Aspects of Myocardial Infarction Incidence and Prognosis

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ASPECTS OF MYOCARDIAL INFARCTION INCIDENCE AND PROGNOSIS

PhD thesis

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Karam Sadoon Majeed Al-Zuhairi

Aalborg, September 2015

ORIGINAL PAPERS

This dissertation is based on the following studies:

Study I

Alzuhairi KS, Søgaard P, Ravkilde J, Gislason G, Køber L, Torp-Pedersen C.

Incidence and outcome of first myocardial infarction according to gender and age in Denmark over a 35-year period (1978–2012).

European Heart Journal- Quality of Care and Clinical Outcomes. 2015:qcv016. doi:10.1093/ehjqcco/qcv016. (E-pub a head of print, first published online 24 July 2015).

Study II

Alzuhairi KS, Søgaard P, Ravkilde J, Azimi A, Mæng M, Jensen LO, Torp-Pedersen C.

Long-term outcomes of patients with non-ST-segment elevation myocardial infarction according to coronary artery pathology on the angiography.

The article is submitted for publication.

Study III

Alzuhairi KS, Hjortshøj S, Kristensen SR, Ravkilde J.

A third troponin T blood sample is not cost-effective in patients with suspected non-ST segment elevation acute coronary syndrome.

Scandinavian Journal of Clinical and Laboratory Investigations. 2011 Apr;71(2):117-22.

ENGLISH SUMMARY

Background

This Ph.D. review addresses 3 problems with relevance to myocardial infarction (MI). (1) The mortality rate due to ischemic heart disease has declined in western countries. Changes in MI risk factors and treatment strategies may have potentially influenced incidence and mortality rates. However, the change in risk factors was not similar in all age and gender groups. Therefore, the changes over time in incidence and mortality rates associated with MI in various age and gender groups are important factors to understand. (2) There are established medical treatments and revascularization recommendations for MI patients with stenosis of coronary vasculature. Nevertheless, many MI patients have no significant stenosis, and these patients do not receive the same medical treatment as those with significant stenosis. Therefore, the prognosis of those without stenosis need further study. (3) Costs of admissions for patients with MI and suspected MI comprise a huge burden on the health care system. One aspect of that lies in the management of patients admitted with suspected acute coronary syndrome. Before patients can be discharged from the hospital, a routine draw of three or more blood samples of cardiac troponin must be taken before ruling out MI. This routine practice leads to extended hospital stays and increased costs. The cost-effectiveness of this approach has not been examined until now.

Objectives: The following aims in this thesis address these unresolved aspects of MI incidence, prognosis, and health care costs:

1. To examine temporal trends in myocardial infarction incidence and mortality according to age and gender in Denmark over a 35-year period (1978-2012).

2. To investigate long-term outcomes of patients with non-ST-segment elevation myocardial infarction according to coronary artery pathology on the angiography.

3. To analyse the cost-effectiveness of the third blood sample to measure troponin in patients admitted with a suspected non-ST-segment elevation acute coronary syndrome.

Methods

Studies I and II were historical prospective studies in which data collected from different Danish registries were used. Study I included patients aged ≥30 years admitted for first time MI to all Danish hospitals between 1978-2012 (n=316.790). Mortality status was collected from Danish Civil registry.

Study II included 8.889 patients admitted for first time non-ST-segment elevation myocardial infarction (NSTEMI) to hospitals in western Denmark, who underwent coronary angiography within 30 days during 2000-2011. Patients were classified as: zero-vessel disease (0-vessel group) indicating angiographically normal coronary arteries or very mild atherosclerosis; diffuse atherosclerosis (atherosclerosis group) indicating moderate focal or diffuse atherosclerosis without stenosis ≥50%, one-vessel disease (1-vessel group), two-vessel disease (2-vessel group), and three-vessel disease (3-vessel group) with stenosis ≥50%. Follow-up period: 13 years (median 4.5) to 31/12/2012.

Study III was a cost-effectiveness analysis of the third blood sample of cardiac troponin. This study included 534 consecutive patients admitted for suspected non-ST-segment elevation acute coronary syndrome at Aalborg University Hospital between March and November 2003. Three blood samples, 6-12 hours apart, to analyse troponin were drawn from all patients according to the department's practice guidelines.
The cost of troponin analysis (Euro 12) and one day stay in Coronary Care Unit which estimated to be Euro 1,550 were obtained. The extended length of stay due to the third blood sample was estimated to be 0.5 days on average. The effectively was measured by the impact of the third troponin blood sample on clinical decision making and management plan.

Results

In Study I: first MI incidence per 100.000 person-years ($/10^5$ p-y.) decreased significantly among males from 500 to $297/10^5$ p-y., and among females from 229 to $156/10^5$p-y.. The majority of age groups experienced incidence decline. Nevertheless, incidence rates increased among men aged 30-39 and ≥90 years, as well as women aged 30-39, 40-49, and ≥90 years. In addition, after an initial period of incidence decline from 1978 to 1996, MI incidence rates increased among men aged 40-49 and women aged 50-59 years from 1996 through 2012. One-year case fatality for MI patients decreased significantly among men from 50% to 9%, and among women from 53% to 15% comparing the year 1978 to 2012.

In Study II: one-year mortality for NSTEMI patients with 0-vessel, atherosclerosis, 1-vessel, 2-vessel, and 3-vessel disease was 3.7%, 5.7%, 2.5%, 4.8 %, and 11.5%, respectively. Non-diabetic NSTEMI patients in the 0-vessel group had a higher risk of mortality than those in the 1-vessel group (multi-variable adjusted (HR:1.59; 95% CI:1.21-2.02; P<0.001), while diabetic patients had no significant difference in mortality risk. In addition, the 0-vessel group had a higher risk of heart failure (HR:1.61; 95% CI:1.39-1.88; P <0.001), a non-significant different risk of stroke, and a lower risk of recurrent MI (HR:0.55; 95% CI:0.39-0.77; P <0.001) compared with the 1-vessel group. Patients in the atherosclerosis group had a higher risk of mortality and heart failure, and a non-significant difference in the risk of recurrent

MI and stroke compared with patients in the 1-vessel group. Moreover, both diabetic and non-diabetic atherosclerosis patients compared with the 2-vessel group had a non-significant difference in the risk of mortality (HR:1.63; 95% CI:0.85-3.13; P 0.14; HR:1.45; 95% CI:0.99-2.13; P 0.06, respectively), a non-significant difference in the risk of heart failure and stroke, but a lower risk of recurrent MI (HR:0.55; 95% CI:0.36-0.84; P 0.005). In addition, diabetic patients in the 0-vessel group had a lower risk of mortality compared with the atherosclerosis group (HR:0.16; 95% CI:0.05-0.51; P 0.002), but this difference was not found if patients had no diabetes mellitus. The atherosclerosis group had a higher risk of recurrent MI than the 0-vessel group (HR:1.7; 95% CI:1.05-2.89; P 0.03), and these two groups had similar long-term heart failure and stroke risks.

In study III: 124 out of 534 patients had an elevated cardiac troponin level in at least one blood sample. Among these 124, 4 patients (3.2 %) had troponin levels elevated solely in the third sample. All 4 patients were eligible to be referred for urgent or acute coronary angiography due to their risk profile and/or ECG changes, irrespective of the results of the third sample. 275 patients had to extend their hospital stay by half a day on average waiting for the results of the third sample, thus the incremental costs of the third blood sample was: [534 patients x Euro 12 per troponin analysis] + [275 patients x 0.5 day x Euro 1,550] = Euro 219,533. Approximately 1,400 patients with suspected non-ST-segment elevation acute coronary syndrome are admitted to our department per year. Thus, the total cost per year is: (1,400/534) x Euro 219,533 = Euro 575,555.

Conclusion

Myocardial infarction continues to constitute a burden on the health care system, even though incidence rates have decreased and prognosis has improved during the last few decades. There is, however, a worrying increase in incidence rates observed in this study among women under 60 years, men under 50 years, and patients over 90 years. This should be addressed with further studies to confirm and understand this trend, which might lead to changes in preventive measures focusing on these age groups (study I). The prognosis of NSTEMI patients with zero-vessel disease is not better than that of patients with one-vessel disease, and the out-come of NSTEMI patients with diffuse atherosclerosis is not better than two-vessel disease. Furthermore, the outcome of diffuse atherosclerosis patients is worse than those with zero-vessel disease. These findings call for considering these two groups (zero-vessel disease and diffuse atherosclerosis) separately in the future research and need further studies to explore the mechanisms causing myocardial injury and the optimal management of these NSTEMI subgroups (study II). The third blood sample of cardiac troponin is not cost-effective in the management of patients admitted with a suspected acute coronary syndrome, and leads to increased hospital stays and health care costs (study III).

DANSK RESUME

Baggrund

Denne Ph.d.-afhandling adresserer tre problemstillinger med relevans for myokardieinfarkt (MI): (1) Mortaliteten, som er relateret til iskæmisk hjertesygdom, er faldet signifikant i de vestlige lande. Ændringer i risikofaktorer og behandlingsstrategier kunne have haft en effekt på incidensen og mortaliteten. Men ændringer i risikofaktorer har ikke været ens i alle køns- og aldersgrupper. Derfor skal ændringer i incidens og mortalitet over tid undersøges inden for forskellige alder- og kønsgrupper. (2) Der er veletableret medicinske samt revaskularisationsanbefalinger for MI patienter med stenose i deres koronararterier. Imidlertid er der mange patienter med MI uden signifikant stenoser. Disse patienter modtager ikke den samme medicinske behandling som dem med signifikante stenoser. Derfor skal prognosen af MI patienter uden signifikante stenoser nærmere karakteriseres. (3) Omkostningerne for indlæggelser på grund af MI og observation for MI udgør en stor del af det samlede sundhedsbudget. Ét af aspekterne er rutine indsamling af tre blodprøver med henblik på analyse af troponin, før MI kan afkræftes og patienten kan forsvarligt udskrives. Denne rutine praksis medfører til øget indlæggelsestid og dermed øgede omkostninger. Derfor er en Cost-effective analyse ønskelig for denne praksis.

