with a beta-blocker had a lower HR (0.77, 95% CI 0.63-0.95) than patients without a history of heart failure (HR 0.90, 95% CI 0.78-1.03), indicating a slightly more beneficial effect in patients with concurrent heart failure.

Paper III

In 18624 patients enrolled in the randomized PLATO trial, COPD was identified in 1085 subjects (5.8%). COPD patients were older (median age 67 vs. 62) and more often active smokers (45.3% vs. 35.3%), They often had multiple cardiovascular risk factors and comorbidities, including a history of heart failure (14.0% vs. 5.1%) and coronary artery disease (40.6% vs. 26.7%). In addition, COPD patients had worse renal function (median creatinine clearance 73.3 vs. 80.7), were less often treated with beta-blockers (62.0% vs. 70.4%), and more often treated with diuretics. They were less frequently invasively investigated and fewer COPD patients were diagnosed with STEMI (32.2% vs. 41.0%).

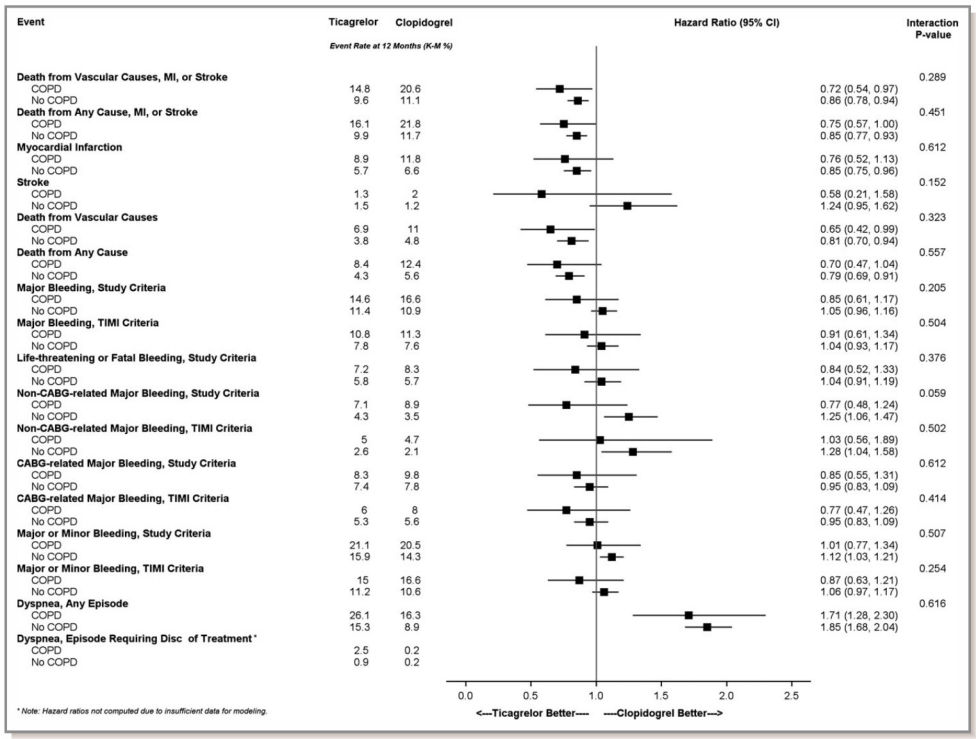


Figure 9.
Forest plot of efficacy and safety endpoints at 12 months.

Absolute rates of both ischemic and bleeding events were higher in patients with COPD (figure 9). All-cause mortality was doubled (10.4% vs. 4.9%). The univariable, age- adjusted, and multivariable HRs for the primary composite endpoint of cardiovascular death, non-fatal MI, or stroke for COPD patients vs. non-

COPD patients were 1.75 (95% CI: 1.50 to 2.04), 1.53 (95% CI: 1.31 to 1.79), and 1.31 (95% CI: 1.09 to 1.57), respectively.

Ticagrelor significantly reduced the primary endpoint, both in patients with and without COPD (figure 10). The relative reduction in the rate of the primary endpoint with ticagrelor was similar between COPD and non-COPD patients and consistent with the main trial findings, but the absolute reduction was substantially greater in patients with COPD (5.8% vs. 1.5%). There were no significant treatment interactions. Overall major bleeding was not increased with ticagrelor (figure 11), irrespective of PLATO definition or Thrombolysis In Myocardial Infarction (TIMI)-defined major bleeding. In line with main trial, there was an increase in non-CABG-related major bleeding in non-COPD patients, but in COPD patients ticagrelor and clopidogrel showed similar rates.

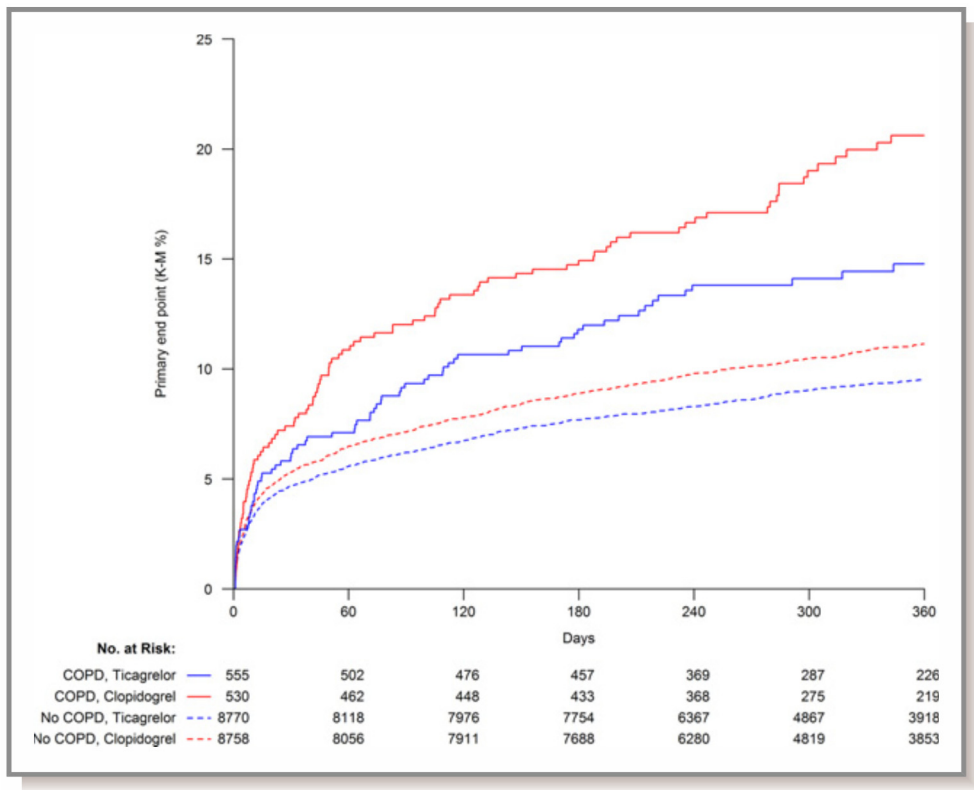


Figure 10.
Kaplan–Meier estimates of the time to first adjudicated occurrence of the primary efficacy endpoint (a composite of death from vascular causes, myocardial infarction, or stroke).

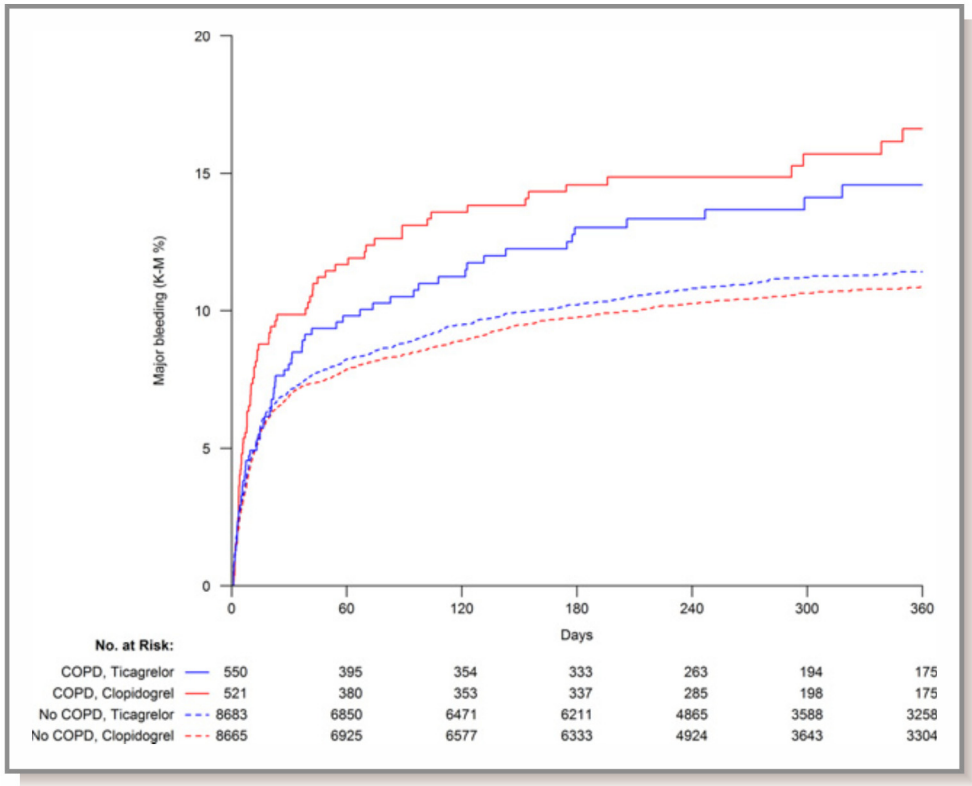


Figure 11.
Kaplan–Meier estimates of the time to first adjudicated occurrence of the primary safety endpoint of a PLATO-defined major bleeding event.

Ticagrelor significantly increased the dyspnea incidence in both COPD and non-COPD patients (Figure 9). The absolute dyspnea event rates were higher in COPD patients, but the ticagrelor-associated relative risks were similar (HR for COPD 1.71 vs. HR for non-COPD 1.85) and the p-value for interaction was not significant.

Paper IV

Out of 6985 patients who presented with ACS and three-vessel disease or left main coronary artery stenosis and underwent CABG, 556 cases (8.0%) had COPD at baseline. Patients with COPD were older (median age 71 vs. 69), less often male, more often current smokers, and to a higher extent burdened with several comorbidities, including heart failure (12.9% vs. 6.2%), previous MI (27.9% vs. 22.1%) and peripheral artery disease (12.4% vs. 4.6%). PCI preceding CABG was

less common in the COPD group (11.3% vs. 15.0%). Patients with COPD less often had a normal LV function on an echocardiogram during the hospitalization (52.3% vs. 59.0%) and they more often showed clinical signs of heart failure (32.2% vs. 22.5%). Their stay in the coronary care unit was generally longer (median 10 days vs. 8). At discharge, they were less often treated with beta-blockers and statins. COPD patients had a doubled operative risk (median logistic euroSCORE [European System for Cardiac Operative Risk Evaluation] 8% vs. 4%).

Table 3.
Associations between age, sex, comorbidities and CABG surgery

Characteristic	Odds ratio (95% CI)
COPD	1.04 (0.94-1.17)
Age spline 1	1.04 (1.03-1.05)
Age spline 2	0.90 (0.89-0.91)
Female sex	0.86 (0.80-0.92)
Current smoker	0.88 (0.82-0.95)
Diabetes	1.13 (1.06-1.21)
Hypertension	1.07 (1.00-1.14)
Heart failure	0.78 (0.69-0.88)
Previous MI	1.18 (1.08-1.28)
Previous stroke	0.97 (0.88-1.07)
Previous PCI	0.52 (0.47-0.59)
CKD stage ≥III	1.22 (1.12-1.32)
Peripheral artery disease	1.14 (0.99-1.31)
Cancer within 2 years	0.66 (0.54-0.83)

COPD was not an independent predictor of being ruled out of surgery (table 3). Increasing age, female sex, current smoking, heart failure, previous PCI and cancer within 2 years were independent predictors of being ruled out of surgery in favor of PCI. Younger age, diabetes, hypertension, previous MI and renal disease were independent predictors of undergoing CABG.

The primary endpoint of 5-year mortality (figure 12) was significantly higher in patients with COPD (unadjusted event rates: 27.2% vs. 14.5%, log-rank p-value <0.001). After adjustment for age, sex and comorbidities, mortality following CABG remained significantly higher in COPD patients (HR 1.52, 95% CI 1.25-1.86). In-hospital complications of infection in need of antibiotic treatment and pneumonia following surgery were also significantly more common in COPD (multivariable OR 1.48, 95% CI 1.07-2.04 and multivariable OR 2.21, 95% CI 1.39-3.52, respectively). Several other in-hospital outcomes were numerically higher in COPD patients.

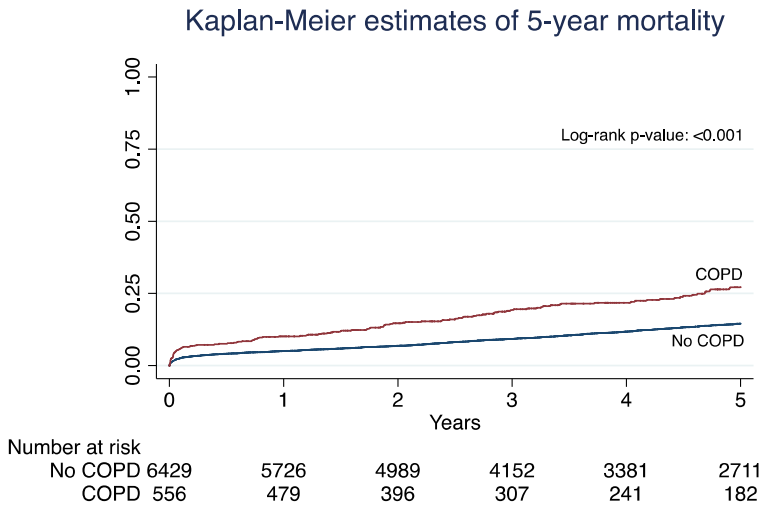


Figure 12.
Cumulative Kaplan-Meier estimates of 5-year mortality in ACS patients with severe CAD undergoing CABG, stratified by COPD status.

Discussion

The COPD phenotype in ACS

All papers included in this thesis highlight COPD patients as a particularly high-risk population in ACS. There seem to be several underlying reasons for this, with many complicating aspects in regard to presentation, diagnosis, treatment patterns that consequently affect long-term outcomes detrimentally.

Presentation

Paper I found patients with COPD to be distinctively different from patients without COPD at MI presentation. From the thorough information collected in the SWEDEHEART registry, there were a number of factors that stood out and highlighted the complexity of identified cases. COPD patients were considerably older than non-COPD patients, averaging a total of five years older at presentation. This was a somewhat paradoxical finding since a lot of evidence point toward COPD being an important risk factor for cardiovascular disease,[73,86,170] and if that would be the case it would be expected that COPD patients present with ACS at a younger age than non-COPD patients. However, COPD often stays undiagnosed for a long time after disease onset, especially in early stages before major symptoms arise.[64,66,67] The definition and identification of COPD in paper I, II and IV was via ICD diagnosis codes from the NPR, which is only linked to hospitalizations in the inpatient and specialized outpatient care but not to primary care practices. Thus, it is likely that the true prevalence of COPD in MI patients is much higher than around 6-8% found in our studies,[77] and that identified cases from the NPR reflect a more advanced COPD in need of hospitalizations, naturally taking longer time to develop and perhaps explaining why COPD patients in our studies were much older at baseline. The validation study of COPD in the NPR supports this explanation since the majority of cases identified had suffered from acute or chronic episodes of respiratory failure.[168] COPD patients identified from the NPR also had doubled prevalence of previous MI, and had undergone more CABG and PCI procedures, indicating that many ischemic events likely preceded the COPD diagnosis.