Formål

Formålet for denne afhandling er dermed at undersøge de ovennævnte uløste aspekter af MI forekomst, prognose, samt udgifter til sundhedssystemet.

1. At undersøge tidsmæssige tendenser i myokardieinfarkt forekomst og dødelighed afhængig af alder og køn over en 35-årig periode (1978-2012) i Danmark.
2. At undersøge en langsigtet prognose af patienter med non-ST-segment elevation myokardieinfarkt fordelt over 5 grupper afhængige af kranspulsåren patologi på koronarangiografi.
3. At analysere cost-effectiveness af den tredje blodprøve for at måle troponin hos patienter indlagt på grund af mistanke om non-ST-segment elevation akut koronart syndrom.

Metoder

Studie I og II er historiske prospektive studier, hvor data er indsamlet fra forskellige danske registre.

I studie I patienter i alderen ≥30 år indlagt med førstegangs MI på alle danske sygehuse i årene 1978-2012 (n = 316,790) var inkluderet.

Studie II omfatter 8.889 patienter, indlagt for førstegangs non-ST-segment elevation myokardieinfarkt (NSTEMI) på sygehuse i det vestlige Danmark, som gennemgik koronarangiografi inden for 30 dage, i løbet af 2000-2011. Patienterne er klassificeret som: nul karsygdom (0-kar gruppe) indikere angiografisk normale koronararterier eller minimal aterosklerose; diffus aterosklerose uden stenose ≥ 50% (aterosklerose gruppe), 1 karsygdom (1-kar gruppe), 2 karsygdom (2-kar gruppe), og 3 karsygdom (3-kar gruppe) med stenose ≥50%. Opfølgningsperiode: 13 år (median 4,5) til 31-12-2012.

Studie III er en analyse af omkostningerne versus effektiviteten af den tredje blodprøve af kardial troponin. Studiet inkluderede 534 konsekvative patienter som var indlagt på mistanke om akut koronart syndrome uden ST-elevation ved EKG på Aalborg Universitetshospital fra mars til november 2003.

Udgifterne beregnet ud fra udgifterne til troponinanalyse (Euro 12) samt et-døgns ophold på kardiologisk afdeling med overvågning, som skønnes at være Eruo 1.550. Det forlængede ophold på grund af den tredje blodprøve er estimeret til at være 0,5 dag i gennemsnit. Effektiviteten er estimeret udfra, hvordan den tredje troponin blodprøve påvirker patienternes undersøgelse- og behandlingsplan.

Resultater

Studie I: Førstegangs MI incidens pr 100.000 person-år (/ 10^5 p-y.) faldt betydeligt blandt mænd fra 500 til 297/10^5 p-y. og blandt kvinder fra 229 til 156 / 10^5p-y. De fleste af aldersgrupperne oplevede forekomst tilbagegang. Ikke desto mindre er forekomsten steget blandt mænd i alderen 30-39 og ≥90 år, samt kvinder i alderen 30-39, 40-49, og ≥90 år. Hertil kommer, at MI forekomsten, efter en indledende periode, hvor incidensen faldt fra 1978 til 1996, steg blandt mænd i alderen 40-49 og kvinder i alderen 50-59 år fra 1996 til 2012.
1-års mortalitet efter første MI faldt markant blandt mænd fra 50% til 9%, og blandt kvinder fra 53% til 15% sammenlignet år 1978 med 2012.

Studie II: 1-års mortalitet for NSTEMI patienter med 0-karsydomme, aterosklerose, 1-karsygdom, 2-karsygdom, og 3-karsygdomme var henholdsvis 3,7%, 5,7%, 2,5%, 4,8% og 11,5%. NSTEMI patienter uden diabetes, som har 0-karsygdom, havde en højere risiko for dødelighed end 1-karsygdoms gruppen (multi-variable justeret HR:1,59; 95% CI:1,21-2,02; P <0,001), mens diabetikere havde en ikke signifikant forskel på dødelighedens risiko. Desuden havde den gruppe med 0-karsydom en højere risiko for hjertesvigt (HR:1,61; 95% CI:1,39-1,88; P <0,001), en ikke signifikant anderledes risiko for slagtilfælde, og en lavere risiko for tilbagevendende MI (HR:0,55; 95% CI:0,39-0,77; P <0,001) sammenlignet med 1-karsygdoms gruppen; mens patienter med aterosklerose havde en højere risiko for dødelighed og hjertesvigt, og en ikke signifikant anderledes risiko for tilbagevendende MI og slagtilfælde sammenlignet med patienter med 1-karsygdom. Desuden havde både diabetiske og ikke-diabetiske aterosklerose patienter

sammenlignet med 2-karsygdom en ikke signifikant anderledes risiko for dødelighed (henholdsvis HR:1,63; 95% CI:0,85-3,13; P 0,14, HR:1,45; 95% CI:0,99-2,13; P 0,06,). Desuden havde de heller ikke en signifikant anderledes risiko for hjertesvigt og slagtilfælde, men en lavere risiko for tilbagevendende MI (HR:0,55; 95% CI:0,36-0,84; P 0,005). Endvidere havde diabetes patienter med 0-karsydom en lavere risiko for dødelighed end patienter med aterosklerose (HR:0,16; 95% CI:0,05-0,51; P 0,002), men lignende risiko, hvis ikke de var diabetikere. Patienter i aterosklerose gruppen havde en højere risiko for tilbagevendende MI end patienter i 0-karsydom gruppen (HR:1,7; 95% CI:1,05-2,89; P 0,03), og disse to grupper var ens med hensyn til de langsigtet hjertesvigt og slagtilfælde risici.

Studie III: 124 ud af 534 patienter havde et forhøjet kardial troponin i mindst én blodprøve. Blandt disse 124, 4 patienter (3,2%) havde forhøjet troponin alene i den tredje prøve. Alle disse 4 patienter var berettiget til at blive henvist til subakut eller akut koronar angiografi grundet deres risikoprofil og/eller EKG-forandringer, uanset resultatet af den tredje prøve. 275 patienter fik forlænget deres hospitalsophold en halv dag i gennemsnit, menes de ventede på resultaterne af den tredje prøve, således var de ekstra omkostninger forbundet med den tredje blodprøve: [534 patienter x Euro 12 per troponin analyse] + [275 patienter x 0,5 dag x Euro 1.550] = Euro 219.533. Cirka 1.400 patienter er indlagt på vores afdeling om året med observation for non-ST-elevation akut koronart syndrom. Således er de samlede omkostninger per år: (1400/534) x Euro 219.533 = Euro 575.555.

Konklusion

Myokardieinfarkt fortsætter med at udgøre en udfordring for sundhedssystemet, selvom forekomsten er faldet og prognosen forbedret i løbet af de sidste par årtier. En foruroligende stigning i forekomsten af myokardieinfarkt er blevet observeret i denne undersøgelse blandt kvinder under 60 år, mænd under 50 år, og patienter over 90 år. Dette bør undersøges nærmere for at bekræfte og forstå denne tendens som kan føre til ændring i forebyggende foranstaltninger, der fokuserer på disse aldersgrupper (studie I). Prognosen for NSTEMI patienter med nul-karsydom er ikke bedre end for patienter med 1-karsygdom, og prognosen af NSTEMI patienter med diffus aterosklerose er ikke bedre end 2- kar-sygdom. Desuden er prognosen for aterosklerose patienter værre end for patienter med nul-karsygdom. Disse resultater appellerer for at betragte nul-karsygdom og diffus aterosklerose separat i fremtidig forskning samt kræver yderligere undersøgelser af mekanismerne af myokardieskade samt den optimale behandling af disse NSTEMI undergrupper (studie II). Den tredje troponinblodprøve er ikke cost-effective i behandlingen af patienter indlagt med et formodet akut koronart syndrom, og fører til en unødvendig forlængelse af hospitalsophold og dermed forøgede sundhedsudgifter (studie III).

ABBREVIATIONS:

ATC:	Anatomical Therapeutic Chemical
CI:	Confidence Interval
EF:	Ejection Fraction
HF:	Heart Failure
ICD:	International Classification of Diseases
MI:	Myocardial Infarction
NSTE-ACS:	Non-ST-segment Elevation Acute Coronary Syndrome
NSTEMI:	Non-ST-segment Elevation Myocardial Infarction

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1. INTRODUCTION

1.1 Myocardial infarction definition and significance

Death rates attributed to Ischemic Heart Disease (IHD) declined consistently over the last 50 years.[1] Nevertheless, IHD is still the most common cause of death in the world accounting for 7.4 million deaths in 2012.[2] In Europe it is responsible for 888,194 deaths among men and 915,548 deaths among women comprising 20% and 22% of all deaths, respectively,[3] and in the U.S. it accounts for one sixth of all deaths.[4] Therefore, it remains a necessity to evaluate the efforts of prevention and treatment of Myocardial Infarction (MI).

MI is defined pathologically as myocardial cell death due to prolonged ischemia, which is accepted to be the result of thrombosis caused by plaque rupture or erosion in coronary arteries with significant stenosis ≥50%.[5–7] However, there are many reports of MI without significant coronary artery disease with either normal coronary arteries or atherosclerosis with stenosis <50% which does not require revascularization procedure in term of per coetaneous intervention or coronary bypass operation.[8–10]

The definition of the clinical syndrome designated as MI has been refined several times over the last few decades; from being based on classical symptoms of ischemic chest pain and ECG changes, to be based on biomarkers of cardiac necrosis, which can detect small injury to the myocardium.[11] These biomarkers have developed over the years from the non specific serum glutamic oxaloacetic transaminase and lactate dehydrogenase to creatinin kinase with its more cardiac specific isofrom (CK-MB), and the more sensitive and specific cardiac troponin. The assay of the later has furthermore developed through the recent years to be a high sensitive troponin I & T. The Third Universal definition of Myocardial Infarction is therefore based on rise/or fall in cardiac biomarkers (preferably troponin) accompanied by either typical symptoms, pathological Q waves, ST-segment elevation or depression, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.[12]

Clinically and for the sake of acute management decisions regarding reperfusion therapy, MI is classified according to ECG changes, in the presence of ischemic symptoms, into ST-segment elevation MI (STEMI) and non-ST-segment elevation MI (NSTEMI).

Modifiable traditional risk factors for acquiring IHD such as hypertension, hypercholesterolemia, diabetes mellitus, obesity, smoking, and physical inactivity have changed in society over the last few decades. On the one hand, some risk

factors have declined like cigarette smoking, hypercholesterolemia and hypertension because of improved awareness and treatment of these conditions;[1,13-14] On the other hand, obesity and diabetes mellitus have increased in society, [15–17] especially among the younger populations.[18–20]

1.2. Temporal changes in incidence rate of myocardial infraction over time

Reports on the incidence rate of MI which used data collected before the year 2000 were contradictory; some of which reported a stable or increased incidence, [21–24] while others reported a decline in incidence rates. [25–29] However, studies extended to more recent years show a decline in MI incidence rates.[30–33]

These studies, however, did not examine in details the changing incidence among different age groups for both genders. The change in risk factors for MI, which disproportionally affected different age groups, as well as, the change of MI definition might have altered the incidence of MI over the last few decades differently across age groups for both genders. This information could be crucial to focus future preventive and treatment efforts if the change in incidence is age and/or gender specific. Moreover, the use of evidence based treatment after MI including both reperfusion therapy and medical therapy for secondary prevention have been increasing over time,[30] which might have led to a decrease in one-year mortality rates after MI.

1.3. Non-ST-segement elevation myocardial infarction with non-obstructive coronary artery disease

As previously mentioned, NSTEMI can be associated with non-obstructive coronary artery disease. There are many proposed mechanisms of myocardial injury among these patients; some of these mechanisms involve ischemia as the major cause,[34–36] including disruption in plaques which did not lead to significant stenosis on the angiography because the clot might have dissolved before the angiography was done.[37] Other mechanisms of myocardial injury in these patients are not related to ischemia.[9]

Previous studies suggested that factors predicting non-obstructive coronary arteries among MI patients are: female gender, younger age, renal insufficiency, and lack of smoking or diabetes.[38–41]

NSTEMI patients without obstructive coronary artery disease are less likely to receive recommended medical treatment after MI,[42] and more likely to discontinue double platelet inhibitors than patients with NSTEMI and obstructive coronary artery disease.[39,43] This difference in management can affect their prognosis.

Some studies suggested that NSTEMI patients without significant stenosis have a benign prognosis, with a lower one-year mortality risk,[44] and less in-hospital mortality, re-infarction, congestive heart failure, or cardiogenic shock than NSTEMI patients with obstructive coronary artery disease.[38] Nevertheless, there are other reports both from pooled data of large international studies [45] and from real-world observations [39] which doubted the good prognosis of these patients. These studies illustrated a substantial risk among these patients with higher risk of one-year all cause mortality,[41] or no difference in combined major cardiovascular adverse events comparing non-obstructive to obstructive coronary artery disease.[39] These studies, however, are either from controlled trials[45] with a small sample size,[43] or with a short duration of follow-up.[38]

In addition, most of these prognostic studies divided NSTEMI patients into obstructive versus non-obstructive coronary artery disease, but there are only a few studies which differentiated patients with non-obstructive coronary artery disease into angiographically normal coronary arteries, and atherosclerosis without stenosis >50% subgroups;[45] or divided patients with obstructive coronary artery disease according to the severity of the disease defined by the number of coronary vessels involved which is an important prognostic factor.[44] This subgroup distinction is of importance because patients with angiographically normal or near-normal coronary arteries might have different mechanisms of myocardial injury and by that represent another patient group than those with moderate diffuse atherosclerosis without significant stenosis. Thus their prognosis and potential management might differ accordingly.

1.4. Cost-Effectiveness of cardiac troponin in the management of suspected non-ST-segment elevation acute coronary syndrome

Health care costs attributed to admissions for both MI and suspected acute coronary syndrome are increasing,[46,47] and a strategy that can reduce the length of stay in hospital is highly desirable.

As part of the standard clinical care for patients admitted with a suspected acute coronary syndrome, three or more serial blood samples are drawn to determine troponin level changes with 6-12 hour intervals during the observation period. This strategy has been adopted over a long time.[48,49]

Nonetheless, taking into consideration the kinetics of cardiac troponin that troponin level increases within 3-6 hours from the onset of symptoms,[50–52] it would be sufficient to draw two blood samples from the patient to detect a change in cardiac troponin level 6-9 hours apart. The strategy of drawing more than two samples costs at least an extra 12-24 hour length of stay in the hospital before the diagnosis of

NSTEMI can be ruled out, and before the patient can be safely discharged. The cost-effectiveness of this strategy has not yet been evaluated.

Overall, there are many aspects of MI diagnosis, prognosis and health care costs yet to be illuminated. The aforementioned observations resulted in three main aims of this thesis in order to answer some unresolved questions.

2. HYPOTHESES AND AIMS

The global aim of this dissertation is to contribute to the knowledge surrounding myocardial infarction incidence, prognosis, and health care costs.

Hypotheses:

1- The temporal changes in incidence rates of MI over the last few decades are unequal among all age groups for both genders, and mortality following MI has decreased over the last few decades.

2- The long-term prognosis of NSTEMI patients with angiographically normal coronary arteries is different from those with atherosclerosis without stenosis >50%, and the prognosis of both these two groups is better than NSTEMI patients with obstructive coronary artery disease of different degrees.

3- The diagnostic value of the third blood sample to measure cardiac troponin levels in patients under observation for suspected acute coronary syndrome does not justify the cost of extended length of stay in the hospital.

These hypotheses were formed into the following aims for the three studies:

1. To examine temporal trends in myocardial infarction incidence and one-year case fatality according to age and gender in Denmark over a 35-year period (1978-2012).

2. To investigate the long-term outcome of patients with non-ST-segment elevation myocardial infarction according to coronary artery pathology on the angiography.

3. To analyse the cost-effectiveness of the third blood sample to measure troponin in patients admitted with a suspected non-ST-segment elevation acute coronary syndrome.

3. METHODS AND MATERIALS

3.1. Study design

Study I and II were historical prospective cohort studies based on data collected from the following Danish registries: the Civil Registration System and the Danish National Patient Register (study I&II), the National Prescription Register and the Western Denmark Heart Registry (study II). Study III was a cross sectional study.

3.2. The registries

All residents in Denmark have a unique identification number which facilitate the linkage of information from various registers on person-level.

The Civil Registration System contains information on date of birth, sex, and date of death of all Danish citizens at birth and residents upon immigration.[53]

The Danish National Patient Register has collected data on all non-psychiatric admissions to Danish hospitals since 1977, which become more complete in 1978, and out-patients visits since 1995. This data includes discharge diagnosis using the International Classification of Diseases version 8 (ICD-8) from the year 1977 to 1994, and ICD-10 thereafter. The register is a valuable tool for research.[54,55]

The National Prescription Register holds information on prescriptions like date of purchase, size of package, number of package, dosage, and drug code according to the international Anatomical Therapeutic Chemical (ATC) classification system.[56]

The Western Denmark Heart Registry is a clinical database. It was launched on 1 January 1999 to monitor and improve the quality of cardiac interventions in western Denmark (3,071,110 persons, 54,3% of Denmark's population).[57] This database collects detailed patients and procedures data for all interventions performed, and is a validated valuable research source.[58]

3.3. Study population

Study I:

Consecutive patients aged 30 year and older admitted with first time MI to Danish hospitals during the period January 1st, 1978 to December 31st, 2012 were included in the study. Figure 1 shows the inclusion process. Final study population was 316,790 patients. Study period was divided into seven periods of five years. Each period started with January 1^{s} of the first year and ended on December 31st of the

last year of the period. Patients were then divided into male and female genders and within each gender; patients were divided into seven age groups of 10-year intervals.

Study II:
This study included consecutive patients admitted to hospitals in the western part of Denmark with a first time NSTEMI, who underwent coronary angiography within 30 days of their admission, during the period January 1st, 2000 to August 31st, 2011. Exclusion criteria: unavailable description of coronary artery pathology, previous MI, previous revascularization procedure with either per coetaneous intervention or coronary bypass operation, and known heart failure. The final study population was 8,889 patients. The study population was divided into five subgroups according to angiographic description of the degree of stenois of the coronary arteries as: zero-vessel disease (0-vessel group) indicating angiographically normal coronary arteries or very mild atherosclerosis; diffuse atherosclerosis (atherosclerosis group) indicating moderate focal or diffuse atherosclerosis with stenosis <50%; one-vessel disease with stenosis ≥50% (1-vessel group); two-vessel disease with stenosis ≥50% (2-vessel group); or three-vessel disease with stenosis ≥50% (3-vessel group). Left main with stenosis ≥50% was considered as two-vessel disease if the right coronary artery was without significant stenosis, and three-vessel disease if the right coronary artery was hypoplastic or with significant stenosis ≥50%.

Study III:
534 consecutive patients who were admitted with chest pain and suspected non-ST-segment elevation acute coronary syndrome at Aalborg University Hospital between March and November 2003 were included.
All patients were subject to the following routine diagnostic procedures: Clinical history and examination, chest x-ray, 12 leads ECG, and laboratory assessment (electrolytes, hepatic and renal status, lipids, screening for infection in urine and blood, as well as cardiac biomarkers).