There were relatively more females in the COPD population than in the non-COPD population, somewhat surprising since the prevalence of COPD is believed to be higher in men, although COPD prevalence and hospitalizations are rising in women.[171] Furthermore, the burden of comorbidity was large in COPD patients, with a threefold increase in heart failure and renal dysfunction, 50% more previous stroke, doubled peripheral artery disease, cancer and previous bleedings, although this may in part be explained by age differences at presentation. Other observational studies confirm the high presence of comorbidities in COPD,[78,172,173] and this is in line with COPD nowadays increasingly considered a systemic disease with various organ systems affected.[75,174] Despite the burden of previous ischemic events and a threefold increase of heart failure, COPD patients were less often treated with beta-blockers or renin-angiotensin-aldosterone system blockade at admission, hinting at undertreatment of important comorbidities before baseline. In regard to presenting symptoms, COPD patients less often presented with central chest pain and more frequently with dyspnea compared to non-COPD patients, also found in other studies[78,79]. This could represent diagnostic difficulties leading to time delays, especially in the presence of major concomitant comorbidities, but we did not observe any clinically relevant differences in time delays in our study, regardless of applied metric, and other studies report conflicting findings.[78,80] In accord with other studies, NSTEMI was relatively more common than STEMI in COPD patients than in the whole MI population, perhaps pertaining to higher age at presentation and the burden of comorbidities.[55,79,80]

Management

In our and others' studies, COPD patients underwent less invasive investigation and subsequent reperfusion therapy with PCI.[78–80,85] There are a number of possible explanations for this, one being that COPD patients more often presented with NSTEMI, a more disparate diagnosis than STEMI, ranging from mild and transient symptoms with only a small elevation in biomarkers to very symptomatic and severe multivessel coronary artery disease, the former not always results in an angiographic investigation. In addition, patients with COPD had substantial comorbidities and were much older, likely reflecting a frailer patient category in where the risk-benefit considerations probably ruled out patients due to high procedure-associated risk and poor general outcome, overshadowing the potential benefits of the invasive procedure. We did not investigate whether COPD was an independent determinant of not undergoing an invasive investigation, or if this was mainly explained by higher age and a greater burden of comorbidity. In patients who underwent invasive investigation, the angiographic findings differed only slightly, with numerically fewer single vessel disease in COPD. Likewise, a study of COPD in STEMI patients did not find multivessel disease more common in COPD.[173]

Complications did not differ between the groups, but CPAP use during hospitalization was more common in COPD perhaps both due to the higher prevalence of heart failure and the COPD in itself. At discharge, there was more evidence pointing toward a higher heart failure prevalence in COPD, who more often had echocardiography-ascertained left ventricular dysfunction. The most perplexing finding in relation to different management approaches and treatment patterns in patients with COPD was that despite the MI diagnosis and presence of major comorbidities, guideline-recommended secondary prevention was less often prescribed to these patients, across the whole spectrum of agents but with the largest differences seen in beta-blockers and surprisingly statins. The latter are believed to have pluripotent anti-inflammatory effects besides lowering low-density-lipoprotein, which theoretically would be ideal for COPD, and several observational studies have shown positive effects in patients with COPD, ranging from decreasing exacerbation rates to lowering mortality.[175,176] Unfortunately, these promising results were not replicated in a recent large randomized study investigating the effect of statins on COPD exacerbations or disease progression, leading to a current disbelief in statins for COPD.[177,178]

Impact of COPD on outcome

We found a substantially higher long-term mortality in COPD patients following MI. At one year, it was nearly doubled compared to non-COPD patients in relative rates, and as high as 25% in absolute rates. Considering the huge differences in patient characteristics between the groups, this was not all that surprising. After we adjusted for differences in known confounders in a step-wise manner, we found that age and comorbidities explain a large part of the increased mortality in COPD following MI. Other studies including a systematic review report similar effect magnitudes of COPD on mortality after MI.[74] Arguably the most interesting finding in paper I was that additional adjustment for differences in treatment during hospitalization and discharge medications further decreased the higher risk associated with COPD, perhaps indicating that modifiable factors, such as treating COPD patients with guideline-recommended secondary prevention, may improve outcome.

In regard to other outcomes studied in paper I, we found no associations between COPD and reinfarctions, new-onset stroke or bleeding, but we found new-onset heart failure to be higher in COPD patients post-MI. Other studies have reported similar findings, and in an analysis from the *Valsartan in Acute Myocardial Infarction Trial* COPD was an independent predictor of long-term mortality and heart failure hospitalizations.[79,87] Looking at the prevalence of heart failure in the COPD population, there seems to be a link between the diseases, but both the endpoint of new-onset heart failure and previous heart failure were defined by

diagnosis codes, and we know that COPD and heart failure share similar symptoms in dyspnea and exercise intolerance, meaning that some of the heart failure diagnoses may have been COPD exacerbations and vice versa. However, we also found echocardiography-verified worse left ventricular functions in patients with COPD following MI, and they were treated to a lesser degree with secondary prevention that preserve left ventricular function, which can also explain an increase in incident heart failure. If so, it may be an important contributor to the higher mortality associated with COPD post-MI.

Secondary prevention

Beta-blockers

Following the results from paper I, that beta-blockers more often were withheld in COPD patients, paper II specifically investigated oral beta-blocker treatment at discharge in patients with COPD after MI and found it to be associated with lower long-term all-cause mortality in patients with COPD, even after multivariable adjustments. Historically, COPD patients have been undertreated with beta-blockers (figure 13) due to fear of adverse pulmonary effects, including bronchospasm.[179,180] The newer cardio-selective family of beta-blockers have been studied extensively in terms of effects on pulmonary function, and meta-analyses found them to be safe in COPD and of potential outcome benefit.[181–183] Previous observational studies have investigated beta-blockers in COPD and found surprisingly good results,[184,185] but few have directly looked into them in regard to secondary prevention after MI. In our study of MI hospital survivors, 15.9% of COPD patients were not discharged with a beta-blocker, a low number compared to other countries, such as the UK where undertreatment appears to be more severe.[186,187] In our study, patients who did not receive beta-blocker treatment at discharge were in general two years older and slightly more comorbid, including a higher prevalence of heart failure, a perplexing finding since it is one of the indications for beta-blockers treatment. Whether these patients had unmeasured contraindications or if it reflected true undertreatment remains speculative.

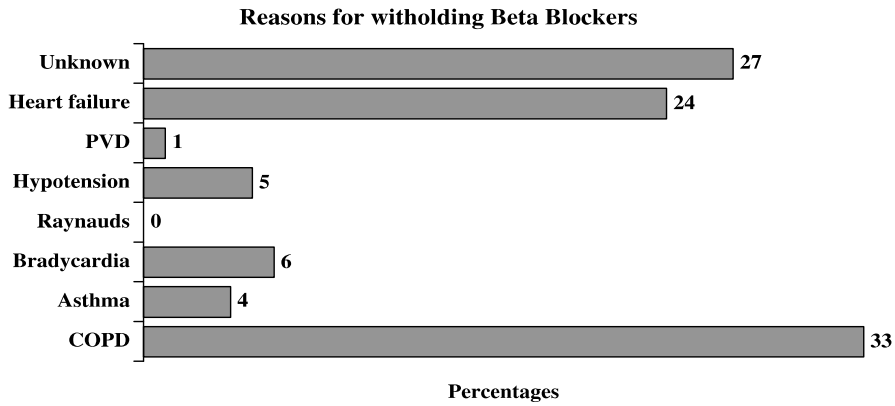


Figure 13.
In a retrospective study by Egred et al from the UK, 211 of 457 (46%) ACS patients were not treated with a beta-blocker. Major reasons for withholding these are illustrated by bars in percentages. Reprinted with permission from Egred et al, Under-use of beta-blockers in patients with ischaemic heart disease and concomitant chronic obstructive pulmonary disease. QJM 2005;98(7):493–7 by permission of Oxford University Press.

In a study from the UK by Quint and colleagues,[187] they demonstrated a remarkable decrease in mortality in MI patients with COPD who were discharged with a beta-blocker with a significant hazard ratio of 0.64. We also found a beneficial effect but with a more modest effect estimate, a significant hazard ratio of 0.87. In our study, the beneficial effect of beta-blockers was numerically increased in patients with a history of heart failure, a setting where beta-blockers have a very established benefit,[188] arguably strengthening the validity of our findings. All in all, current scarce evidence on the subject of secondary prevention with beta-blocker treatment following MI in COPD favors treatment and it needs to be reiterated that COPD is not a general contraindication to cardio-selective beta-blockers.

Ticagrelor

In paper III, we found ticagrelor to have a strong beneficial effect in patients with COPD, and the most important finding was that ticagrelor, compared to clopidogrel, significantly reduced the primary efficacy endpoint consisting of death from vascular causes, MI, and stroke without increasing the rate of overall major bleeding. In the COPD subset, the absolute risk reduction by ticagrelor vs. clopidogrel amounted to 5.8%, which was nearly four times greater than in non-COPD patients. Even though it was a post-hoc analysis, the results are promising and in line with previous data from the PLATO trial, that high-risk groups seem to get the most benefit from ticagrelor. Previous prespecified substudies from PLATO

have shown ticagrelor to be superior to clopidogrel in many different high-risk populations, including patients with diabetes, impaired renal function, and in the elderly.[88,189,190]

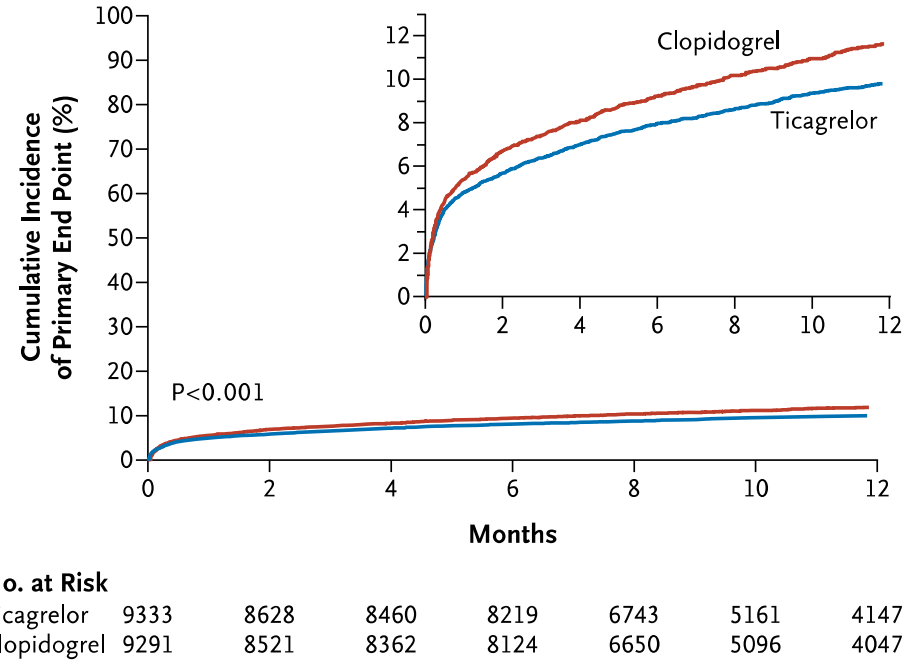


Figure 14.
Cumulative Kaplan-Meier estimates of the primary composite endpoint - cardiovascular death, myocardial infarction, or stroke at 12 months - in the main PLATO trial. Compared to clopidogrel, ticagrelor reduced the relative risk by 16% and the absolute risk by 1.9% in the total population. Reproduced with permission from the New England Journal of Medicine, Copyright Massachusetts Medical Society.

With regard to dyspnea, a relatively common side effect associated with ticagrelor, we found no differential increase in COPD, a reassuring finding since clinicians may have been reluctant to prescribe ticagrelor in COPD because of this side effect. When the PLATO trial first was published, there was an accompanying editorial in the New England Journal of Medicine that discouraged the use of ticagrelor in patients with obstructive lung disease, and the European Medical Agency emphasizes caution when prescribing ticagrelor to patients with a history of COPD, owing to a potential increase in the absolute risk of dyspnea.[20,191] Since then, ticagrelor-associated dyspnea has been thoroughly studied and found to have no effect on cardiac or pulmonary function and most often be mild to modest in severity and transient, often occurring just the first few days after initiation.[158–160] With that

said, some patients do find it intolerable and need to change $P2Y_{12}$ inhibitor. A recent paper on the management of ticagrelor-related dyspnea is now available.[192]

The PLATO study was a randomized clinical trial and therefor the patient inclusion was different from real-world patients, as illustrated by a much younger age at baseline than in our studies from the SWEDEHEART registry. However, the associated risks with COPD were similar in the PLATO study, pointing at a doubled crude absolute mortality rate, similar to what we found in paper I, and also illustrating the heavy burden of comorbidity and undertreatment with beta-blockers.

Our finding, that there was a substantial net clinical benefit with ticagrelor in COPD, should incline clinicians to test ticagrelor in ACS patients with COPD, and if the side effects are tolerable, the decrease in ischemic events without increasing overall bleeding certainly motivate ticagrelor use instead of clopidogrel. In consideration of COPD patients being such a high-risk population with a particularly poor prognosis, ticagrelor presents a rare opportunity to improve outcome.

CABG in COPD patients

In paper IV, we targeted a slightly different and more narrow population by looking into ACS patients with three-vessel disease or left main coronary artery lesions, treated with CABG within 30 days after the event. Our main findings were that ACS patients with COPD who underwent CABG had a substantially higher long-term mortality compared to non-COPD patients, not explained by age or comorbidities. However, this should not discourage CABG in COPD patients, since withholding surgery might render even higher mortality rates. There were also significantly more postoperative infections including pneumonias. Interestingly, we did not find COPD to be an independent determinant in the choice of revascularization strategy between PCI or CABG, which was somewhat surprising considering that COPD is included in risk scores of perioperative risks, including euroSCORE and Society of Thoracic Surgeons' score. Our study indicates that the COPD population is a high-risk population, where extra surgical and postoperative care should be taken.