Blood sampling was scheduled according to the department's routine procedure with blood samples for cardiac troponin T (cTnT) obtained on arrival, after 6-9 hours, and after 12-24 hours from admission. All patients had three blood samples taken to exclude/verify acute MI diagnosis.

cTnT was determined from serum samples on Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). For cTnT (4th generation assay), the lowest concentration exhibiting imprecision coefficient of variation (CV) < 10 % was 0.03 µg/L.[59]

All patients were transferred to the department of cardiology with monitoring with a standard treatment regimen for patients suspected of non-ST-elevation acute coronary syndrome according to the guidelines at the time of the study.[52]

3.4. Study definitions

Definition of MI:

The discharge diagnosis of myocardial infarction in Danish Patient Register was validated previously and found reliable with positive predictive value of 92-93%[60,61]

In study I, first time MI was defined as the first hospital admission with MI diagnosis recorded in the Danish National Patient Register. We used ICD-8 code 410 (from 1978 to 1994) and ICD-10 code I21 (from 1994 to 2012). Only primary discharge diagnoses were used. As the register started in 1977, we could not confirm that patients in the early years of the study did not have a MI diagnosis before 1977, therefore a sensitivity analysis was performed using all MI (both first time and recurrent MI). The results did not diverge significantly from first MI analysis.

In Study II, first time NSTEMI was defined as first hospital admission registered in the Patient Register with a primary discharge diagnosis using ICD-10 code: I21.4 (NSTEMI) or I21.9 (acute MI, unspecified), the latter was considered as NSTEMI if the diagnosis of NSTEMI was confirmed from the Western Denmark Heart Registry. A period of 6 years from 1994-2000 was used to ensure that patients did not acquire MI previously.

A recurrent MI as an outcome in study II was defined as any hospital admission with a MI diagnosis using ICD-10 code: I21. We performed a program that merged all related admissions in one admission to avoid the transfer of patients between hospitals being misclassified as a new admission with recurrent MI. We also used a safety period of 5 days after discharge day where no MI diagnosis can be taken into consideration. Moreover, we performed a sensitivity analysis were we considered recurrent MI only if it occurs ≥30 days from the first MI.

In study III, Patients were classified as having acute MI according to the universal definition of MI used at the time of the study.[62] These included detection of rise and/or fall of cardiac troponin, together with signs indicative of ischemia (clinical symptoms, ECG changes, or imaging evidence of new loss of viable myocardium). Troponin level above the 99th percentile of the Upper Reference Limit given coefficient of variation <10% was consider diagnostic, and for fourth generation cTnT, this level was >0.03 µg/L.

Definition of heart failure (HF):

In Study I, one-year heart failure outcome defined as any hospital contact (either admission or out-patient visit) using ICD-8 code 4270, 4271 or 428 (1978–1994) and ICD-10 code I50 or I255 from 1994 in Danish Patient Register.

In study II, heart failure outcome after first NSTEMI defined as either first hospital contact with heart failure diagnosis using ICD-10 code: I509 or I255, or first time purchase of prescription of loop diuretics after the index admission for first NSTEMI, using ATC code: C03C in the Danish National Prescription Register. The prescription of loop diuretics as proxy for heart failure diagnosis was used because the sensitivity of heart failure diagnosis in Patient Register was proven to be 29% but the specificity was 99%.[63] Moreover patients with a loop diuretics prescription or heart failure diagnosis prior to NSTEMI were excluded from the study, thus the most likely indication for loop diuretics after MI is heart failure. This approach considered acceptable as the majority of heart failure patients have previously been reported to use loop diuretics,[64,65] and the same approach was used in a previously published report.[66] Moreover, in Denmark it is very rare to use loop diuretics for hypertension but mostly thiazide diuretics which are not included in our analysis.

Definition of stroke:

In Study II, stroke event after first NSTEMI was defined as either hemorrhagic or ischemic stroke using ICD-10 code: I63, I62, I61, or I64. Patients, who had a stroke diagnosis before their NSTEMI diagnosis, were labeled as known with previous stroke and were not included in stroke outcome analysis after MI.

3.5. Health care cost assessment

In Study III, the total cost attributed to the third cTnT sample, was calculated taking into account:

1. The cost of a cTnT analysis (Euro 12).

2. The cost of an extended length of stay in the department of cardiology with monitoring solely due to the third troponin sample (on average 0.5 day per patient). The system which calculates the cost of each admission to Danish hospitals is a diagnosis-related system, which assigns Euro 1,550 to the diagnosis: observation due to a suspected acute coronary syndrome. This is calculated from an average admission of one day for those patients.

3. Approximately 1,400 patients are admitted to the department of cardiology at Aalborg university hospital per year with a suspected non-ST-elevation acute coronary syndrome.

3.6. Outcomes and follow up duration

In Study I, the primary outcomes were incidence rates of first time MI and one-year all-cause case fatality after first MI. Follow-up duration: 365.25 days from the admission day.

In Study II, the primary outcomes were all-cause mortality, recurrent MI, heart failure, and stroke after first admission for NSTEMI. Follow-up duration: median 4.5 years, inter quartile range (1.3 (2.6-6.8) 13) years.

In Study III, the outcome was the estimated cost attributed to the third blood sample of troponin versus the impact of the third sample results on clinical decisions of patients' management.

3.7. Statistical analysis

Continuous variables were presented as a mean with standard deviation or median with inter quartile range, and the difference between multiple groups was tested using a parametric test one-way analysis of variance (ANOVA) as data was normally distributed with a large sample size.

Categorical variables were presented as frequencies and percentages, and compared by chi-square test.

In Study I, an incidence density rate (person-time incidence rate) was calculated as number of new cases per 100.000 person-years. One-year mortality was assessed both as person-time mortality rate in population per 100,000 person-years within one year of admission for a first time MI, and as one-year case fatality proportion from first MI patients.

Population was stratified according to gender and age, and incidence and mortality rates were calculated for each stratum.

Rate ratio was calculated using poisson regression model, which is a type of general linear regression model. The assumption of independency was fulfilled. Age, sex, and time period were included in the model as covariates. Male gender, age group 70-79 year, and period 1978-1982 were used as reference groups for comparison because these groups were with the largest number of cases.

In Study II, Aalan-Neilson estimator for cumulative incidence was used taking into account death as a competing risk for other outcomes than mortality.

To estimate Hazard Ratio, Cox proportional hazard ratio was applied with the date of admission for first NSTEMI (date of entry into the study) as the time scale.

Model assumption of proportional hazards was examined with cumulative hazard plot and tested based on Schoenfeld residuals and found valid. The model was adjusted for age, sex, hypertension, diabetes, smoking, overweight (defined as body mass index ≥25, and renal insufficiency (defined as estimated glumerular filtration rate <60 ml/min/1.73m^2 according to MDRD equation). These parameters condemned as confounders because they were risk factors for the outcomes of interest, and they were associated with the exposure but were not located in the causal pathway between the exposure and outcome. Cox model was primarily performed using one-vessel disease group as a reference group because this group was with the largest number of cases, and because it is of a primary interest to compare the two sub-groups of non-obstructive coronary artery disease to this group. Cox model was performed afterward with diffuse atherosclerosis as the reference group, then zero-vessel disease, two-vessel disease, and lastly three-vessel disease as the reference group in order to get most possible details on the differences among all groups.

Ejection fraction (EF) was not used as a confounder because of too many missing observations (55% missing), but an additional analysis was performed for the subgroup of patients with available measurement of EF.

Effect modification was tested for several clinically relevant variables; namely age, sex, smoking, overweight, hypertension, diabetes mellitus, and renal insufficiency. An evidence of diabetes mellitus being an effect modifier of coronary pathology subgroups on the mortality outcome was found. Therefore two types of analysis approach were performed; one using a designed variable which combined coronary pathology subgroup with diabetes status, and the other was done by applying the model with and without diabetes. In the designed variable approach, one-vessel disease without diabetes group was used as a reference group for comparison. No major differences were found between these two approaches, thus the results were presented separately for patients with and without diabetes.

Linearity for the continuous variable age was tested using likelihood ratio test, and we found that there is strong evidence against the absence of linear effect of age categories ($P < 0.002$).We decided therefore to use age as a continuous variable.

P value of <0.05 (two-tailed) was considered as strong evidence against the null hypothesis and thus a sign of statistical significance. Results were reported with 95% confidence interval (CI).

Management of data and statistical analyses were run in SAS 9.2/9.4 (SAS Institute Inc., Gary, NC, USA) and R 3.0.2. (R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing.

3.8. Ethical considerations

Register–based studies do not require ethical approval in Denmark. Study I&II were approved by the Danish Data Protection Agency (RE: 2007-58-0015, int. ref.: GEH-2014-014 I-Suite no: 02732) and (RE: 2008-58-0028, int.ref.: 2015-50). Study III was performed in accordance with the revised Helsinki Declaration, approved by the local scientific ethical committee, and participants gave informed written consent.

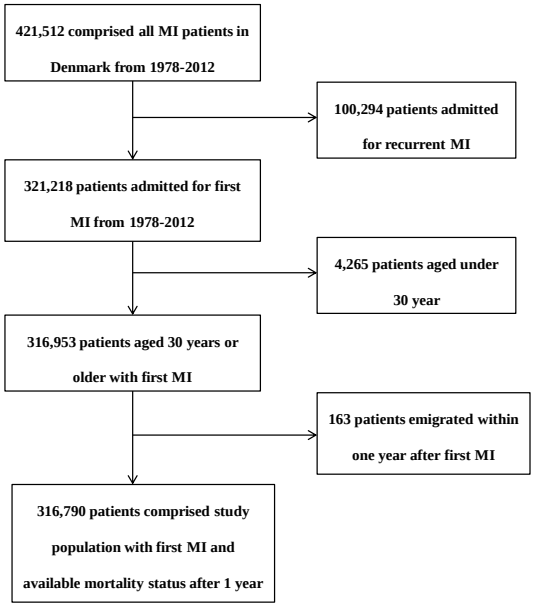

Figure 1: Inclusion process in Study I.