Previous studies on the subject of COPD and post-CABG outcomes show inconsistent results. The study behind the euroSCORE risk model found chronic airway disease to significantly increase surgical mortality.[193,194] Other small studies since then have found significantly higher mortality in COPD in terms of both in-hospital and long-term mortality, and the adverse outcome seem to be proportional to COPD severity.[195–197] Another study neither found the presence nor the severity of COPD to influence short-term mortality, but similar to our study they found increases in pulmonary infections and prolonged hospital stays.[198] Data from the

large SYNTAX trial that randomized all-comers with three-vessel disease or left main coronary artery involvement to PCI or CABG, found COPD to be highly influential on 4-year mortality independent of age and other characteristics.[150,199] Our study also found COPD to be an independent predictor of long-term mortality, but our effect estimate was lower than in the SYNTAX trial. In regard to absolute mortality rates, both studies findings align well, the SYNTAX study showed a 4-year mortality rate of 22.1% for COPD compared to the 27.2% 5-year mortality seen in our study, also similar in a study by O'Boyle et al that found patients with obstructive pulmonary disease to have 25% 5-year mortality after CABG.[200]

It is reasonable that the burden of comorbidity in COPD likely contributes to the high mortality rate following CABG. Additionally, a greater risk of postoperative complications including a significant increase in infections likely also plays its part. Clinicians should be aware of this increased risk and remain observant at early signs of infections and promptly treat these when indicated. It has also been shown that preoperative cessation of smoking can reduce postoperative pulmonary complications, something that always warrants reiterated emphasis.[201]

Conclusions

This thesis characterized MI/ACS patients with concomitant COPD and investigated certain treatment aspects effects on long-term outcome. The following conclusions were drawn:

- MI patients with concomitant COPD are a high-risk population, with a heavy burden of comorbidity and a doubled unadjusted one-year mortality. After adjustments for comorbidities and different treatment patterns, the residual remaining increase in mortality was modest. There was also an independent association between COPD and rehospitalizations for heart failure. Improved guideline-recommended secondary prevention may improve outcome in MI patients with COPD.
- COPD patients were less often treated with beta-blockers after MI at discharge. Secondary prevention with beta-blockers in MI patients with COPD was independently associated with lower long-term mortality. The association was stronger in COPD patients who also had a history of heart failure. MI patients with COPD may benefit from treatment with beta-blockers and should not routinely be withheld this treatment.
- The $P2Y_{12}$ inhibitor ticagrelor significantly reduced the risk of ischemic events in ACS patients with COPD, without an increase in overall major bleeding. The absolute reduction was substantial and almost four times as great as in ACS patients without COPD. There was no differential increase in the relative risk of ticagrelor-associated dyspnea compared to patients without COPD, but the absolute risk was greater. The benefit-risk profile supports the use of ticagrelor in ACS patients with COPD.
- ACS patients with severe coronary artery disease and COPD treated with CABG have higher long-term mortality and more in-hospital infections than patients without COPD. Preventive measures, including careful monitoring of infection signs and prompt antibiotic treatment when indicated, should be considered.

Perspectives

The relationship between COPD and ACS is increasingly getting more and more established, but further research is needed. Here I briefly present what I consider are three important strategies in regard to the current challenges we should work to resolve in order to improve outcomes in ACS patients with concomitant COPD.

First, to better understand the scope of the problem it would be beneficial to perform a prospective spirometric screening study in an all-comer population of ACS patients. This could help verify the true prevalence of COPD in ACS and previously undiagnosed cases could be referred to instances specializing in COPD management. It has been shown that smokers diagnosed with COPD stop smoking to a higher degree,[202] which would have major beneficial cardiac and pulmonary implications in this population. Furthermore, COPD is clearly not a binary disease, and with spirometric data we could stratify outcome analyses by pulmonary function to elucidate the importance of COPD severity, currently a knowledge gap. In addition, observational studies highlight the heavy burden of comorbidity in COPD, therefor it would be wise to carefully look for these in diagnosed COPD patients, and to treat them according to current guidelines.

Second, COPD should be more recognized as a major risk factor of incident cardiovascular events and for adverse outcomes following these. Diabetes has rightfully received a lot of attention in the field of cardiovascular disease, leading to many seminal discoveries that have gained this patient group. I would like to see a similar initiative for COPD from the cardiovascular community. Information campaigns to involve and educate patients and clinicians alike of the association between COPD and cardiovascular disease would certainly help raise awareness of the challenges we are facing. More specifically for the clinical research community, COPD patients should be more involved in future cardiovascular trials, preferably included in prespecified subgroup analyses to help increase evidence on how to best treat and manage this patient group.

Third, no thesis regarding COPD is complete without advocacy for further antismoking actions since it remains the most effective primary preventive measure. The World Health Organization estimated that over 1.1 billion were smokers in 2015, and although tobacco prevalence is decreasing worldwide, it is increasing in some regions like the Eastern Mediterranean Region and the African Region.[203] The World Health Organization and other actors should continue to combat this to prevent future epidemics of both COPD and cardiovascular disease.

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Paper I

openheart

Impact of chronic obstructive pulmonary disease on morbidity and mortality after myocardial infarction

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ABSTRACT

Aim: To gain a better understanding of the impact of chronic obstructive pulmonary disease (COPD) on long-term mortality in patients with myocardial infarction (MI) and identify areas where the clinical care for these patients may be improved.

Methods: Patients hospitalised for MI between 2005 and 2010 were identified from the nationwide Swedish SWEDEHEART registry. Patients with MI and a prior COPD hospital discharge diagnosis were compared to patients with MI without a prior COPD hospital discharge diagnosis for the primary endpoint of all-cause mortality at 1 year after MI. Secondary endpoints included rates of reinfarction, new-onset stroke, new-onset bleeding and new-onset heart failure at 1 year.

Results: A total of 81 191 MI patients were included, of which 4867 (6%) had a COPD hospital discharge diagnosis at baseline. Patients with COPD showed a significantly higher unadjusted 1-year mortality (24.6 vs 13.8%) as well as a higher rate of reinfarction, new-onset bleeding and new-onset heart failure post-MI. After adjustment for potential confounders, including comorbidities and treatment, the patients with COPD still showed a significantly higher 1-year mortality (HR 1.14, 95% CI 1.07 to 1.21) as well as a higher rate of new-onset heart failure (HR 1.35, 95% CI 1.24 to 1.47), whereas no significant association between COPD and myocardial reinfarction or new-onset bleeding remained.

Conclusions: In this nationwide contemporary study, patients with COPD frequently had an atypical presentation, less often underwent revascularisation and less often received guideline-recommended secondary preventive medications of established benefit. Prior COPD was associated with a higher 1-year mortality and a higher risk of subsequent new-onset heart failure after MI. The association seems to be mainly explained by differences in background characteristics, comorbidities and treatment, although a minor part might be explained by COPD in itself. Improved in-hospital MI treatment and post-MI secondary prevention according to the guidelines may lower the mortality in this high-risk population.

KEY MESSAGES

- Patients with COPD have a high risk of death when suffering from a myocardial infarction.
- The increased risk of death seems to partly be based on comorbidities and undertreatment post-MI.
- By reducing the undertreatment with guideline recommended secondary prevention, their prognosis may be improved.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death worldwide but is expected to be the third leading cause in 2030[1] in parallel with an expected global increase in tobacco smoking.[2] The prevalence of COPD varies between countries and age groups but is estimated to be 9–10% in adults over 40 years of age.[3] COPD is an underdiagnosed[4 5] and undertreated[6] disease with as little as only one-fifth of patients aged over 40 years being diagnosed and treated in a primary care setting.[7]

COPD and ischaemic heart disease share common risk factors such as high age and smoking[8] and a high portion of morbidity and mortality in patients with COPD is attributable to cardiovascular disease.[9–11] Patients with mild COPD seem to have a higher risk of dying from cardiovascular causes than from respiratory insufficiency.[12] Reduced lung function, independent of smoking, has been shown to correlate with a higher risk of cardiovascular death[10 13] and ventricular arrhythmia.[14] A reduced forced expiratory volume in 1 s (FEV1) has been implicated as a prognostic marker for all-cause and cardiovascular mortality.[15 16] Chronic inflammation of the lungs is thought to result in systemic inflammation,[17] measured by increased plasma levels of inflammation markers such as C reactive protein (CRP).[18] This could possibly aggravate atherosclerosis, induce arterial stiffness[19] and contribute to an increased risk of cardiovascular disease.

When suffering from a myocardial infarction (MI), patients with COPD often have comorbidities and commonly present with atypical symptoms, such as dyspnoea, which may result in diagnostic difficulties and delayed treatment leading to a worse prognosis.[20] Furthermore, they are less likely to receive reperfusion therapy during hospitalisation[21] and other MI therapies of proven benefit.[22]

The aim of the present study was to characterise the population with MI with a concurrent COPD diagnosis and investigate the prognostic impact of COPD when suffering from an MI, in a contemporary patient population with widespread use of percutaneous coronary intervention (PCI) and dual antiplatelet inhibition.

MATERIALS AND METHODS

Study sample

Consecutive patients with MI admitted to Swedish coronary care units and entered in the nationwide Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART)[23] registry between 2005 and 2010 were available for analyses. The study population consisted of a total of 81 191 patients with MI, including ST elevation myocardial infarction (STEMI) and non-STEMI. Of these patients, 4867 (6%) had a previous COPD hospital discharge diagnosis while 76 324 did not. The COPD diagnoses were based on International Classification of Diseases (ICD) codes that can be found in online supplementary table S1.

The SWEDEHEART registry enrols consecutive patients admitted to a coronary care unit because of symptoms suggestive of an acute coronary syndrome. On admission, patients receive written information about SWEDEHEART and other quality-of-care registries; patients are permitted to deny participation in the registry, although few of them exercise this right. According to Swedish law, written consent is not required because quality control is an inherent element of hospital healthcare. Research based on the registry is approved by an institutional ethics committee and all personal identifiers are removed from the SWEDEHEART data file when used for research purposes. Information is collected prospectively regarding baseline characteristics such as age and smoking status as well as ECG findings, examinations, interventions, in-hospital complications, discharge medication and diagnoses.[23] Information on time of death was obtained from the Swedish National Cause of Death Registry. Information regarding medical history, including previous COPD diagnoses, and re-admissions for reinfarction, stroke or bleeding was obtained from the Swedish National Patient Registry,[24] which includes diagnoses for all patients hospitalised in Sweden from 1987 and forward. Since 2001, the specialised outpatient care is also included. The validity of COPD diagnoses in the Swedish National Patient Registry has recently been reported to be good, with a diagnosis likely to be misclassified in less than 10%.[25]

Endpoints

The primary analysis tested the relationship between a prior COPD hospital discharge diagnosis and the primary endpoint of all-cause mortality during 1 year of follow-up after the initial coronary care unit hospitalisation. Secondary endpoints included 1-year re-admission for reinfarction, defined as a new hospitalisation with an MI diagnosis, new-onset admission for stroke, new-onset bleeding and new-onset heart failure. The corresponding ICD codes that the secondary endpoints are based on can be found in online supplementary table S1.

Statistical analyses

Rates of predefined endpoints in patients with and without a prior COPD hospital discharge diagnosis were calculated with the Kaplan-Meier estimator. Univariate and multivariate HRs were estimated using the Cox proportional hazards models. Covariates were tested for proportionality by visual inspection. Adjustments for potential confounders were performed stepwise in two models, the first including age, sex, smoking status and comorbidities (previous MI, previous stroke, heart failure, renal failure, hypertension, diabetes, peripheral artery disease, cancer and previous bleeding). The second model also included treatments during hospitalisation and at discharge (heparin, fondaparinux, dalteparin, enoxaparin, GPIIbIIIa-inhibitors, β-blockers, balloon angioplasty, coronary stenting, as well as discharge medications including ACE inhibitors, angiotensin II receptor blockers, aspirin, clopidogrel, prasugrel, β-blockers, calcium channel blockers, digoxin, diuretics, statins, nitrates and warfarin). The selection of covariates included in these models was performed with the use of a direct acyclical graph[26] via a web-based tool (http://www.dagitty.net), as illustrated in online supplementary figure S1. Differences between continuous variables were evaluated using the Student t test. Differences between categorical variables were analysed with the Pearson χ^2 test. All tests were two-sided with a p value for significance <0.05. All analyses were performed in SPSS (SPSS V.20, IBM SPSS statistics).

RESULTS

Patient characteristics

Baseline characteristics for patients with MI and without COPD are outlined in table 1. Many variables differ between the two groups. The mean age was 5 years higher in patients with COPD as well as a threefold higher prevalence of prior heart failure. Furthermore, there was a more than twice as high proportion of renal failure, peripheral artery disease and cancer in patients with COPD. Patients with COPD were also more likely to have suffered from previous MI and stroke as well as being treated with more cardiovascular medications

Table 1 Baseline characteristics of 81 191 consecutive patients with MI with and without COPD in Sweden between 2005 and 2010

	Non-COPD	COPD	p Value
Number of patients	76 324 (94.0)	4867 (6.0)	
Age	70±13	75±9	<0.001
Female gender	27 466 (36.0)	2239 (46.0)	<0.001
Body mass index (n=55 516)	26.7±4.7	25.4±5.4	<0.001
Smoking status (n=80 879)			<0.001
Current smoker	16 522 (21.7)	1596 (32.9)	
Ex–smoker	20 791 (27.3)	2222 (45.9)	
Never smoked	31 850 (41.9)	681 (14.1)	
Unknown	6872 (9.0)	345 (7.1)	
Comorbidities			
Previous MI	5990 (7.8)	665 (13.7)	<0.001
Previous stroke	6904 (9.0)	650 (13.4)	<0.001
Heart failure	4836 (6.3)	983 (20.2)	<0.001
Renal failure	1478 (1.9)	231 (4.7)	<0.001
Hypertension	14 848 (19.5)	1537 (31.6)	<0.001
Diabetes	14 613 (19.1)	999 (20.5)	0.018
Peripheral artery disease	3121 (4.1)	498 (10.2)	<0.001
Cancer	1638 (2.1)	258 (5.3)	<0.001
Previous bleeding	3541 (4.6)	428 (8.8)	<0.001
Prior CABG	2625 (3.4)	208 (4.3)	0.002
Prior PCI	1548 (2.0)	127 (2.6)	0.006
Prior medication before MI			
ACE inhibitor	12 216 (16.0)	967 (19.9)	<0.001
Angiotensin II receptor blocker	7894 (10.5)	580 (12.1)	<0.001
Aspirin	23 023 (30.2)	1913 (39.3)	<0.001
Clopidogrel	2603 (3.4)	217 (4.5)	<0.001
β-blocker	23 315 (30.6)	1544 (31.7)	0.161
Calcium channel blocker	11 615 (15.2)	878 (18.0)	<0.001
Digitalis	1918 (2.5)	290 (6.0)	<0.001
Diuretic	17 170 (22.5)	1910 (39.2)	<0.001
Statin	14 452 (18.9)	1069 (22.0)	<0.001
Nitrate	6331 (8.3)	630 (12.9)	<0.001
Warfarin	2816 (3.7)	275 (5.7)	<0.001

The mean and SD are presented for continuous variables and count and percentage for categorical variables.
CABG, coronary arterial bypass graft surgery; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

than the patients with non-COPD at baseline, with the exception of β-blockers.

Clinical presentation, laboratory findings and ECG changes

The pattern of symptoms differed between the two groups, as shown in table 2. Patients in the COPD group presented more frequently with dyspnoea and less frequently with chest pain as the main presenting symptom compared to patients without COPD. For the patients with COPD, the mean heart rate was higher, while the lab findings revealed lower mean total cholesterol and low-density lipoprotein levels with a higher mean CRP value. More often, the presenting ECG showed atrial fibrillation or flutter in the COPD group and the QRS complex revealed higher percentages of left bundle branch block and right bundle branch block. In contrast, ST elevation was more frequent in the non-COPD group.

Treatments, angiographic findings, complications during hospitalisation and discharge medications

The in-hospital characteristics for patients with MI with and without COPD are outlined in table 3. Invasive investigation and treatments in the form of coronary angiography, balloon angioplasty and stenting were less frequent among patients with COPD while the rate of coronary arterial bypass graft surgery did not differ. The indications for PCI differed between the groups, with STEMI being more prevalent among patients in the non-COPD group while the extent of coronary disease was similar.

Continuous positive airway pressure usage was more common for the COPD group as well as a bleeding requiring transfusion and/or surgery. Patients in the COPD group were also more likely to be discharged with atrial flutter or atrial fibrillation as well as with a lower left ventricular ejection fraction.

Patients with COPD were discharged with fewer medications that have been proven to reduce mortality such as

Table 2 Characteristics at presentation for 81 191 consecutive patients with MI with and without COPD in Sweden between 2005 and 2010

	Non-COPD	COPD	p Value
Number of patients	76 324 (94.0)	4867 (6.0)	
Presenting symptoms			<0.001
Chest pain	63 143 (82.9)	3191 (65.6)	
Dyspnoea	5429 (7.1)	1092 (22.5)	
Cardiac arrest	836 (1.1)	45 (0.9)	
Other	6343 (8.3)	505 (10.4)	
Delays from symptom onset			
Symptom onset to ER <12 h	41 897 (88.7)	2461 (87.6)	0.092
Symptom onset to ICCU <12 h	60 084 (87.4)	3508 (84.0)	<0.001
Symptom onset to PCI <12 h	17 623 (91.9)	690 (91.1)	0.488
Clinical findings			
Pulmonary oedema	1542 (2.1)	140 (3.0)	<0.001
Heart rate	80±23	90±25	<0.001
Systolic blood pressure	147±30	141±30	<0.001
Diastolic blood pressure	84±17	80±18	<0.001
Lab findings			
Total cholesterol	5.1±1.2	4.8±1.2	<0.001
LDL	3.1±1.1	2.8±1.0	<0.001
HDL	1.2±0.4	1.3±0.5	<0.001
Creatinine	95±57	100±60	0.001
CRP	25±50	38±60	<0.001
Hb	138±18	134±18	<0.001
Presenting ECG			
Rhythm			<0.001
Sinus	66 131 (86.7)	3958 (81.4)	
Atrial fibrillation/flutter	7686 (10.1)	706 (14.5)	
QRS			<0.001
Normal	47 474 (62.7)	2711 (56.1)	
LBBB	4329 (5.7)	397 (8.2)	
RBBB	3231 (4.3)	300 (6.2)	
ST-T segment			<0.001
Normal	14 595 (19.2)	941 (19.4)	
ST elevation	27 012 (35.5)	1294 (26.7)	
ST depression	16 717 (22.0)	1205 (24.8)	
Abnormal T wave	7681 (10.1)	528 (10.9)	
Other	9056 (11.9)	791 (16.3)	

The mean and SD are presented for continuous variables and count and percentage for categorical variables.
COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; ER, emergency room; Hb, haemoglobin; HDL, high-density lipoprotein; ICCU, intensive coronary-care unit; LDL, low-density lipoprotein; LBBB, left bundle branch block; PCI, percutaneous coronary intervention; RBBB, right bundle branch block.

aspirin and other platelet inhibitors as well as β-blockers, statins and ACE inhibitors but more of angiotensin receptor blockers. In contrast, patients in the COPD group were more often discharged with calcium channel blockers, digoxin, diuretics, nitrates and warfarin.

Outcomes

The crude 1-year mortality was significantly higher in the COPD group compared to the non-COPD group, 24.6% vs 13.8% (HR 1.86, 95% CI 1.76 to 1.98), as shown in figure 1 and table 4. After adjusting for differences in baseline characteristics, the mortality remained higher in the COPD group but the HR was significantly lowered (HR 1.32, 95% CI 1.24 to 1.40). After additional adjustment for treatments during hospitalisation and discharge medications, the difference in mortality was further decreased but remained statistically significant (HR 1.14, 95% CI 1.07 to 1.21).

The results of the secondary endpoint analyses are shown in table 4. Patients with COPD had a higher rate of reinfarction 16.6% vs 14.2% (HR 1.17, 95% CI 1.09 to 1.26), new-onset bleeding 4.1% vs 2.8% (HR 1.45, 95% CI 1.25 to 1.69) and new-onset heart failure 17.2% vs 9.7% (HR 1.84, 95% CI 1.70 to 1.99) compared to the non-COPD group in univariate analyses, while there was no difference in the rate of new-onset strokes. However, after adjusting for differences in baseline characteristics, treatment during hospitalisation and discharge medications, no differences in reinfarction rates or new-onset bleeding rates were noted. In contrast, the rate of new-onset heart failure remained higher for patients with COPD (HR 1.35, 95% CI 1.24 to 1.47).

Table 3 In-hospital characteristics of 81 191 consecutive patients with MI with and without COPD in Sweden between 2005 and 2010

	Non-COPD	COPD	p Value
Number of patients	76 324 (94.0)	4867 (6.0)	
Prehospital thrombolysis	946 (1.4)	34 (0.8)	0.007
Anticoagulant therapy			<0.001
Heparin	5413 (7.1)	198 (4.1)	
Dalteparin/enoxaparin	34 266 (44.9)	2311 (47.5)	
Fondaparinux	15 705 (20.6)	1147 (23.6)	
GPIIBIIIA-inhibition			<0.001
Abciximab	12 342 (16.2)	434 (8.9)	
Tirofiban	1464 (1.9)	48 (1.0)	
Eptifibatide	4078 (5.3)	145 (3.0)	
β-blocker			<0.001
Intravenous	17 746 (23.3)	908 (18.7)	
Oral	35 500 (46.5)	2072 (42.6)	
Coronary angiography	55 330 (72.5)	2697 (55.4)	<0.001
Indication for angiography			<0.001
Unstable angina/NSTEMI	30 015 (54.2)	1610 (59.9)	
STEMI	21 136 (38.2)	883 (32.9)	
Other	4251 (7.6)	194 (7.2)	
Angiographic findings			<0.001
Normal/atheromatosis	760 (1.7)	47 (2.4)	
1-vessel, no left main disease	20 788 (47.3)	860 (43.8)	
2-vessel, no left main disease	13 038 (29.7)	575 (29.3)	
3-vessel, no left main disease	7534 (17.1)	367 (18.7)	
Left main disease	226 (0.5)	14 (0.7)	
PCI	42 540 (55.7)	1837 (37.7)	<0.001
Stented	40 662 (53.3)	1746 (35.9)	<0.001
CABG	2211 (2.9)	120 (2.5)	0.081
Complications			
Prehospital CPR	1129 (1.6)	48 (1.2)	0.040
Cardiogenic shock	1990 (2.7)	135 (2.8)	0.717
Defibrillated VT/VF	1903 (2.5)	110 (2.3)	0.285
Rupture	107 (0.1)	6 (0.1)	0.097
Reinfarction during hospital stay	956 (1.3)	67 (1.4)	0.422
CPAP usage	3700 (4.8)	477 (9.8)	<0.001
Bleeding causing surgery/transfusion	1233 (1.6)	117 (2.4)	0.001
AV block II/III	1424 (1.9)	94 (1.9)	0.160
Permanent pacemaker	735 (1.0)	52 (1.1)	0.344
New onset atrial fibrillation	3462 (4.6)	249 (5.2)	0.107
Discharged with flutter/fibrillation	4519 (6.3)	417 (9.3)	<0.001
LVEF at discharge			<0.001
Normal LVEF ≥50%	28 988 (53.8)	1422 (45.0)	
LVEF 40–49%	12 338 (22.9)	770 (24.3)	
LVEF 30–39%	7748 (14.4)	545 (17.2)	
LVEF <30%	3809 (7.1)	342 (10.8)	
Discharge medications			
ACE inhibitor	42 350 (55.5)	2460 (50.6)	<0.001
Angiotensin II blocker	8276 (11.1)	602 (12.6)	0.001
Aspirin	68 693 (90.1)	4158 (85.5)	<0.001
Other platelet inhibitor			<0.001
Clopidogrel	54 439 (71.4)	3003 (61.8)	
Prasugrel	331 (0.4)	9 (0.2)	
Other	341 (0.4)	23 (0.5)	
β-blocker	65 675 (86.1)	3778 (77.7)	<0.001
Statin	60 387 (79.2)	3323 (68.4)	<0.001

Continued

Table 3 Continued

	Non-COPD	COPD	p Value
Calcium channel blocker	9530 (12.5)	735 (15.1)	<0.001
Digoxin	2309 (3.0)	294 (6.0)	<0.001
Diuretic	22 910 (30.0)	2397 (49.3)	<0.001
Nitrate	9736 (12.8)	878 (18.1)	<0.001
Warfarin	4039 (5.3)	314 (6.5)	0.008

The count and percentage are presented for all categorical variables.
AV, atrioventricular; CABG, coronary arterial bypass graft surgery; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; CPR, cardiopulmonary resuscitation; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

DISCUSSION

Currently, there is limited knowledge about the effect of concomitant COPD on patients with MI regarding mortality and other cardiovascular events, especially in patients with contemporary treatment including PCI, dual antiplatelet therapy and statins. Our nationwide and contemporary study has a large patient population and reflects the present MI care in Sweden well. Thus, it provides new information to the field of patients with MI with a concurrent COPD diagnosis.

Patient characteristics

In our study, 6% of the study population had a COPD hospital discharge diagnosis, lower than the estimated prevalence of COPD in the general population (9–10%), a finding in accordance with the previously reported problems of underdiagnosis.[3] The increased age in the COPD group probably reflects that COPD is a late effect of lifelong smoking, but it could also be explained by underdiagnosis since COPD is relatively silent in early stages, and therefore the diagnosis does not surface until the manifestations are severe. As table 1 outlines, many of these patients also have previous cardiovascular events, in part due to a heavy smoking history but perhaps also due to reduced lung function and chronic inflammation of the lungs.

With regard to baseline characteristics and clinical presentation, several findings in our study are supported by previous studies. We found that patients with COPD had a larger burden of comorbidity and more atypical MI symptoms at presentation, in accordance with the findings of a previous study.[20] However, we did not observe any differences in time delays from symptom onset to PCI or to the emergency room, as previously reported.[20] Our data also did not support a previous study showing higher rates of cardiogenic shock in patients with COPD.[27]

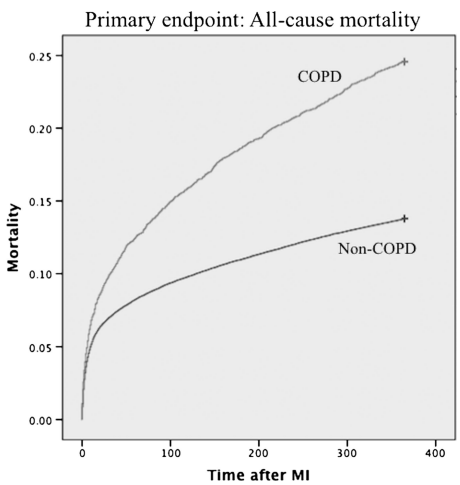

Figure 1 A Kaplan-Meier plot showing the crude 1-year mortality for patients with chronic obstructive pulmonary disease (COPD) versus patients without COPD.

Treatments

After an MI, many patients with COPD have previously not been prescribed β-blockers[28] because clinicians fear that β-blockers will provoke bronchospasm and induce respiratory failure, even though cardioselective β-blockers have been proven to be safe and should not be routinely withheld from patients with COPD.[29] Other types of standard post-MI treatment such as aspirin may also be used less often.[22]

As table 3 outlines, our findings are in line with these previous studies and show that standard post-MI treatment is withheld from patients with COPD more often than patients without COPD, especially with respect to β-blockers and surprisingly also statins which previously in observational studies have shown a dual cardiopulmonary protective effect.[30] A systematic review including nine previous studies suggests that statins may also have a beneficial role in the treatment of COPD in itself.[31]

Outcomes

Previous studies have reported conflicting findings. Bursi *et al*[21] reported a worse 5-year survival rate in patients with COPD (46%) compared to those without COPD (68%), and the association between COPD and

Table 4 Clinical endpoints for patients with COPD as compared to patients without COPD at 1 year

	Crude HR (95% CI)	Adjusted† HR (95% CI)	Adjusted‡ HR (95% CI)
All-cause mortality	1.86 (1.76 to 1.98)***	1.32 (1.24 to 1.40)***	1.14 (1.07 to 1.21)***
Reinfarction	1.17 (1.09 to 1.26)***	1.00 (0.93 to 1.08)	0.99 (0.92 to 1.06)
New-onset stroke	1.14 (0.93 to 1.40)	0.90 (0.73 to 1.12)	0.89 (0.72 to 1.11)
New-onset bleeding	1.45 (1.25 to 1.69)***	1.13 (0.96 to 1.32)	1.12 (0.96 to 1.31)
New-onset heart failure	1.84 (1.70 to 1.99)***	1.46 (1.34 to 1.58)***	1.35 (1.24 to 1.47)***

*p<0.05; **p<0.01; ***p<0.001.
†Adjustment for age, gender, smoking and comorbidity.
‡Adjustment for age, gender, smoking, comorbidity, treatment during hospitalisation and discharge medications.
COPD, chronic obstructive pulmonary disease.

death was independent of age and risk factors (HR 1.30, 95% CI 1.10 to 1.54). In another study by Salisbury *et al*[22], patients with COPD had a twofold higher 1-year mortality rate after adjustment for baseline differences (HR 2.00, 95% CI 1.44 to 2.79) and higher rehospitalisation rates (HR 1.22, 95% CI 1.01 to 1.48). On the other hand, the older study by Behar *et al*[32] did not find an independent association between COPD and a higher risk of early death or long-term mortality among survivors of acute MI.

Our study showed that patients with a prior COPD hospital discharge diagnosis had a considerably higher crude 1-year mortality after an MI (HR 1.86, 95% CI 1.76 to 1.98) compared to patients without COPD with an MI. However, we could show that this association was greatly lowered after adjusting for baseline characteristics and comorbidities (HR 1.32, 95% CI 1.24 to 1.40) and, perhaps most importantly, after also adjusting for different treatment patterns, only a modest increase in adjusted mortality remained (HR 1.14, 95% CI 1.07 to 1.21).

Therefore, our results indicate that patients with COPD with an MI constitute a very high risk group with a nearly doubled unadjusted mortality rate compared to patients without COPD with an MI and that the excess mortality could perhaps be lowered with more aggressive evidence-based treatments for both the MI as well as concomitant diseases. However, our results are only suggestive and it would require a prospective, interventional study to confirm our findings. COPD was not independently associated with a higher 1-year re-admission for reinfarction, new-onset stroke or new-onset bleeding rate but was independently associated with an increased new-onset heart failure rate.

The observed association between a prior COPD diagnosis before MI and a higher frequency of subsequent new onset of heart failure even after multivariate adjustment raises several questions. Not much is known about the association of heart failure and COPD. Previous authors have suggested a common inflammatory background between the conditions.[33] The actual prevalence of decreased left ventricular function in patients with COPD is largely unknown and clinically poorly defined.[33 34] Shared signs, symptoms and pulmonary function test findings between heart failure and COPD further complicate the relationship. Patients with COPD may suffer from pulmonary hypertension,[35] which could lead to right ventricular dysfunction,[36] and because of a similar symptomatology between cor pulmonale and true left ventricular failure, it is hard to discern and distinguish the exact aetiology of the heart failure diagnosis. Dyspnoea and exercise intolerance are cardinal symptoms for COPD and heart failure resulting in diagnostic difficulties, and misclassification in the National Patient Registry cannot be ruled out. However, in the present study, patients with COPD did have a higher rate of decreased left ventricular ejection fraction at discharge and they were also undertreated post-MI with guideline recommended secondary prevention medications. This could lead to a higher frequency of new-onset heart failure.

Limitations

Our study design was observational, and thus a certain degree of residual confounding cannot be ruled out. Since COPD is an underdiagnosed disease,[4 5] a number of patients in the non-COPD group could have met the criteria for COPD if they had been thoroughly investigated with spirometry, an inherent limitation of any retrospective COPD study.[37] The underdiagnosis of COPD could potentially result in an under-representation in the registry that could underestimate our findings. Furthermore, we did not have optimal data regarding the patients' smoking history, as pack-years, date of smoking cessation and information about smoking post-MI were lacking. We also did not have information on pulmonary function testing, such as FEV1/forced vital capacity ratios, and therefore the severity of COPD diagnoses cannot be evaluated in our patient population. Moreover, a wide range of physicians has diagnosed the COPD cases, and thus the criteria for COPD may differ between patients in the population. The same problem is applicable to the heart failure diagnoses. However, the validity of COPD and heart failure diagnoses in national Swedish registers has recently been reported to be good.[25 38]

CONCLUSIONS

The main finding in this nationwide study of patients with MI with contemporary treatment including dual antiplatelet treatment and PCI was that a COPD

diagnosis at baseline was associated with a high 1-year mortality. However, after multivariate adjustment for comorbidities and different treatment patterns, the residual increase in mortality was only modest (HR 1.14, 95% CI 1.07 to 1.21). There was also an independent association between a COPD diagnosis and re-admission for new-onset heart failure. The mechanisms behind these associations are not clear. However, our findings suggest that improved cardiac treatment in patients with MI with COPD according to current guidelines could potentially result in improved survival.