4. RESULTS

4.1. Study I:

Incidence and outcome of first myocardial infarction according to gender and age in Denmark over a 35-year period (1978-2012)

The objective of this study was to examine temporal changes in first MI incidence rates and one-year mortality in various age groups for both genders in Denmark over a 35-year period.

Methods: From 1978 through 2012, there were 316,953 hospitalizations for first time MI in patients aged 30 years or older. 163 patients were excluded from the study due to emigration, thus study population was 316,790 patients.

Results: During the first 25 years of the study period, the male proportion of first MI patients fell from 66% to 62% (P<0.001), but it increased in the remainder time to 64% (P<0.001). The mean age of patients at diagnosis increased gradually from 68.6 to 69.1 years (P<0.001) during the first 30 years, but it declined thereafter to 68.2 years (P<0.001). The length of hospital stay decreased consistently and significantly during the study period.

For all patients, first MI incidence per 100.000 person-years ($/10^5$ p-y.) decreased significantly from $359/10^5$ p-y. in 1978 to $225/10^5$ p-y. in 2012, this was a 37% decline in incidence rates. Incidence rate decrease was more pronounced in males, with a decline from 500 to $297/10^5$p-y. (41% reduction), than in females in which MI incidence rate was reduced from 229 to $156/10^5$p-y. comparing 2012 to 1978 (32% reduction). (Figure 2).

Dividing gender into seven age groups revealed that the greatest reduction in first MI incidence rates were observed among males aged 70–79 years from 1460 to $643/10^5$p-y. (-56%), next came males aged 60–69 (-54%) followed by females aged 70–79 (-50%). (Figure 3)

On the other hand, males aged 30–39 years as well as females aged 30–39 and females aged 40–49 years experienced an increase in incidence rates of MI. A similar pattern was found among patients aged ≥90 years for both genders. Moreover, a downward trend in incidence rates from 1978 to 1996 was observed among males aged 40–49 and females aged 50–59 years, but the incidence rates increased in the remainder of the study period.

This study showed a remarkable decrease in one-year case fatality from 50% to 9% of MI male patients, and from 53% to 15% of MI female patients comparing the year 1978 to 2012. This decline was appreciated for all age groups for both genders. (Figure 4).

Statistical analysis with poisson model demonstrated that the mortality risk decreased through the study period, increased with increasing age, and there was no significant difference in mortality risk between genders. (Figure 5)

Conclusions: The incidence rate of first myocardial infarction decreased significantly during the period from 1978 to 2012. This decline was observed among most age groups for both genders, however an incidence increase was observed in men under 50 and women under 60 years, and ≥90 years for both genders. One-year case fatality decreased constantly during the study period.

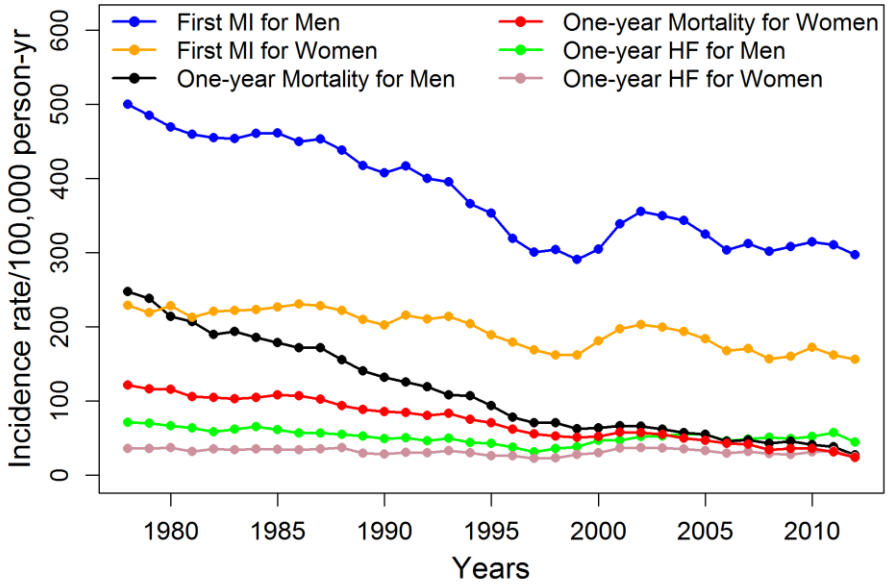

Figure 2: Incidence rates of first myocardial infarction, one-year mortality, and one-year heart failure after first myocardial infarction for both genders.
MI = myocardial infarction; HF = heart failure.

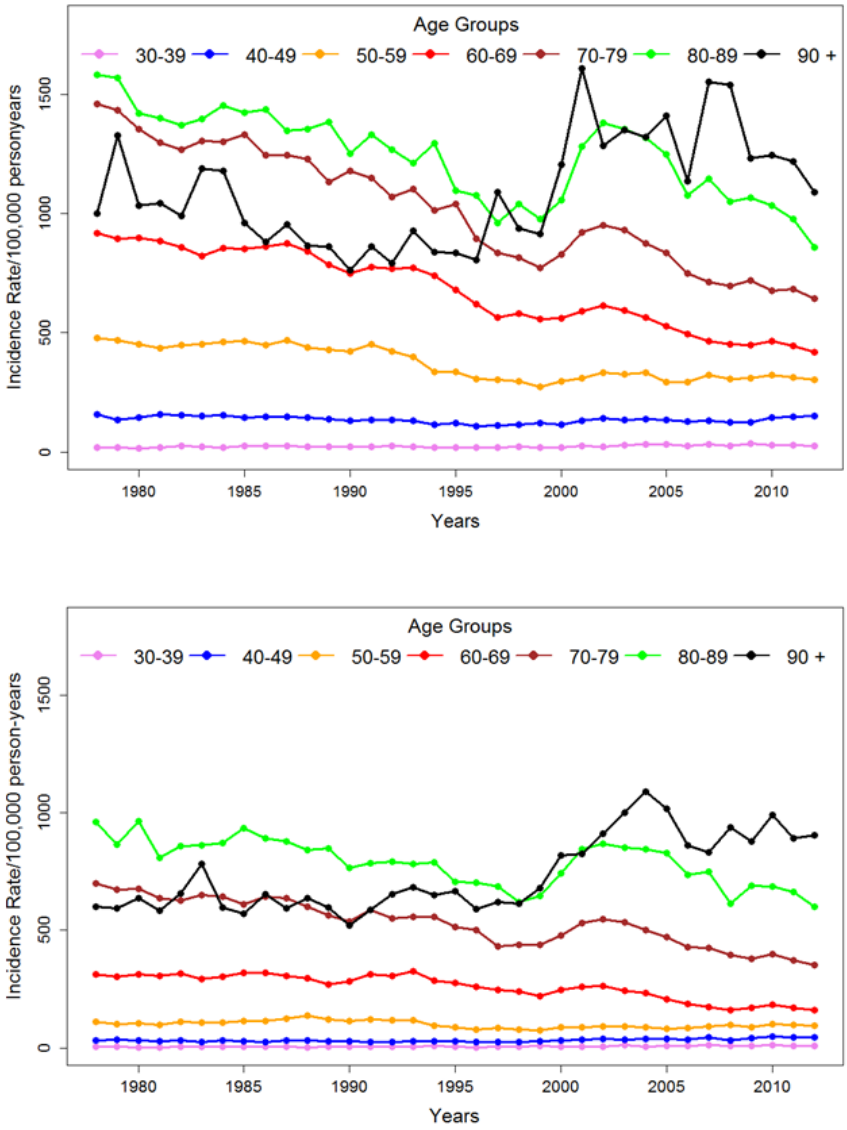

Figure 3: Incidence rates of first myocardial infarction in various age groups in males (upper panel) and in females (lower panel).

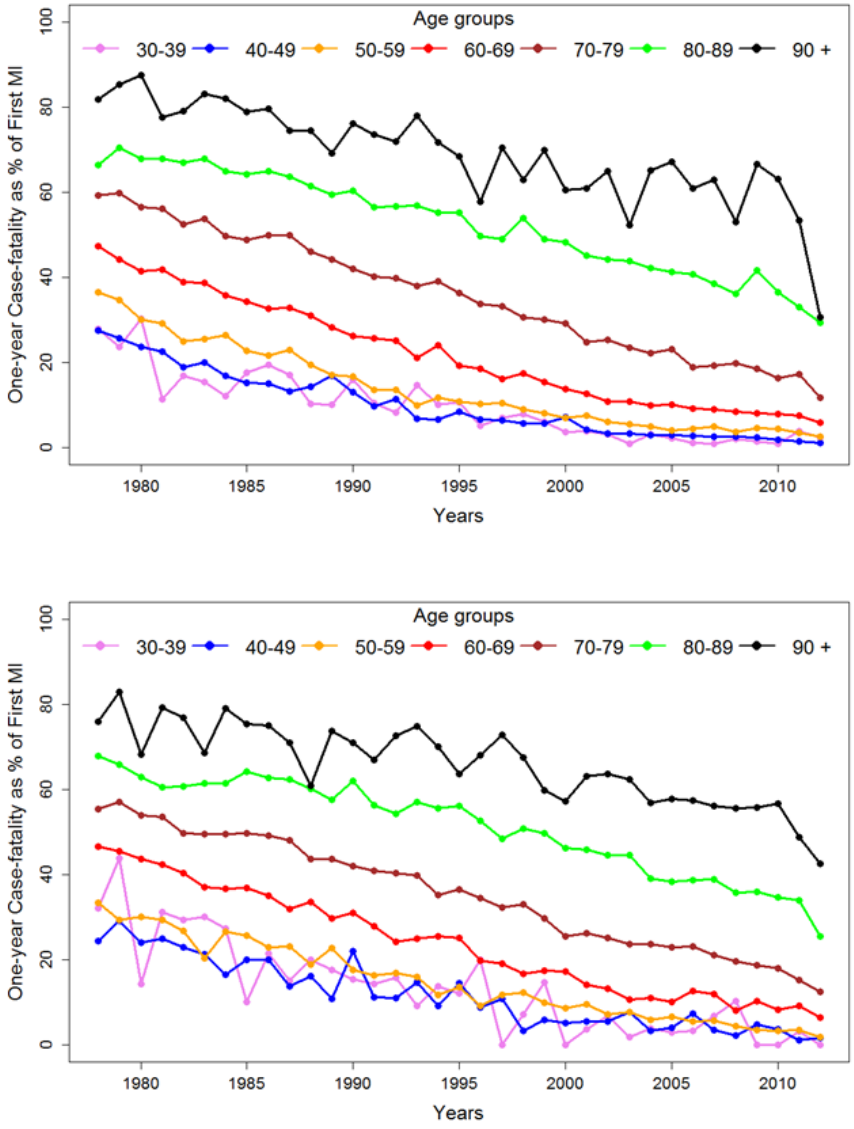

Figure 4: One-year case fatality after first myocardial infarction in various age groups in males (upper panel) and in females (lower panel).