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Contributors All authors fulfil all three of the guidelines for authorship. (1) Substantial contributions to conception and design, acquisition of data or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content and (3) final approval of the version to be published.

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Competing interests None.

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Paper II

ORIGINAL RESEARCH

β-Blocker Use and Mortality in COPD Patients After Myocardial Infarction: A Swedish Nationwide Observational Study

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***Background*—**Patients with myocardial infarction (MI) and concomitant chronic obstructive pulmonary disease (COPD) constitute a high-risk group with increased mortality. β-Blocker therapy has been shown to reduce mortality, prevent arrhythmias, and delay heart failure development after an MI in broad populations. However, the effect of β-blockers in COPD patients is less well established and they may also be less treated due to fear of adverse reactions. We investigated β-blocker prescription at discharge in patients with COPD after MI.

***Methods and Results*—**Patients hospitalized for MI between 2005 and 2010 were identified from the nationwide Swedish SWEDEHEART registry. Patients with COPD who were alive and discharged after an MI were selected as the study population. In this cohort, patients who were discharged with β-blockers were compared to patients not discharged with β-blockers. The primary end point was all-cause mortality. A total of 4858 patients were included, of which 4086 (84.1%) were discharged with a β-blocker while 772 (15.9%) were not. After adjusting for potential confounders including baseline characteristics, comorbidities, and in-hospital characteristics, patients discharged with a β-blocker had lower all-cause mortality (hazard ratio 0.87, 95% CI 0.78 to 0.98) during the total follow-up time (maximum 7.2 years). In the subgroup of patients with a history of heart failure, the corresponding hazard ratio was 0.77 (95% CI 0.63 to 0.95).

***Conclusions*—**Patients with COPD discharged with β-blockers after an MI had a lower all-cause mortality compared to patients not prescribed β-blockers. The results indicate that MI patients with COPD may benefit from β-blockers. **(*J Am Heart Assoc*. 2015;4: e001611 doi: 10.1161/JAHA.114.001611)**

Key Words: epidemiology • mortality • myocardial infarction • prevention

β-Blockers have long been a cornerstone in secondary prevention after a myocardial infarction (MI). The European Society of Cardiology recommends treatment with oral β-blockers in all acute coronary syndromes with concomitant left ventricular dysfunction and consideration of β-blockers in all other acute coronary syndrome patients.[1,2] β-Blockers have been proven to reduce mortality, reduce the risk of malignant arrhythmias, and delay heart failure development, although most of the clinical trials proving these benefits stem from before the modern reperfusion era.[3–6]

Patients with MI and chronic obstructive pulmonary disease (COPD) constitute a high-risk group.[7–9] They often present with atypical symptoms, such as dyspnea, and more often have aggravating comorbidities.[9,10] Furthermore, they less often receive reperfusion therapy during hospitalization and are less often treated with standard post-MI secondary prevention.[9,11] These complicating factors might contribute to the high mortality seen after MI for COPD patients.[9]

Historically, β-blockers have sometimes been withheld from COPD patients.[12] There has been a fear that β-blockers would induce respiratory adverse reactions such as bronchospasm, but cardioselective β-blockers have been proven safe in meta-analyses.[13,14] Furthermore, several studies including a meta-analysis of observational studies involving COPD and β-blocker treatment found a protective effect on all-cause mortality,[15,16] and a previous study showed a lower rate of COPD exacerbations, suggesting dual cardiopulmonary protective properties.[17] However, the established benefit of β-blockers as secondary prevention post-MI has not been

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This study was presented as an oral presentation at the European Society of Cardiology Congress held from August 30, 2014 to September 3, 2014 in Barcelona, Spain.

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studied extensively in patients with COPD, although a recent observational study from the United Kingdom seems to suggest benefit in these patients.[18]

In this study, we aimed to study the association between prescription of β-blockers at discharge after MI and all-cause mortality for COPD patients in the present era of interventional cardiology and dual antiplatelet therapy in Sweden.

Materials and Methods

Registries

Consecutive MI patients admitted to Swedish coronary care units and entered in the nationwide Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART)[19] registry were available for analyses. The SWEDEHEART registry enrolls consecutive patients admitted to a Swedish coronary care unit because of symptoms suggestive of an acute coronary syndrome. On admission, patients receive written information about SWEDEHEART and other quality-of-care registries; patients are permitted to deny participation in the registry, although few of them exercise this right. According to Swedish law, written consent is not required because quality control is an inherent element of hospital health care. An institutional ethics committee approved this study. Information was collected prospectively regarding baseline characteristics such as age and smoking status as well as electrocardiographic findings, examinations, interventions, in-hospital complications, diagnoses, and discharge medications such as β-blockers.[19] Information on time of death was obtained from the Swedish National Cause of Death Registry. Information regarding previous medical history, including previous COPD diagnoses and other comorbidities, were obtained from the Swedish National Patient Registry[20] that includes diagnoses based on International Classification of Diseases (ICD) codes for all patients hospitalized in Sweden from 1987 and onward. Since 2001 the specialized outpatient care has also been included. All of the information from the different registries was merged into a single database for analysis.

MI and COPD Definitions

An MI diagnosis in the SWEDEHEART registry is a clinical diagnosis made by the patient's treating physician based on patient history, laboratory values, electrocardiographic findings, angiography, and other examinations based on current definitions of MI.[21] For a COPD diagnosis, we used J41 to J44 from ICD-10 and 491 to 492, 496 from ICD-9, not including Asthma. This definition has previously been validated[22] with a misclassification of <10% in the Swedish National Patient Registry.

Study Sample

MI patients, both ST-segment elevation myocardial infarction (STEMI) and non-STEMI, enrolled in the SWEDEHEART registry between 2005 and 2010 with a concurrent COPD diagnosis were included in the study. COPD was defined as having an electronic healthcare record of ICD codes either at baseline or during follow-up. The rationale for also including patients diagnosed during follow-up was that since COPD is an underdiagnosed disease and often diagnosed in a late stage that takes many years to reach, patients diagnosed during follow-up would have undiagnosed COPD at the time of the MI. A similar approach has been adopted previously.[18] Since the study aimed to investigate the effect of β-blockers for secondary prevention, all patients who died in the hospital were excluded (341/6476, 5.3%). Missing information on whether the patient was being discharged with β-blocker or not led to exclusion from the study (n=16). Patients with relative or absolute contraindications (discharged with digoxin [n=355], bradycardia [n=566], AV block II or III [n=65], hypotension [n=232], and cardiogenic shock [n=43]) to β-blockers were excluded.

End point

The primary analysis tested the relationship between the exposure of being discharged with a β-blocker and the predefined primary end point of all-cause mortality at 30 days, at 1 year, and during the total available follow-up time after the initial coronary care unit hospitalization.

Statistical Analyses

Differences between normally distributed continuous variables were evaluated using the Student *t* test. Differences between non-normally distributed continuous variables were evaluated using the Mann–Whitney *U* test. Differences between categorical variables were tested with the Pearson χ^2 test. Rates of the end point in patients with and without a β-blocker were calculated with the Kaplan–Meier estimator. Univariate and multivariate hazard ratios were estimated using Cox proportional hazard models. Covariates were tested for proportionality of hazards by visual inspection. Potential confounders were identified using an a priori direct acyclic graph[23] via a web-based tool (http://www.dagitty.net). The multivariate model included the following covariates: age, sex, smoking status, comorbidities (previous MI, previous stroke, heart failure, renal failure, hypertension, diabetes, and cancer), in-hospital characteristics (STEMI, angiography, coronary stenting), β-blocker therapy at presentation, COPD medication at presentation, and discharge medications (angiotensin-converting enzyme inhibitors, angiotensin-II

receptor blockers, aspirin, clopidogrel, statins, calcium channel blockers, and diuretics). To crosscheck the results data from different angles, several sensitivity analyses were conducted. A second adjustment method using a propensity score as a continuous covariate in a Cox proportional hazard model was tested to ascertain whether a different adjustment model would impact the result differently. The propensity score was calculated using a logistic regression model, and using the direct acyclic graph, the following covariates were identified as dependent determinants for the exposure of being discharged with β-blockers: age, sex, smoking status, previous stroke, previous MI, heart failure, diabetes, hypertension, renal failure, cancer, β-blockers therapy at presentation, STEMI, coronary angiography, coronary stenting, and COPD medications at presentation. All tests were 2-sided with a *P*-value for significance of <0.05. All analyses were performed in SPSS (SPSS version 20, IBM SPSS statistics).

Results

Patient Characteristics

Out of 62 855 MI hospital survivors with complete data on β-blocker treatment at discharge and exclusion criteria applied, 4858 (7.7%) COPD patients were identified. Out of these 4858 patients, 4086 (84.1%) were discharged with a β-blocker while 772 (15.9%) were not. Baseline characteristics are outlined in Table 1, both in patients with and without COPD for comparison. Patients with COPD were more often discharged without β-blockers (15.9 versus 9.6%, *P*<0.001) compared to patients without COPD.

COPD patients not receiving β-blocker treatment at discharge were older, had a lower body mass index, were less frequently current smokers, and had a higher prevalence of previous stroke and heart failure but a lower prevalence of hypertension. COPD patients not receiving β-blocker treatment at discharge had less β-blocker treatment, more digoxin, and more diuretics at baseline.

In-Hospital Characteristics

In-hospital characteristics in patients with and without COPD are outlined in Table 2. Blood pressure at presentation was lower for patients with COPD not receiving β-blocker treatment at discharge. Use of in-hospital anticoagulants and in-hospital β-blockers differed between the groups. STEMI was less common in COPD patients not receiving β-blocker treatment at discharge, as well as angiography and percutaneous coronary intervention. This group also received more continuous positive airway pressure treatment. In patients investigated with echocardiography, patients not receiving β-blocker treatment at discharge had a lower frequency of reduced left ventricular ejection fraction. However, this group had a higher rate of patients discharged without receiving an echocardiographic investigation at all.

Patients with COPD not receiving β-blocker treatment at discharge were also discharged to a lower degree with the standard guideline-recommended post-MI secondary prevention medications. In contrast, they were more often discharged with calcium channel blockers and diuretics.

Outcomes

The median follow-up time for MI patients with concomitant COPD was 1033 days (interquartile range 1141 days). The unadjusted hazard ratio (HR) for all-cause mortality in COPD patients with β-blocker treatment at discharge was 0.64 (95% CI 0.58 to 0.71). After adjusting for potential confounders using the multivariate model, COPD patients with β-blocker treatment at discharge still showed lower all-cause mortality compared to COPD patients without β-blocker treatment at discharge, but the HR was increased (HR 0.87, 95% CI 0.78 to 0.98, *P*=0.017). In the other predefined time intervals of 30 days and of 1 year, similar trends were seen although not statistically significant. These analyses are illustrated in Figure 1.

Sensitivity and Subgroup Analyses

A sensitivity analysis testing the effect of β-blocker treatment at discharge for the whole MI hospital survivor population of 62 855 patients between 2005 and 2010, regardless of COPD status, yielded similar results using the multivariate model (HR 0.87, 95% CI 0.83 to 0.91, *P*<0.001).

Testing the multivariate model in patients only diagnosed with COPD before the MI admission did not change the results (HR 0.87, 95% CI 0.76 to 0.99, *P*=0.039).

Landmark analysis from 30 days after the MI up to the maximum follow-up time showed the same HR of 0.87 (95% CI 0.78 to 0.98, *P*=0.017) as the main analysis.

A sensitivity analysis using a propensity score as a continuous covariate in a Cox proportional hazard model was also performed. Patients with COPD not discharged with β-blockers had a median propensity score of 0.76 (25th to 75th percentile: 0.67 to 0.85). Patients with COPD discharged with β-blockers had a median propensity score of 0.88 (25th to 75th percentile: 0.80 to 0.94). The HR in this analysis was 0.84 (95% CI 0.75 to 0.94, *P*=0.002).

Subgroup analyses in patients with or without a history of congestive heart failure are shown in Figure 2. Patients with COPD and a history of congestive heart failure had a hazard ratio of 0.77 (95% CI 0.63 to 0.95, *P*=0.012) for all-cause mortality. Patients with COPD without a history of congestive heart failure had a hazard ratio of 0.90 (95% CI 0.78 to 1.03).

Table 1. Baseline Characteristics of Consecutive MI Hospital Survivors With COPD (4858) and Without COPD (57 997) in Sweden Between 2005 and 2010

	Patients With COPD			Patients Without COPD		
	No β-Blocker	β-Blocker	*P* Value	No β-Blocker	β-Blocker	
Characteristic	n=772	n=4086		n=5548	n=52 449	*P* Value
Age	77 (69 to 83)	74 (67 to 80)	<0.001	75 (64 to 83)	70 (60 to 79)	<0.001
Body mass index	24.3 (21.1 to 27.7)	25.1 (22.3 to 28.7)	<0.001	25.7 (23.4 to 28.4)	26.3 (24.1 to 29.2)	<0.001
Female sex	390 (50.5)	1785 (43.7)	0.004	2269 (40.9)	18 059 (34.4)	<0.001
Smoker	234 (33.5)	1521 (39.6)	<0.001	939 (19.2)	11 674 (24.0)	<0.001
Comorbidities						
Previous stroke	157 (20.3)	612 (15.0)	0.001	747 (13.5)	5223 (10.0)	<0.001
Previous MI	156 (20.2)	810 (19.8)	0.908	739 (13.3)	6039 (11.5)	<0.001
Heart failure	204 (26.4)	814 (19.9)	<0.001	646 (11.6)	4223 (8.1)	<0.001
Renal failure	32 (4.1)	159 (3.9)	0.739	118 (2.1)	904 (1.7)	0.030
Diabetes	164 (21.2)	913 (22.3)	0.499	1084 (19.5)	10 688 (20.4)	0.139
Peripheral artery disease	80 (10.4)	385 (9.4)	0.415	261 (4.7)	1846 (3.5)	<0.001
Cancer	37 (4.8)	170 (4.2)	0.425	150 (2.7)	1030 (2.0)	<0.001
Hypertension	376 (48.7)	2227 (54.5)	0.003	2417 (43.6)	24 903 (47.5)	<0.001
Previous CABG	43 (5.6)	206 (5.0)	0.542	269 (4.8)	2134 (4.1)	0.006
Previous PCI	35 (4.5)	174 (4.3)	0.730	155 (2.8)	1712 (3.3)	0.059
Previous cardiovascular medications						
ACE inhibitor	140 (18.3)	792 (19.5)	0.434	867 (15.7)	8089 (15.5)	0.664
Angiotensin II receptor blocker	97 (12.7)	502 (12.4)	0.814	598 (10.9)	5504 (10.6)	0.500
Warfarin	36 (4.7)	167 (4.1)	0.457	227 (4.1)	1455 (2.8)	<0.001
Aspirin	310 (40.5)	1581 (38.8)	0.398	1801 (32.6)	15 044 (28.8)	<0.001
Clopidogrel	40 (5.3)	173 (4.3)	0.238	177 (3.2)	1483 (2.9)	0.114
β-Blocker	107 (14.0)	1640 (40.3)	<0.001	844 (15.3)	18 486 (35.4)	<0.001
Calcium channel blocker	160 (20.9)	714 (17.6)	0.028	927 (16.8)	7761 (14.9)	<0.001
Digoxin	21 (2.7)	83 (2.0)	0.222	115 (2.1)	476 (0.9)	<0.001
Diuretic	339 (44.2)	1406 (34.6)	<0.001	1437 (26.1)	10 512 (20.1)	<0.001
Statin	153 (19.9)	894 (22.0)	0.210	982 (17.8)	9883 (18.9)	0.042
Nitrate	116 (15.1)	481 (11.8)	0.010	515 (9.3)	4070 (7.8)	<0.001
Previous COPD medications						
Any inhalation therapy	464 (60.1)	2118 (51.8)	<0.001	464 (7.3)	2118 (3.7)	<0.001
Long-acting anticholinergic	201 (26.0)	897 (22.0)	0.013	25 (0.5)	163 (0.3)	0.081
Short-acting anticholinergic	118 (15.3)	431 (10.5)	<0.001	15 (0.3)	139 (0.3)	0.941
Glucocorticoid	133 (17.2)	579 (14.2)	0.028	190 (3.4)	1020 (1.9)	<0.001
β-2-Agonist	258 (33.4)	1097 (26.8)	<0.001	260 (4.7)	1484 (2.8)	<0.001
β-2-agonist combo (ATC: R03AK)	263 (34.1)	1112 (27.2)	<0.001	152 (2.7)	884 (1.7)	<0.001

For normally distributed continuous variables, mean and SD are presented. For non-normally distributed continuous variables (age and body mass index), median and 25th to 75th percentiles are presented. Count and percentage are presented for categorical variables. ACE indicates angiotensin-converting enzyme; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 2. In-Hospital Characteristics of Consecutive MI Hospital Survivors With COPD (4858) and Without COPD (57 997) in Sweden Between 2005 and 2010

	Patients With COPD			Patients Without COPD		
	No β-Blocker	β-Blocker	*P* Value	No β-Blocker	β-Blocker	
Characteristic	n=772	n=4086		n=5548	n=52 449	*P* Value
Heart rate	89±23	88±23	0.534	78±22	81±21	<0.001
Systolic blood pressure	143±29	146±28	0.004	146±28	150±28	<0.001
Diastolic blood pressure	79±18	83±17	<0.001	81±16	86±17	<0.001
Creatinine	85 (67 to 109)	85 (69 to 108)	0.977	84 (70 to 103)	82 (70 to 98)	<0.001
In-hospital anticoagulant			<0.004			<0.001
Heparin	25 (3.2)	205 (5.0)		255 (4.6)	3934 (7.5)	
Enoxaparin	393 (51.0)	2038 (50.0)		2415 (43.6)	23 017 (44.0)	
Fondaparinux	149 (19.3)	932 (22.9)		1261 (22.8)	1 2017 (23.0)	
In-hospital β-blocker			<0.001			<0.001
Intravenous	78 (10.1)	869 (21.3)		797 (14.4)	12 616 (24.1)	
Oral	128 (16.6)	2088 (51.3)		1337 (24.2)	27 582 (52.7)	
STEMI	131 (17.1)	1034 (25.4)	<0.001	1421 (25.7)	17 304 (33.1)	<0.001
Angiography	324 (42.0)	2544 (62.3)	<0.001	3459 (62.3)	40 400 (77.0)	<0.001
PCI	195 (25.3)	1761 (43.1)	<0.001	2349 (42.3)	31 262 (59.6)	<0.001
Stented	194 (25.1)	1698 (41.6)	<0.001	2251 (40.6)	30 089 (57.4)	<0.001
CABG	18 (2.3)	102 (2.5)	0.787	149 (2.7)	1614 (3.1)	0.106
CPAP	73 (9.5)	287 (7.0)	0.018	219 (4.0)	1790 (3.4)	0.039
AF at discharge	51 (6.9)	270 (6.8)	0.909	413 (7.8)	2332 (4.6)	<0.001
Bleeding req. surgery/transfusion	10 (1.3)	79 (1.9)	0.229	101 (1.8)	707 (1.4)	0.004
LVEF at discharge			<0.001			<0.001
Normal (≥50%)	213 (27.6)	1317 (32.2)		2155 (38.8)	21 595 (41.2)	
Mildly reduced (40% to 49%)	95 (12.3)	711 (17.4)		681 (12.3)	8921 (17.0)	
Moderately reduced (30% to 39%)	56 (7.3)	516 (12.6)		351 (6.3)	5361 (10.2)	
Severely reduced (<30%)	32 (4.1)	279 (6.8)		166 (3.0)	1980 (3.8)	
Unknown (missing data)	376 (48.7)	1263 (30.9)		2195 (39.6)	14 592 (27.8)	
Discharge medications						
ACE inhibitor	313 (40.6)	2310 (56.6)	<0.001	2414 (43.6)	31 156 (59.5)	<0.001
Angiotensin II receptor blocker	112 (14.5)	518 (12.7)	0.166	635 (11.4)	5935 (11.3)	0.782
Warfarin	44 (5.7)	231 (5.7)	0.963	306 (5.5)	2465 (4.7)	0.007
Aspirin	638 (82.6)	3748 (91.8)	<0.001	4789 (86.3)	49 521 (94.4)	<0.001
Clopidogrel	405 (53.2)	2826 (69.7)	<0.001	3437 (62.8)	40 221 (77.5)	<0.001
Calcium channel blocker	193 (25.0)	563 (13.8)	<0.001	992 (17.9)	6435 (12.3)	<0.001
Diuretic	407 (52.7)	1947 (47.7)	0.010	1747 (31.5)	14 635 (27.9)	<0.001
Statin	441 (57.1)	3195 (78.2)	<0.001	3718 (67.1)	44 938 (85.7)	<0.001
Nitrate	162 (21.0)	753 (18.5)	0.100	834 (15.1)	6539 (12.5)	<0.001

For normally distributed continuous variables, mean and SD are presented. For non-normally distributed continuous variables (creatinine), median and 25th to 75th percentiles are presented. Count and percentage are presented for categorical variables. ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

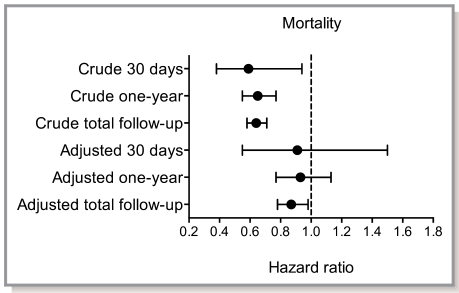

Figure 1. Hazard ratio and confidence intervals for MI patients with COPD discharged with β-blocker compared to MI patients with COPD not discharged with β-blocker. Crude all-cause mortality was calculated with the univariate Cox proportional hazard model. Adjusted all-cause mortality was calculated with the multivariate Cox proportional hazard model. Total follow-up time was up to 7.2 years. COPD indicates chronic obstructive pulmonary disease; MI, myocardial infarction.

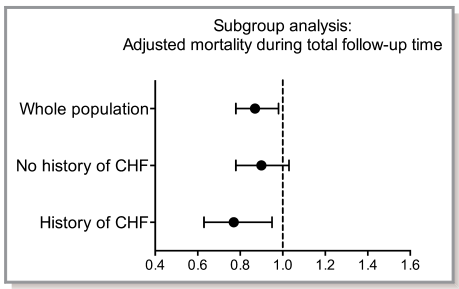

Figure 2. Hazard ratio and confidence intervals for MI patients with COPD discharged with β-blocker compared to MI patients with COPD not discharged with β-blocker. Adjusted all-cause mortality was calculated with the multivariate Cox proportional hazard model. CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

Discussion

The main finding in this study was an association between prescription of β-blockers at discharge and lower all-cause mortality in MI hospital survivors with concomitant COPD. After adjustment for potential confounders identified a priori, the association remained statistically significant but with lower relative risks. Patients with COPD and heart failure showed a numerically larger mortality difference; however, a trend toward lower mortality was also seen in patients with COPD without heart failure.

A total of 15.9% of the MI hospital survivors with COPD were not discharged with β-blockers. This group was older, had a higher frequency of previous stroke, less hypertension and more heart failure, yet less β-blockers at baseline. Instead, this group was more often prescribed calcium channel blockers and diuretics. Also, this group had more COPD medications at baseline, suggesting a more severe COPD. As a result, this group may have experienced more side effects and discontinued β-blockers earlier, or the treating physicians might have been more reluctant to prescribe β-blockers to these patients. Patients who were not discharged with β-blockers also underwent less invasive investigation during hospitalization and were also undertreated with other proven secondary prevention agents upon discharge, suggesting that a more conservative treatment approach was adopted.

Comparison With Previous Studies

Several other studies have reported that COPD patients are less likely to be discharged with β-blockers.[8,24,25] As shown in Table 1, our findings are consistent with these studies, but the frequency of β-blocker prescriptions was higher than in a recent study by Quint and co-workers.[18] This could reflect more underuse of β-blockers in COPD patients in the United Kingdom compared to Sweden as supported by a recent study investigating acute MI care in Sweden compared to the United Kingdom.[26] Differences in baseline- and in-hospital characteristics between the groups defined by β-blocker prescription were similar to findings from other studies.[18,25] Taken together, the evidence indicates that patients not treated with β-blockers have more cardiovascular comorbidities and especially more heart failure, which is problematic considering that one of the main indications for β-blocker treatment is heart failure. Whether these patients have unmeasured contraindications or if this reflects true undertreatment remains speculative.

After adjustments for confounders, the HR for all-cause mortality between the groups was 0.87. This effect estimate is lower compared to previous studies.[15,17,18,27] Reasons for this could range from different study population characteristics to slightly different study designs. Our study population was particularly old, which could be due to underdiagnosis of mild COPD leading to a later diagnosis when symptoms are more pronounced in an older patient population. Our study design excluded patients who died in-hospital, in part because of patients often being incorrectly classified as receiving no β-blockers when they died before being discharged, which creates a strong reverse causal link between not receiving β-blocker treatment and death, confounding the results in favor of β-blocker treatment. Our study goal was to study the effect of β-blockers as secondary prevention after patients leave the hospital.

Study Strengths and Limitations

Our study has several strengths. First, it was conducted in a modern setting, reflecting conditions in the present era of interventional cardiology with widespread use of percutaneous coronary intervention and modern secondary prevention, including dual antiplatelet treatment and statins. Second, it was a multicenter, nationwide study in a heterogeneous patient population with many complicating risk factors and comorbidities, reflecting real-life clinical circumstances. Third, the study sample size was large, considering the clinical question of β-blockers effect on all-cause mortality after MI in COPD patients.

The main limitation of our study is its observational nature, and thus a certain degree of residual confounding cannot be excluded. Also, we do not know whether patients not receiving a β-blocker at discharge were introduced to β-blockers at a later time, or if patients actually discharged with a β-blocker discontinued them during the follow-up time. We did not have data on COPD severity as we did not have measurements on pulmonary function. Furthermore, a wide range of physicians diagnosed the COPD cases and therefore diagnostic criteria might have varied between patients. However, the validity of a COPD diagnosis in our registry has recently been reported to be good.[22] Lastly, we want to point out that this study investigated all-cause mortality, instead of cardiovascular mortality, to account for the high probability of competing risk of death since the patients with COPD were at high risk of both respiratory and infectious causes of death. As such, the manuscript does not provide insights into the specific cardioprotective effects of β-blockers in MI patients with concomitant COPD.

Conclusions

Being discharged with a β-blocker after an MI in COPD patients was associated with lower all-cause mortality compared to being discharged without a β-blocker. The association was stronger in patients with a history of congestive heart failure. The results indicate that MI patients with COPD may benefit from treatment with β-blockers.

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Disclosures

None.

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Paper III

ORIGINAL RESEARCH

Ticagrelor Versus Clopidogrel in Patients With Acute Coronary Syndromes and Chronic Obstructive Pulmonary Disease: An Analysis From the Platelet Inhibition and Patient Outcomes (PLATO) Trial

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***Background*—**Patients with chronic obstructive pulmonary disease (COPD) experiencing acute coronary syndromes (ACS) are at high risk for clinical events. In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor versus clopidogrel reduced the primary endpoint of death from vascular causes, myocardial infarction, or stroke after ACS, but increased the incidence of dyspnea, which may lead clinicians to withhold ticagrelor from COPD patients.

***Methods and Results*—**In 18 624 patients with ACS randomized to treatment with ticagrelor or clopidogrel, history of COPD was recorded in 1085 (5.8%). At 1 year, the primary endpoint occurred in 17.7% of patients with COPD versus 10.4% in those without COPD ($P<0.001$). The 1-year event rate for the primary endpoint in COPD patients treated with ticagrelor versus clopidogrel was 14.8% versus 20.6% (hazard ratio [HR]=0.72; 95% confidence interval [CI]: 0.54 to 0.97), for death from any cause 8.4% versus 12.4% (HR=0.70; 95% CI: 0.47 to 1.04), and for PLATO-defined major bleeding rates at 1 year 14.6% versus 16.6% (HR=0.85; 95% CI: 0.61 to 1.17). Dyspnea occurred more frequently with ticagrelor (26.1% vs. 16.3%; HR=1.71; 95% CI: 1.28 to 2.30). There was no differential increase in the relative risk of dyspnea compared to non-COPD patients (HR=1.85). No COPD status-by-treatment interactions were found, showing consistency with the main trial results.

***Conclusions*—**In this post-hoc analysis, COPD patients experienced high rates of ischemic events. Ticagrelor versus clopidogrel reduced and substantially decreased the absolute risk of ischemic events (5.8%) in COPD patients, without increasing overall major bleeding events. The benefit-risk profile supports the use of ticagrelor in patients with ACS and concomitant COPD.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00391872. **(*J Am Heart Assoc*. 2015;4: e002490 doi: 10.1161/JAHA.115.002490)**

Key Words: cardiovascular diseases • lung • myocardial infarction

Patients with chronic obstructive pulmonary disease (COPD) are at high risk of experiencing acute coronary syndromes (ACS).[1] This high risk is partly attributed to shared common risk factors, such as higher age, smoking,[2] and systemic inflammation.[3] In addition, reduced pulmonary function, independent of smoking, has been associated with increased risk of ACS, arrhythmias, and cardiovascular death.[4–7] Patients with COPD experiencing ACS have

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Accompanying Tables S1 and S2 are available at http://jaha.ahajournals.org/content/4/10/e002490/suppl/DC1

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subsequent increased risk of recurrent ischemic events and increased all-cause mortality compared to those without COPD.[8–11] This is, to a certain extent, explained by comorbidities,[11] but it has been shown that patients with COPD are less likely to receive reperfusion therapy and guideline-recommended secondary prevention therapies, which could further worsen long-term outcomes.[8,9,11,12]

The PLATO study showed superior efficacy of the non-thienopyridine platelet $P2Y_{12}$–receptor inhibitor, ticagrelor, as compared to clopidogrel in preventing death from vascular causes, myocardial infarction (MI), or stroke in patients with ACS, without an increase in overall major bleeding events.[13] However, patients randomized to ticagrelor had increased incidence of dyspnea, a known adverse effect commonly characterized as mild to moderate and often transient without being associated with either differences in efficacy or safety outcomes[14] or an adverse effect on pulmonary function.[15] Previous substudies from PLATO have shown ticagrelor to be superior to clopidogrel in different high-risk patient populations, including patients with diabetes[16] or impaired renal function,[17] and in the elderly.[18]

Despite ACS patients with concomitant COPD being at higher risk thus warranting efficacious therapies, clinicians may be reluctant to prescribe ticagrelor to these patients owing to the increased incidence of dyspnea. At the time the PLATO trial was published, an accompanying editorial discouraged the use of ticagrelor in patients with COPD.[19] Furthermore, the European Medicines Agency assessment report indicates caution when prescribing ticagrelor to patients with history of COPD, owing to a potentially increased absolute risk of dyspnea.[20] Thus, the aim of the present study was to study the efficacy and safety profile of ticagrelor versus clopidogrel in ACS patients with COPD.