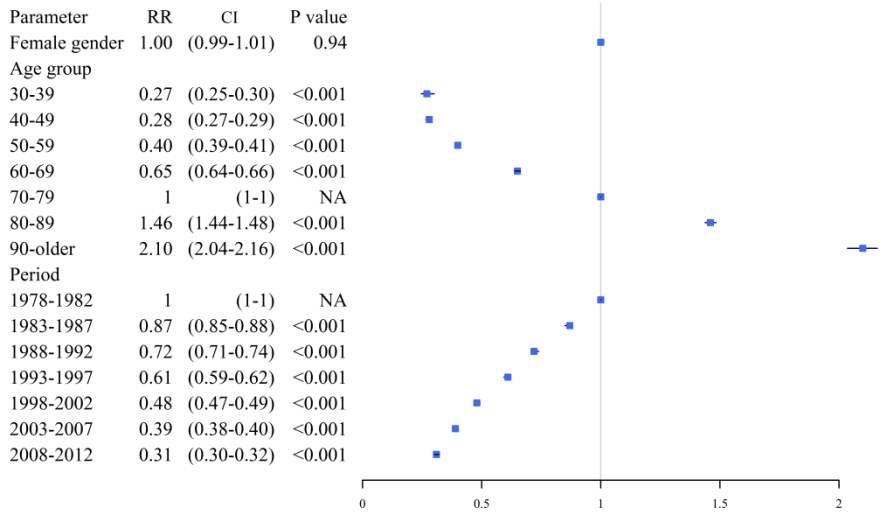

Figure 5: Rate ratio of one-year mortality after first myocardial infarction.

Male gender, age group 70–79 years, and period 1978–1982 were used as reference groups for comparison.

4.2. Study II:

Long-term outcome of patients with non-ST-segment elevation myocardial infarction according to coronary artery pathology on the angiography.

The objective of this study was to examine the long-term outcome of patients with non-ST-segment elevation myocardial infarction (NSTEMI) according to their coronary artery disease on the angiography.

Methods: this study recruited 8.889 consecutive patients admitted for first time NSTEMI to one of the hospitals in western Denmark, to whom angiography was performed within 30 days of admission, during the period 2000 through 2011. Patients were classified according to coronary angiography's description of coronary pathology into five groups: zero-vessel disease (0-vessel group) indicating either angiographically normal coronary arteries or minor focal atherosclerosis, diffuse atherosclerosis (atherosclerosis group) indicating moderate focal or diffuse atherosclerosis without stenosis ≥50%, one-vessel disease (1-vessel group) with stenosis ≥50%, two-vessel disease (2-vessel group) with stenosis ≥50%, and three-vessel disease (3-vessel group) with stenosis ≥50%. Follow-up period: 13 years (median 4.5) to 31/12/2012.

Results: the prevalence of NSTEMI with non-obstructive coronary artery disease (both the 0-vessel and atherosclerosis groups) was 14.5% of all NSTEMI population.

NSTEMI patients in the 0-vessel group had baseline characteristics which were not significantly different from those in the 1-vessl group except that they were less likely to be current smokers or overweight ((32.4% vs. 42.7, P <0.001; 57.7 vs. 67.3, P <0.001, respectively), and more likely to be females (59.9% vs. 29.6%, P <0.001) (Table 1). Patients in the atherosclerosis group had a non-significantly different risk profiles compared with the 2-vessel group, except that they were less likely to be overweight (55.6% vs. 66.7, P <0.001), and more likely to be females (44.0% vs. 23.3%, P <0.001). On the other hand, patients with atherosclerosis were older and more likely to have hypertension and diabetes mellitus but less likely to be females compared with 0-vessel patients.

NSTEMI patients in the 0-vessel group had a 3.6% (95% CI: 2.5-4.8 %) one-year all-cause mortality risk and those in the atherosclerosis group had 5.6% (95% CI: 3.0-8.2 %), while patients in the 1-vessel group had 2.5% (95% CI: 2.0-3.0 %), the 2-vessel group had 5.0 % (95% CI: 4.0-5.9 %), and the 3-vessel group had 11.5% (95% CI:10.1-12.8 %) one-year mortality risk.

NSTEMI patients in the 1-vessel group had the lowest unadjusted mortality throughout the study period (Figure 6). After multi-variable adjustment, non-diabetic NSTEMI patients with either 0-vessel disease or diffuse atherosclerosis had a higher mortality risk than those with 1-vessel disease (HR:1.59; 95% CI:1.21-2.02, P<0.001; HR:1.93; 95% CI:1.31-2.83, P<0.001, respectively) (Figure 7). Their mortality risk was not significantly different from the 2-vessel and 3-vessel groups. In contrast, diabetic NSTEMI patients in the 0-vessel group had a not significantly lower mortality risk compared with 1-vessel (HR:0.40; 95% CI:0.14-1.13, P=0.08), and a significantly lower mortality risk compared with all other groups including atherosclerosis group.

The risk of one-year recurrent MI increased linearly among coronary pathology subgroups, thus it was 3.5% (95% CI: 2.4-4.7) in patients in the 0-vessel group, 6.3% (95% CI: 3.6-9.0) in the atherosclerosis group, 8.3 (95% CI: 7.3-9.2) in the 1-vessel, 13.5 (95% CI: 12.0-14.9) in the 2-vessel, and 16.8 (95% CI: 15.3-18.4) in the 3-vessel group. In a sensitivity analysis taking into consideration only recurrent MI 30-365.25 days, these numbers changed to 0.7% (0.2-1.2%) for 0-vessel, 3.3% (1.3-5.5%) for atherosclerosis, 2.4% (1.8-2.8%) for 1-vessel, 4.4% (3.6-5.3%) for 2-vessel, and 7.4% (6.3-8.4%) for the 3-vessel groups, respectively.

Unadjusted cumulative recurrent MI incidence was highest in the 3-vessel group (Figure 6).

After multi-factorial adjustment, patients with atherosclerosis showed no significant difference in recurrent MI risk as compared with the 1-vessel group (HR:0.91; 95% CI:0.60-1.39, P=0.66) (Figure 8), and had a lower risk than both the 2-vessel and the 3-vessel groups. Patients in the 0-vessel group had the lowest risk of recurrent MI in all groups.

Heart failure risk over the first year after first NSTEMI was 15.9% (13.6-18.2) in the 0-vessel group patients, 20.9% (16.3-25.4) in the atherosclerosis patients, 12.0% (10.9-13.1) in the 1-vessel patients, 19.2% (17.5-20.9) in the 2-vessel patients, and 33.6% (31.6-35.6) in the 3-vessel patients. In unadjusted comparison, the 1-vessel group had the lowest, and the 3-vessel group had the highest incidence of heart failure after first NSTEMI over the study period (Figure 6).

After multi-variable adjustment, both the 0-vessel and the atherosclerosis groups had a higher risk of heart failure compared with the 1-vessel group (HR:1.61; 95% CI:1.39-1.88, P<0.001; HR:1.63; 95% CI:1.30-2.06; P<0.001, respectively) (Figure 8), but showed no significant difference in heart failure risk as compared with the 2-vessel group. Moreover, the 0-vessel group had a lower risk of heart failure than the 3-vessel group, while the atherosclerosis group had no difference in heart failure risk compared with the 3-vessel group. Heart failure risk was not different between the 0-vessel and the atherosclerosis groups.

One-year stroke risk was 1.8% in the 0-vessel group, 1.4% in the atherosclerosis group, 1.3% in the1-vessel group, 1.8% in the 2-vessel group, and 3.4% in the 3-vessel group. Incidence of stroke was generally lower than other outcomes, and no significant difference between groups was observed from unadjusted cumulative stroke incidence (Figure 6).

After multi-variable adjustment, there was a nominally higher but not significantly different risk of stroke comparing the 0-vessel group with both the 1-vessel (HR:1.47; 95% CI:0.98-2.20, P=0.06) (Figure 8), and the 2-vessel groups (HR:1.46; 95% CI:0.95-2.23, P=0.09). No difference was observed between the 0-vessel, atherosclerosis, and 3-vessel groups. No difference was observed comparing the atherosclerosis group to all other groups.

Conclusion: NSTEMI patients with zero-vessel disease or diffuse atherosclerosis have a substantial risk of adverse cardiovascular outcomes comparable to those with NSTEMI with one- or two-vessel disease patients. NSTEMI patients with diffuse atherosclerosis have a higher risk profile and worse outcome than patients with angiographically normal coronary arteries or minor focal atherosclerosis.

Table 1: Baseline characteristics of patients with non-ST-segment elevation myocardial infarction according to coronary artery pathology on the angiography.