Methods

The PLATO trial (http://www.clinicaltrials.gov identifier: NCT00391872) enrolled 18 624 patients between October 2006 and July 2008. Details about the study design, patients, outcome definitions, and results have been published.[13,21] In each country, the study was approved by national regulatory authorities and by local ethics committees or institutional review boards, according to local regulations. All patients provided written consent to participate in the study. Patients were eligible for enrollment if they were hospitalized for ACS, with or without ST-segment elevation, and with symptom onset during the previous 24 hours. Major exclusion criteria were contraindication to clopidogrel, fibrinolytic therapy within 24 hours before randomization, a need for oral anticoagulation therapy, an increased risk of bradycardia, and simultaneous therapy with a strong cytochrome P450 3A inhibitor or inducer. Patients were randomized to ticagrelor or clopidogrel in a double-blind, double-dummy fashion. All patients received acetylsalicylic acid unless intolerant. The median treatment duration was 9.1 months.

The primary efficacy endpoint was time to first occurrence of any event from the composite endpoint consisting of death from vascular causes, MI, or stroke. Secondary efficacy endpoints were individual events of MI, stroke, death from vascular causes, and death from any cause. The primary safety endpoint was time to first occurrence of major bleeding, defined by the study criteria. In addition, bleeding events defined according to the TIMI criteria, and life-threatening or fatal bleeding (defined by the study criteria) were also assessed. Other adverse events, including dyspnea, were recorded in the electronic case report form. Each on-site investigator assessed COPD status at the time of randomization and reported in the case report form whether the patient had “current COPD” or “no COPD.”

Statistical Analyses

Baseline patient characteristics were compared by COPD status. Continuous variables are presented as medians (25th to 75th percentile) and differences were compared using the Wilcoxon rank-sum test. Categorical variables are presented as counts (percentages) and differences were compared using the Pearson chi-square test when the cell frequencies were sufficient; otherwise, an exact test was used. For patients with and without COPD, Kaplan–Meier event rates 12 months after randomization were calculated separately for ticagrelor- and clopidogrel-treated groups, for each efficacy and safety endpoint. Cox proportional hazards regression was used to characterize the randomized treatment effect in patients with and without COPD. For each endpoint, the hazard ratio (HR; 95% confidence interval [CI]) for the COPD cohort and non-COPD cohort and treatment-by-COPD interaction *P* value are reported. Cox proportional hazard regression was also used to characterize the univariate, age-adjusted, and multivariate HRs with 95% CI for the primary efficacy endpoint in patients with COPD versus patients without COPD. Adjustment covariates include: previous MI, previous nonhemorrhagic stroke, heart rate, Killip class at entry, age, white blood cells, peripheral artery disease, previous coronary artery bypass grafting (CABG), time from symptoms to randomization, diabetes, hemoglobin, region, changes in electrocardiogram at entry, final diagnosis of index event, previous transient ischemic attack, randomized treatment, and creatinine. Continuous variables were assessed for linearity on the log-hazard scale, and, when appropriate, linear splines were used to account for nonlinear relationships with the primary efficacy endpoint.

Table 1. Baseline Characteristic According to COPD Status

Characteristic	COPD (N=1085)	No COPD (N=17 528)	*P* Value
Demographics			
Age, yr	67 (59 to 73)	62 (54 to 70)	<0.001
Age ≥75 years	236/1085 (21.8)	2640/17 528 (15.1)	<0.001
Female gender	325/1085 (30.0)	4959/17 528 (28.3)	0.239
Race			0.002
Caucasian	1010/1085 (93.1)	16 057/17 528 (91.6)	
Black	19/1085 (1.8)	210/17 528 (1.2)	
Oriental	39/1085 (3.6)	1057/17 528 (6.0)	
Other	17/1085 (1.6)	204/17 528 (1.2)	
BMI, kg/m^2	27.7 (24.2 to 31.1)	27.4 (24.7 to 30.4)	0.644
Waist circumference, cm	100 (90 to 110)	98 (90 to 106)	<0.001
Smoking status			<0.001
Nonsmoker	204/1085 (18.8)	7052/17 525 (40.2)	
Ex-smoker	390/1085 (35.9)	4286/17 525 (24.5)	
Habitual smoker	491/1085 (45.3)	6187/17 525 (35.3)	
Medical history			
Hypertension	783/1085 (72.2)	11 400/17 528 (65.0)	<0.001
Dyslipidemia	585/1085 (53.9)	8104/17 527 (46.2)	<0.001
Diabetes mellitus	292/1085 (26.9)	4370/17 528 (24.9)	0.144
Angina pectoris	632/1085 (58.2)	7726/17 528 (44.1)	<0.001
Myocardial infarction	322/1085 (29.7)	3502/17 528 (20.0)	<0.001
Congestive heart failure	152/1085 (14.0)	898/17 528 (5.1)	<0.001
Coronary artery disease	441/1085 (40.6)	4685/17 528 (26.7)	<0.001
PCI	225/1085 (20.7)	2267/17 527 (12.9)	<0.001
CABG	132/1085 (12.2)	974/17 528 (5.6)	<0.001
Transient ischemic attack	46/1085 (4.2)	453/17 528 (2.6)	0.001
Nonhemorrhagic stroke	47/1084 (4.3)	675/17 528 (3.9)	0.422
Peripheral artery disease	153/1085 (14.1)	991/17 528 (5.7)	<0.001
Pacemaker	23/1085 (2.1)	133/17 528 (0.8)	<0.001
Peptic ulcer disease	122/1085 (11.2)	1151/17 528 (6.6)	<0.001
Gastrointestinal bleeding	44/1085 (4.1)	221/17 528 (1.3)	<0.001
Asthma	118/1085 (10.9)	414/17 528 (2.4)	<0.001
Chronic renal disease	93/1085 (8.6)	692/17 528 (3.9)	<0.001
Biochemistry			
Creatinine clearance [CG], mL/min	73.3 (56.4 to 91.9)	80.7 (63.4 to 99.3)	<0.001
Glucose, mmol/L	6.7 (5.6 to 8.5)	6.9 (5.7 to 8.8)	0.023
HbA1c, %	6.1 (5.7 to 6.7)	6.0 (5.6 to 6.6)	0.020
Hemoglobin, g/L	138 (126 to 148)	140 (129 to 149)	0.002
Total cholesterol, mmol/L	4.8 (4.1 to 5.8)	5.1 (4.4 to 6.0)	<0.001
LDL cholesterol, mmol/L	2.9 (2.2 to 3.6)	3.1 (2.4 to 3.9)	<0.001
HDL cholesterol, mmol/L	1.2 (1.0 to 1.5)	1.2 (1.0 to 1.4)	0.377
First central TnI positive	883/1085 (81.4)	14 205/17 528 (81.0)	0.889

Continued

Table 1. Continued

Characteristic	COPD (N=1085)	No COPD (N=17 528)	*P* Value
Medications at randomization			
Aspirin	997/1085 (91.9)	16 428/17 511 (93.8)	0.011
Unfractionated heparin	536/1085 (49.4)	8922/17 511 (51.0)	0.322
Low molecular weight heparin	460/1085 (42.4)	6855/17 511 (39.1)	0.033
GP IIb/IIIa inhibitors	234/1085 (21.6)	4345/17 511 (24.8)	0.016
Beta blockers	673/1085 (62.0)	12 324/17 511 (70.4)	<0.001
ACE inhibitors	628/1085 (57.9)	9893/17 511 (56.5)	0.372
Angiotensin II receptor blockers	126/1085 (11.6)	1519/17 511 (8.7)	<0.001
Statins	839/1085 (77.3)	13 864/17 511 (79.2)	0.147
Calcium channel blockers	181/1085 (16.7)	2527/17 511 (14.4)	0.041
Diuretics	416/1085 (38.3)	3906/17 511 (22.3)	<0.001
Proton pump inhibitors	427/1085 (39.4)	5946/17 511 (34.0)	<0.001
Nitrates	794/1085 (73.2)	12 235/17 511 (69.9)	0.021
Intended treatment approach			0.004
Invasive	740/1085 (68.2)	12 658/17 528 (72.2)	
Medically managed	345/1085 (31.8)	4870/17 528 (27.8)	
Final diagnosis			<0.001
NSTEMI/UA	736/1085 (67.8)	10 333/17 528 (59.0)	
STEMI	349/1085 (32.2)	7195/17 528 (41.0)	

ACE indicates angiotensin-converting enzyme; BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; GP IIb/IIIa, glycoprotein IIb/IIIa; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TnI, troponin I; UA, unstable angina.

All analyses were performed according to the intention-to-treat definition with SAS software (version 9.2; SAS Institute Inc., Cary, NC). A 2-sided *P* value of 0.05 was considered statistically significant for overall treatment differences.

Results

Patient Characteristics

Of 18 624 patients randomized in the PLATO study, 1085 (5.8%) were reported by the investigators as having COPD. These patients were older and more often current or ex-smokers (Table 1). They more frequently had multiple cardiovascular risk factors and comorbidities, including a history of angina pectoris, MI, congestive heart failure, and coronary artery disease. In addition, COPD patients had lower median creatinine clearance, were less often treated with beta-blockers, and more often treated with diuretics. In regard to treatment approach, patients with COPD were less frequently invasively investigated. Furthermore, fewer COPD patients were diagnosed with ST-segment elevation myocardial infarction (STEMI).

Baseline characteristics, medications, and treatment approach were well matched between the randomized treatment groups (Table S1).

Ischemic and Bleeding Outcomes in Relation to COPD Status and Randomized Treatment

Rates of both ischemic and bleeding events were higher in patients with COPD compared to those without COPD (Figure 1), and crude all-cause mortality was doubled (10.4% vs. 4.9%; HR=2.09; 95% CI: 1.70 to 2.57). The univariate, age-adjusted, and multivariate HRs for the primary composite endpoint for COPD patients versus non-COPD patients were 1.75 (95% CI: 1.50 to 2.04), 1.53 (95% CI: 1.31 to 1.79), and 1.31 (95% CI: 1.09 to 1.57), respectively.

Ticagrelor significantly reduced the primary composite endpoint of death from vascular causes, MI, or stroke, both in patients with or without COPD (Figures 1 and 2). The relative reduction in the rate of the primary endpoint with ticagrelor was similar between COPD and non-COPD patients and consistent with the main trial findings, but the absolute reduction was greater in patients with COPD (5.8% vs. 1.5%).

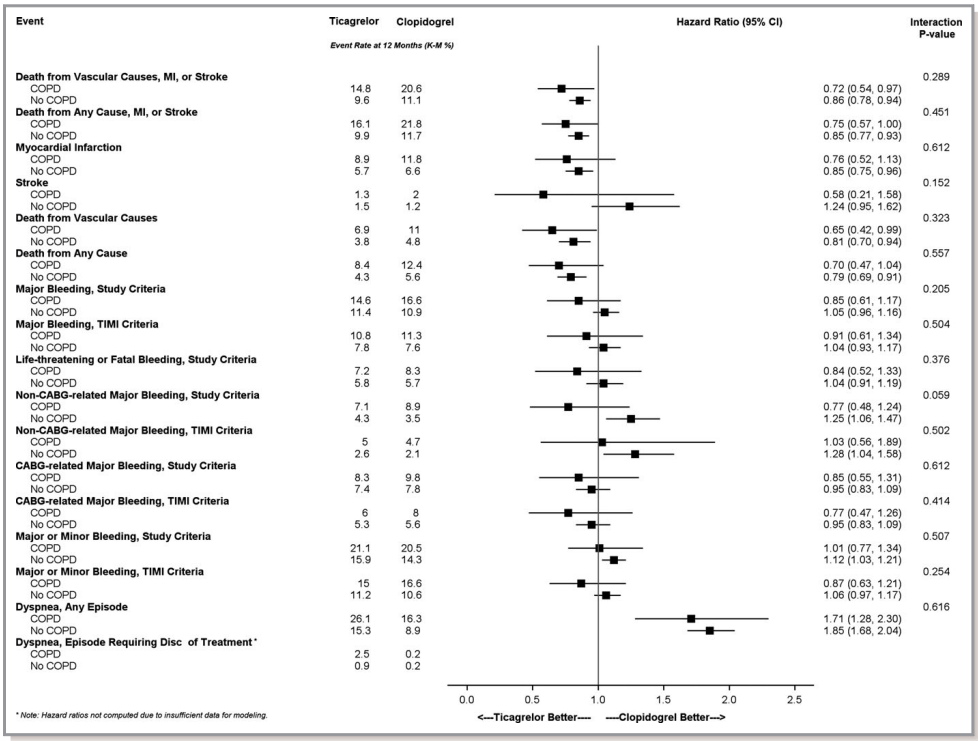

Figure 1. The percentages are Kaplan–Meier (K-M) estimates of the rate of the endpoint at 12 months. CABG indicates coronary artery bypass graft; CI, confidence interval; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction study group.

No COPD status-by-treatment interactions were found in the efficacy endpoint analyses. In line with the main trial, ticagrelor was associated with a reduction in death from any cause in patients with or without COPD (interaction *P*=0.557).

For COPD and non-COPD patients, no significant difference in the rates of overall major bleeding, regardless of using PLATO (Figure 3) or thrombolysis in myocardial infarction study group (TIMI) criteria, was observed between ticagrelor- and clopidogrel-treated patients (Figure 1). In accord with the main trial, ticagrelor was associated with increased PLATO-defined non-CABG-related major bleeding in non-COPD patients, but in COPD patients these rates were similar, although the interaction analysis was not significant (*P*=0.059). No interaction tests were significant irrespective of bleeding type and definition.

Dyspnea-Related Outcomes, Discontinuation of Study Drug, and Adverse Events

Ticagrelor significantly increased the incidence of dyspnea, both in patients with and without COPD (Figure 1). Although absolute dyspnea event rates were higher in COPD patients, ticagrelor-associated relative risks were similar and no COPD status-by-treatment interaction was found (*P*=0.616). Dyspnea-related discontinuation of study drug was more common with ticagrelor, irrespective of COPD status. COPD patients treated with ticagrelor showed numerically more dyspnea-related events leading to discontinuation of study drug compared to non-COPD patients (2.5% vs. 0.9%), although the numbers of discontinuations were very small. Overall premature discontinuation of study drug was more common in COPD patients treated with ticagrelor (Table 2).

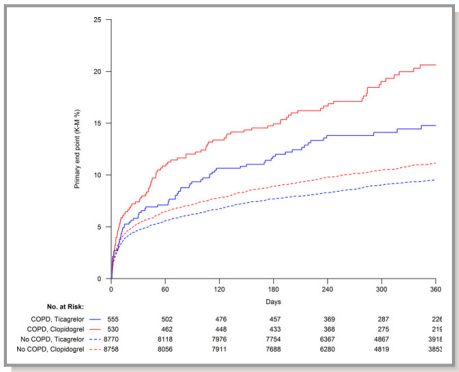

Figure 2. Cumulative Kaplan–Meier estimates of the time to first adjudicated occurrence of the primary efficacy endpoint (a composite of death from vascular causes, myocardial infarction, or stroke). Chronic obstructive pulmonary disease (COPD) patients randomized to ticagrelor or clopidogrel are represented by solid blue and red lines, respectively, and non-COPD patients randomized to ticagrelor or clopidogrel are represented by dashed blue and red lines, respectively. K-M indicates Kaplan–Meier.