	0VD (N=988)	**DA** (N=302)	**1VD** (N=3295)	**2VD** (N=2114)	**3VD** (N2190)	***P* value**
Age (years)	62 {53, 72}	66 {56, 74}	63 {54, 71}	67 {59, 75}	71 {63, 78}	< 0.001
Female gender	585 (59.9)	131 (44.0)	966 (29.6)	489 (23.3)	587 (27.0)	< 0.001
Hypertension	368 (39.2)	143 (49.7)	1290 (41.6)	875 (44.4)	1088 (53.6)	< 0.001
Hyperlipidemia	427 (45.5)	144 (49.5)	1517 (48.9)	1060 (53.6)	1093 (53.9)	< 0.001
Diabetes	106 (11.0)	51 (17.2)	413 (12.9)	342 (16.6)	488 (23.0)	< 0.001
IHD in the family	347 (37.4)	113 (40.1)	1231 (40.5)	765 (39.3)	750 (37.9)	0.3072
Current smoker	293 (32.4)	100 (36.6)	1303 (42.7)	772 (39.4)	654 (33.0)	< 0.001
Overweight*	463 (57.7)	143 (55.6)	1764 (67.3)	1097 (66.7)	1059 (64.4)	< 0.001
Renal insufficiency**	107 (13.8)	39 (15.4)	353 (13.8)	310 (19.0)	457 (28.0)	< 0.001
EF< 50%	107 (22.1)	37 (25.2)	282 (19.5)	258 (28.7)	427 (42.3)	< 0.001
Previous stroke	36 (3.6)	15 (5.0)	113 (3.4)	111 (5.3)	189 (8.6)	< 0.001

Parameters are presented as numbers (percentage from non-missing data) or median (25^{th}, 75^{th} percentile). 0VD = zero-vessel disease; DA = diffuse atherosclerosis; 1VD = one-vessel disease; 2VD = two-vessel disease; 3VD = three-vessel disease; IHD = ischemic heart disease; EF = ejection fraction.

* Overweight was defined as body mass index ≥ 25.

** Renal insufficiency was defined as estimated glomerular filtration rate < 60 ml/min/1.73m^2 using MDRD equation.

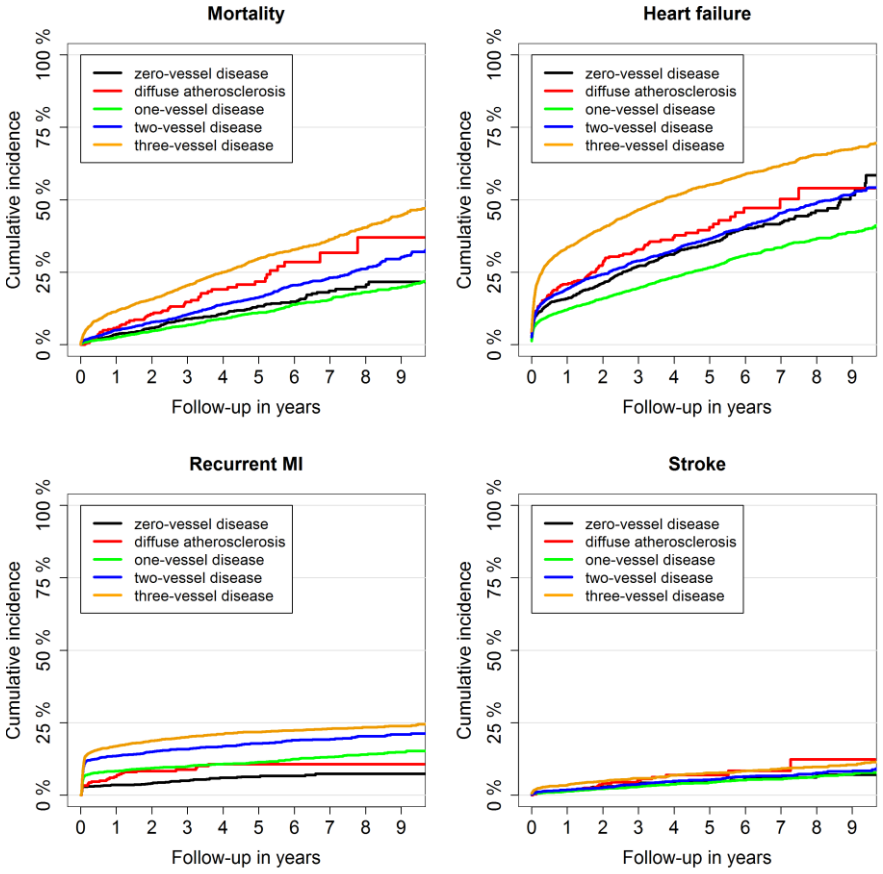

Figure 6: Long-term outcomes of NSTEMI patients according to their coronary artery pathology on the coronary angiography.

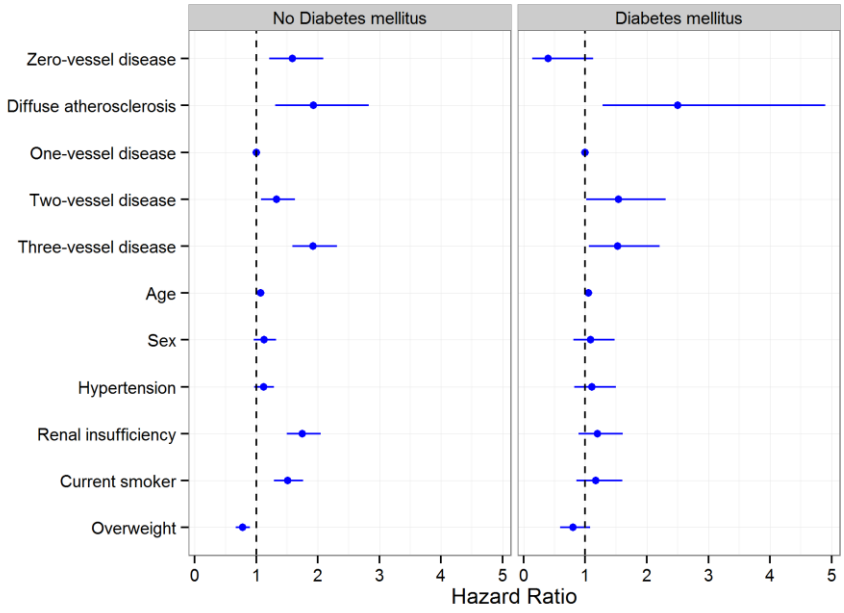

Figure 7: Adjusted mortality hazard ratio for NSTEMI patients according to coronary artery pathology on coronary angiography. The one-vessel disease group was used as a reference group. The model was adjusted for age, sex (female gender as reference), hypertension, renal insufficiency (eGFR<60), current smoker status, and overweight (BMI $\geq$ 25).

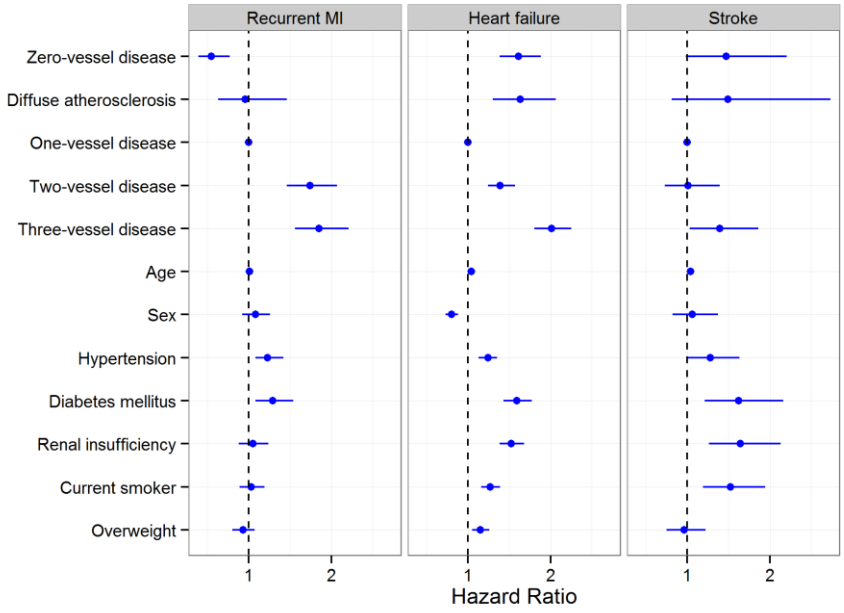

Figure 8: Adjusted hazard ratio for recurrent myocardial infarction, heart failure, and stroke in patients with NSTEMI according to coronary artery disease on coronary angiography. The one-vessel disease group was used as a reference group for comparison. Hazard ratio was adjusted for age, sex (female gender as reference), hypertension, diabetes mellitus, renal insufficiency (eGFR<60), current smoker status, and overweight (BMI ≥ 25).

4.3. Study III:

A third troponin T blood sample is not cost-effective in patients with suspected non-ST-segment elevation acute coronary syndrome.

In many hospitals, including ours, the standard of care for patients admitted for suspected non-ST-segment elevation acute coronary syndrome (NSTE-ACS) includes withdrawing three blood samples to assess the level of cardiac troponin with fast intervals during 24 hours admission before myocardial infarction can be ruled out. The aim of this study was to evaluate the cost-effectiveness of the third blood sample.

Methods: This study included 543 consecutive patients admitted for suspected NSTE-ACS to cardiology department at Aalborg university hospital between March and November 2003. Blood samples for cardiac troponin T (cTnT) were obtained on arrival, after 6-9 hours, and after 12-24 hours. cTnT fourth generation assay was used with a value of >0.03µg/L that satisfied the criteria of over 99th percentile with coefficient of variation <10 %. The costs of cTnT analysis and hospital stay were calculated. The cost of cTnT sample analysis was 12 euro, and the cost of one day admission in the coronary care unit was estimated to be 1,550 euro. The effect of the third troponin results on patients' management plan was examined.