Adherence to study drug, defined as the use of more than 80% of the study medication during each interval between visits, was slightly higher in COPD patients treated with ticagrelor, whereas the exposure, meaning total days on treatment, was slightly lower. There were more adverse

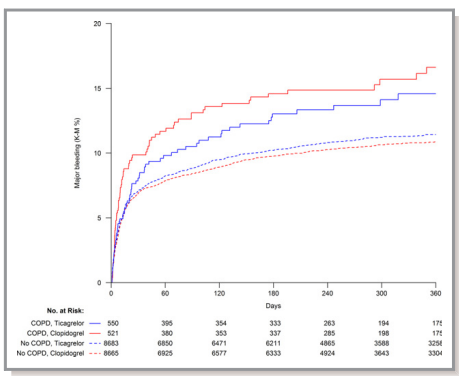

Figure 3. Cumulative Kaplan–Meier estimates of the time to first PLATO-defined major bleeding event. COPD patients randomized to ticagrelor or clopidogrel are represented by solid blue and red lines, respectively, and non-COPD patients randomized to ticagrelor or clopidogrel are represented by dashed blue and red lines, respectively. COPD indicates chronic obstructive pulmonary disease; K-M, Kaplan–Meier; PLATO, Platelet Inhibition and Patient Outcomes.

Table 2. Randomized Treatment Use and Dyspnea-Related AEs

No. of COPD Patients, No. (%)	Ticagrelor (n=555)	Clopidogrel (n=530)
Discontinuation and adherence		
Premature discontinuation of study drug	184 (33.2)	140 (26.4)
Adherence* to study drug	436 (78.6)	395 (74.5)
Exposure to study drug, median (IQR)	266 (65 to 364)	278 (99 to 364)
AE summary		
Dyspnea as the predominant symptom	111 (20.0)	64 (12.1)
SAE	10 (1.8)	5 (0.9)
AE is serious owing to†—No./SAE (%)		
Death	0/10 (0.0)	0/5 (0.0)
Life threatening	3/10 (30.0)	0/5 (0.0)
In-patient hospitalization or prolongation of hospitalization	10/10 (100.0)	5/5 (100.0)
Persistent or significant disability/ incapacity	2/10 (20.0)	1/5 (20.0)
A congenital abnormality/birth defect	0/10 (0.0)	0/5 (0.0)
Important medical event	5/10 (50.0)	1/5 (20.0)

AE indicates adverse event; COPD chronic obstructive pulmonary disease; IQR, interquartile range; SAE, serious AE.
*Adherence to the study drug was defined as the use of more than 80% of the study medication during each interval between visits, as assessed by the site investigator.
†According to the SAE Report form, a patient can have multiple criteria selected for classifying the AE as serious.

events (AEs) related to dyspnea in patients with COPD treated with ticagrelor (Table 2). The numbers of serious AEs (SAEs) were small. The suspected etiologies of dyspnea events are shown in Table S2.

Subgroup Analyses

Efficacy and safety outcomes in subgroups defined by initial treatment approach (invasive investigation vs. medically managed) were consistent with the main findings (data not shown). Likewise, an additional analysis with nonsmokers excluded was also consistent with the main findings (data not shown).

Discussion

In line with other published studies,[8–11] the PLATO trial highlights patients with COPD as a high-risk population when experiencing ACS, shown by both increased risk of recurrent ischemic and bleeding events as well as by doubled crude

all-cause mortality after an ACS. In the present study, patients with COPD were older with a particularly high-risk profile, including higher prevalence of congestive heart failure, coronary artery disease, and chronic renal disease findings similar to previous observational data.[11,22] In regard to treatment approach, COPD patients were slightly less often planned for invasive investigation, but guideline-recommended therapies were still prescribed to a high extent (except beta-blockers), a finding in contrast with the general undertreatment observed in many observational studies.[8,11,12,23]

The most important finding in the present study is that ticagrelor, compared to clopidogrel, significantly reduced the primary efficacy endpoint consisting of death from vascular causes, MI, and stroke regardless of COPD status, without increasing the rate of overall major bleeding. In the COPD subset, the absolute risk reduction by ticagrelor versus clopidogrel was 4 times greater, as compared to those without COPD. The findings in this study and other high-risk subgroup analyses from PLATO suggest that patients at greater risk have increased absolute benefit of ticagrelor.[16,17,24]

In terms of bleeding, the results from the present study align with the main trial results, with similar overall major bleeding rates between ticagrelor- and clopidogrel-treated groups. In the main trial, PLATO-defined non-CABG-related major bleeding was increased in patients treated with ticagrelor. However, in the present study, this increase was found in the non-COPD-cohort, but not in the COPD cohort, though the interaction analysis did not reach statistical significance (P=0.059).

Although there was no relative increase in ticagrelor-related dyspnea in the COPD cohort, there was a higher absolute risk of dyspnea in these patients. Even though more than 1 quarter of the ticagrelor-treated COPD patients experienced dyspnea, only 2.5% of these patients discontinued ticagrelor because of dyspnea, compared to 0.9% among ticagrelor-treated patients without COPD. Furthermore, the number of SAEss related to dyspnea was few and none were fatal. Most important, the overall ischemic event rate was much lower in the ticagrelor-treated COPD subset, despite the high incidence of dyspnea, in accord with previous studies of ticagrelor-related dyspnea showing that it is often transient and usually mild to moderate in severity without any adverse effect on either lung or heart function.[14,15,25]

Limitations

This study was a post-hoc analysis not prespecified in the original trial design. The COPD cohort of 1085 patients was not powered to show a difference in the primary outcome between the randomized groups. The randomization in PLATO was not stratified for COPD status; therefore, some imbalance between the groups may exist among the subset of patients with COPD. Still, the COPD groups stratified by treatment were well balanced regarding baseline characteristics. Furthermore, because COPD status was assessed by the investigators and not based on pulmonary function tests, the COPD cohort may represent a more clinically evident and severe COPD phenotype. However, the assessments performed by the PLATO investigators probably reflect the routine clinical setting.

Conclusions

Patients with ACS and concomitant COPD are a high-risk population with a worse ischemic outcome as well as increased bleeding rates. Ticagrelor significantly reduced the risk of ischemic events with an absolute reduction in COPD patients that was nearly 4 times as great as in non-COPD patients, without an increase in overall major bleeding. There was no differential increase in the relative risk of dyspnea compared to non-COPD patients, but the increase in absolute risk was greater in COPD patients. Although a post-hoc analysis, the benefit-risk profile supports the use of ticagrelor in patients with ACS and COPD. In consideration of the accumulated evidence that patients with COPD constitute a high-risk population with a poor prognosis, who may also be undertreated with guideline-recommended secondary prevention, ticagrelor presents an opportunity to improve outcomes in patients with ACS and COPD.

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Table S1. Baseline Characteristics of the COPD Patients According to Randomized Treatment.

Characteristic	Overall (N=1085)	Ticagrelor (N=555)	Clopidogrel (N=530)
Age, years	67 (59-73)	67 (60-73)	66 (59-73)
Age ≥75 years	236 / 1085 (21.8)	124 / 555 (22.3)	112 / 530 (21.1)
Female Gender	325 / 1085 (30.0)	178 / 555 (32.1)	147 / 530 (27.7)
Race			
Caucasian	1010 / 1085 (93.1)	520 / 555 (93.7)	490 / 530 (92.5)
Black	19 / 1085 (1.8)	8 / 555 (1.4)	11 / 530 (2.1)
Oriental	39 / 1085 (3.6)	18 / 555 (3.2)	21 / 530 (4.0)
Other	17 / 1085 (1.6)	9 / 555 (1.6)	8 / 530 (1.5)
Body Mass Index	27.7 (24.2-31.1)	27.7 (24.3-31.3)	27.6 (24.0-30.7)
Waist Circumference, cm	100 (90-110)	100 (90-110)	100 (90-110)
Smoking Status			

Non-Smoker	204 / 1085 (18.8)	116 / 555 (20.9)	88 / 530 (16.6)
Ex-Smoker	390 / 1085 (35.9)	195 / 555 (35.1)	195 / 530 (36.8)
Habitual Smoker	491 / 1085 (45.3)	244 / 555 (44.0)	247 / 530 (46.6)
Medical History			
Hypertension	783 / 1085 (72.2)	411 / 555 (74.1)	372 / 530 (70.2)
Dyslipidemia	585 / 1085 (53.9)	296 / 555 (53.3)	289 / 530 (54.5)
Diabetes Mellitus	292 / 1085 (26.9)	159 / 555 (28.6)	133 / 530 (25.1)
Angina Pectoris	632 / 1085 (58.2)	332 / 555 (59.8)	300 / 530 (56.6)
Myocardial Infarction	322 / 1085 (29.7)	164 / 555 (29.5)	158 / 530 (29.8)
Congestive Heart Failure	152 / 1085 (14.0)	72 / 555 (13.0)	80 / 530 (15.1)
Coronary Artery Disease	441 / 1085 (40.6)	227 / 555 (40.9)	214 / 530 (40.4)
Percutaneous Coronary Intervention	225 / 1085 (20.7)	110 / 555 (19.8)	115 / 530 (21.7)
Coronary Artery Bypass Graft	132 / 1085 (12.2)	61 / 555 (11.0)	71 / 530 (13.4)
Transient Ischemic Attack	46 / 1085 (4.2)	23 / 555 (4.1)	23 / 530 (4.3)
Non-Hemorrhagic Stroke	47 / 1084 (4.3)	24 / 555 (4.3)	23 / 529 (4.3)
Peripheral Artery Disease	153 / 1085 (14.1)	76 / 555 (13.7)	77 / 530 (14.5)

Pacemaker	23 / 1085 (2.1)	14 / 555 (2.5)	9 / 530 (1.7)
Peptic Ulcer Disease	122 / 1085 (11.2)	63 / 555 (11.4)	59 / 530 (11.1)
Gastrointestinal Bleeding	44 / 1085 (4.1)	31 / 555 (5.6)	13 / 530 (2.5)
Asthma	118 / 1085 (10.9)	54 / 555 (9.7)	64 / 530 (12.1)
Chronic Renal Disease	93 / 1085 (8.6)	42 / 555 (7.6)	51 / 530 (9.6)
Biochemistry			
Creatinine Clearance [CG] (ml/min)	73.3 (56.4-91.9)	73.4 (57.1-92.0)	73.3 (56.1-91.7)
Glucose (mmol/L)	6.7 (5.6-8.5)	6.8 (5.7-8.7)	6.6 (5.6-8.2)
Hemoglobin A1c (%)	6.1 (5.7-6.7)	6.1 (5.7-6.8)	6.0 (5.7-6.6)
Hemoglobin (g/L)	138 (126-148)	138 (126-147)	139 (125-149)
Total Cholesterol (mmol/L)	4.8 (4.1-5.8)	4.9 (4.1-5.7)	4.8 (4.1-5.9)
LDL Cholesterol (mmol/L)	2.9 (2.2-3.6)	2.9 (2.3-3.6)	2.9 (2.2-3.7)
HDL Cholesterol (mmol/L)	1.2 (1.0-1.5)	1.2 (1.0-1.4)	1.2 (1.0-1.5)
First Central Troponin I Positive	883 / 1085 (81.4)	455 / 555 (82.0)	428 / 530 (80.8)
Medications at Time of Randomization			
Aspirin	997 / 1085 (91.9)	517 / 555 (93.2)	480 / 530 (90.6)

Unfractionated Heparin	536 / 1085 (49.4)	274 / 555 (49.4)	262 / 530 (49.4)
Low Molecular Weight Heparin	460 / 1085 (42.4)	248 / 555 (44.7)	212 / 530 (40.0)
GP IIb/IIIa Inhibitors	234 / 1085 (21.6)	121 / 555 (21.8)	113 / 530 (21.3)
Beta Blockers	673 / 1085 (62.0)	345 / 555 (62.2)	328 / 530 (61.9)
ACE Inhibitors	628 / 1085 (57.9)	319 / 555 (57.5)	309 / 530 (58.3)
Angiotensin II Receptor Blockers	126 / 1085 (11.6)	69 / 555 (12.4)	57 / 530 (10.8)
Statins	839 / 1085 (77.3)	419 / 555 (75.5)	420 / 530 (79.2)
Calcium Channel Blockers	181 / 1085 (16.7)	93 / 555 (16.8)	88 / 530 (16.6)
Diuretics	416 / 1085 (38.3)	209 / 555 (37.7)	207 / 530 (39.1)
Proton Pump Inhibitors	427 / 1085 (39.4)	207 / 555 (37.3)	220 / 530 (41.5)
Nitrates	794 / 1085 (73.2)	421 / 555 (75.9)	373 / 530 (70.4)
Treatment Approach			
Invasive	740 / 1085 (68.2)	387 / 555 (69.7)	353 / 530 (66.6)
Medically Managed	345 / 1085 (31.8)	168 / 555 (30.3)	177 / 530 (33.4)
Final diagnosis			
NSTEMI/UA	736 / 1085 (67.8)	376 / 555 (67.7)	360 / 530 (67.9)

STEMI	349 / 1085 (32.2)	179 / 555 (32.3)	170 / 530 (32.1)

Table S1. COPD indicates chronic obstructive pulmonary disease; BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TnI, troponin I; GP IIb/IIIa, Glycoprotein IIb/IIIa; ACE, angiotensin-converting enzyme; NSTEMI, non-ST-elevation myocardial infarction; UA, unstable angina; STEMI, ST-elevation myocardial infarction.

Table S2. Suspected etiology of dyspnea events according to randomized treatment and COPD Status.

Suspected Etiology	Ticagrelor (N=9233)		Clopidogrel (N=9186)	
	COPD (N=550)	No COPD (N=8683)	COPD (N=521)	No COPD (N=8665)
Any episode – no. / total no. (%)	**117/550 (21.3)**	**1153/8683 (13.3)**	**71/521 (13.6)**	**650/8665 (7.5)**
Heart failure (cardiac etiology)	19/117 (16.2)	270/1153 (23.4)	19/71 (26.8)	208/650 (32.0)
Heart failure (non-cardiac etiology)	3/117 (2.6)	3/1153 (0.3)	0/71 (0.0%)	3/650 (0.5)
Other cardiac etiology	1/117 (0.9)	113/1153 (9.8)	4/71 (5.6)	56/650 (8.6)
Asthma	1/117 (0.9)	10/1153 (0.9)	1/71 (1.4)	4/650 (0.6)
COPD	51/117 (43.6)	23/1153 (2.0)	18/71 (25.4)	16/650 (2.5)
Pulmonary vascular disease	0/117 (0.0)	1/1153 (0.1)	0/71 (0.0)	3/650 (0.5)
Parenchymal lung disease	0/117 (0.0)	5/1153 (0.4)	0/71 (0.0)	3/650 (0.5)
Infection	1/117 (0.9)	14/1153 (1.2)	2/71 (2.8)	7/650 (1.1)
Metabolic disorder	0/117 (0.0)	3/1153 (0.3)	0/71 (0.0)	0/650 (0.0)

Anxiety disorder	7/117 (6.0)	56/1153 (0.9)	1/71 (1.4)	34/650 (5.2)
Other known cause	6/117 (5.1)	98/1153 (8.5)	4/71 (5.6)	55/650 (8.5)
Unexplained/unknown	11/117 (9.4)	334/1153 (29.0)	6/71 (8.5)	131/650 (20.2)
Missing	17/117 (14.5)	223/1153 (19.3)	16/71 (22.5)	130/650 (20.0)

Table S2. COPD indicates chronic obstructive pulmonary disease.

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