Results: The median age of study patients was 62 years, male proportion was 62%, and one third of patients were known with angina pectoris (Table 2). Figure 9 presents a flow chart of patients' triage and observation period in the hospital. Out of the study population of 534 patients, 124 had at least one elevated cTnT level above the 99th percentile. Of the 124 patients, there were only four (3.2 %) who had cTnT level increased solely in the third sample. There were 83 patients who continued their stay in the cardiology department after three normal cTnT samples due to different reasons. 58 out of these 83 patients continued their stay because they were referred to an early in-hospital coronary angiography; 35 patients on the basis of unstable angina pectoris and previous PCI or CABG, and 23 patients due to risk factors and/or ECG changes (Table 3). The medical history, clinical presentation, and ECG changes for the four patients with elevated third cTnT level presented in Table 4, which shows that they had the same characteristics as the 58 patients mentioned above, which qualified them to be referred to in-hospital coronary angiography regardless cTnT level. Hospital stay was extended for 275 patients merely because of the third cTnT sample.

Incremental cost of the third blood sample was estimated as (534 patients x Euro 12 per cTnT analysis) + (275 patients x 0.5 day x Euro 1,550) = Euro 219,533.

Approximately 1,400 patients with suspected NSTE-ACS are admitted to our department per year. Thus, total cost per year is: (1,400/534) x Euro 219,533 = Euro 575,555.

Conclusion: The three-blood-sample strategy in the management of patients admitted for suspected NSTE-ACS did not contribute important information or change the patients' management compared with using a two-blood-sample strategy. On the contrary, it resulted in an unnecessary extension of length of stay in the hospital and increased health care costs for these patients.

Table 2: Baseline characteristics of patients admitted for suspected non-ST-segment elevation acute coronary syndrome (n=534).

Sex: male/female, %	62:38
Age years, median (range)	62 (27-96)
Medical history before admission	
Angina pectoris, n (%)	167 (31)
MI, n (%)	48 (9)
CABG, n (%)	22 (4)
Diabetes mellitus, n (%)	53 (10)
Electrocardiogram, n (%)	
Q-waves	41 (8)
Progressive ST-segment changes	61 (12)
Non-progressive ST-segment changes	71 (13)
Normal	284 (53)
Uncodable	77 (14)

MI = myocardial infarction; CABG = coronary artery by-pass graft

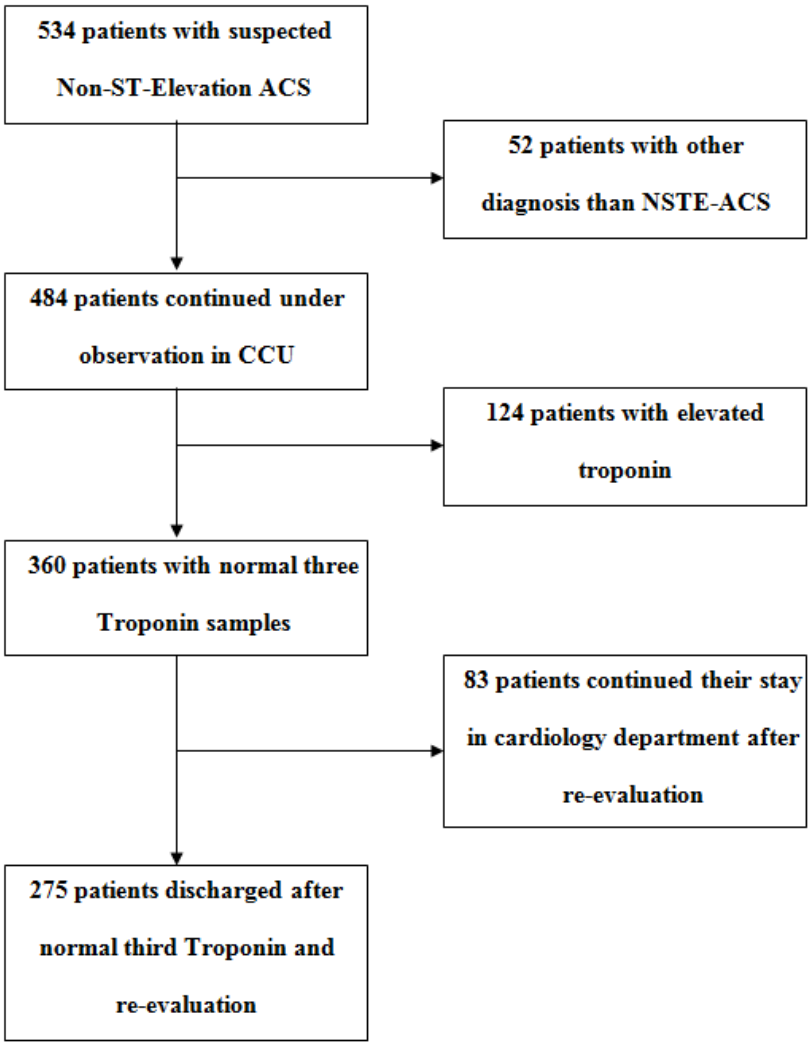

Figure 9: Flow chart over patients triage and management for patients admitted for non-ST-segment elevation acute coronary syndrome. NSTE-ACS = non-ST-segment elevation acute coronary syndrome; CCU = coronary care unit.

Table 3: Causes of extension of hospital stay after three normal cardiac troponin T samples in patients with suspected non-ST-segment elevation acute coronary syndrome.

Causes of extension of admission	**Number of patients**
CAG was performed due to unstable angina and previous PCI or CABG	35
CAG was performed based on risk factors, symptoms and/or ECG changes.	23
Pain management (known IHD with no possibility for revascularization)	7
Hospital stay extended to perform exercise test	12
Other	6
TOTAL	**83**

CAG= coronary angiography; CABG = coronary artery by-pass graft; PCI = percutaneous coronary intervention; ECG = electrocardiogram; IHD = ischemic heart disease.

Table 4: Key information on the four patients with an elevated cardiac troponin T only in the third blood sample.

	Medical History	Symptoms	ECG	cTnT 1,2,3 in µg/L
1.	Angina pectoris	Severe chest pain	Significant ST-segment depression > 0,5 mv	0.02, 0.03, 0.05
2.	Angina pectoris Previous CABG	Typical crescendo angina over 1 month	Normal	0.00, 0.03, 0.06
3.	Angina pectoris NIDDM Family history of IHD Heavy smoker	Severe chest pain radiating to the left arm, disappeared after nitroglycerin	Normal	0.00, 0.00, 0.04
4.	Angina pectoris	Severe continuous chest pain required nitroglycerin infusion	Normal	0.00, 0.02, 0.42

ECG = electrocardiogram; CABG = coronary artery by-pass graft; NIDDM = non-insulin dependent diabetes mellitus; IHD: ischemic heart disease.

5. DISCUSSION

Main Findings:

The overall aim of this dissertation was to analyze aspects of Myocardial Infarction in terms of incidence, prognosis, and health care costs.

The results of Study I confirmed that the overall incidence rate of first time MI declined from the year 1978 to 2012, and this decline was more prominent among males. The overall decline was mostly due to a fall in the incidence rates of the middle age groups, while both ends of the age scale showed a worrying increase in incidence rates of first MI among both genders. One-year case fatality declined significantly throughout the study period.

The results of Study II showed that NSTEMI patients with non-obstructive coronary artery disease (both zero-vessel disease and diffuse atherosclerosis without significant stenosis) had risk of long-term adverse outcomes that is comparable to one-vessel and two-vessel disease patients, and that the atherosclerosis group had a worse prognosis compared with the zero-vessel disease group. Patients with zero-vessel disease had a risk of mortality and heart failure that is similar to the 2-vessel, and higher than the 1-vessel group (for mortality outcome if patients were non-diabetic). Patients with diffuse atherosclerosis had higher risk of mortality and heart failure, and similar risk of recurrent MI and stroke compared with the 1-vessel group. In addition, the atherosclerosis group had similar risk of mortality, heart failure, and stroke, but lower risk of recurrent MI compared with the 2-vessel group. The 3-vessel group had the worst prognosis of all groups. Lastly, the prognosis of the atherosclerosis group was worse than the zero-vessel disease group with higher mortality in diabetic patients, higher recurrent MI risk, and not significantly different heart failure and stroke risks.

The results of Study III emphasized that the third measurement of cardiac troponin level in the blood for patients admitted for suspected acute coronary syndrome is not essential in the decision process regarding further investigations and management plan. Thus two-blood-sample strategy as opposed to the three-blood-sample strategy can save about Euro 575,555 per year in the cardiology department at Aalborg University Hospital and that can be applied to all other hospitals, which can result in a huge reduction in health care costs for this patients' category.

5.1. Incidence rate of first myocardial infarction for all patients (Study I)

This study confirmed a 37% decline in first MI comparing the year 1978 to 2012. These results support the findings of other studies from the USA,[67] UK,[32] and Sweden.[33] In Denmark, a study by Schmidt and colleagues,[31] examined incidence and prognosis of MI between 1984 and 2008 with special emphasis on prognostic impact of sex and co-morbidity. This study, however, did not clarify changes in MI incidence and mortality in different age groups for both genders. Our study in comparison to the above mentioned studies, included a larger cohort, a longer period of time and had particular focus on changing incidence and mortality rates in various age groups for both genders which was not examined in detail in any other study to the best of our knowledge.

Our data truncated in 2012 showed that from 1978 to 1999 a consistent decline in incidence rates was observed, after which an increase by 23% comparing 2002 to 1999, thereafter the incidence declined again. This was also observed in another study.[30] The most likely explanation is the publication and endorsement of international criteria for the diagnosis of MI in Europe and the United States in 2000. It was expected that there would be 26% more patients diagnosed with MI as compared with the previously used WHO criteria.[11] This phenomenon was again observed, although with a limited effect, by an increase in the incidence rate of 2.5% comparing 2006 with 2007 upon the endorsement of the 2007 version of the universal definition of myocardial infarction.[62]

The explanation behind the decrease in incidence rate of first MI is only to be hypothesized upon, however it is not unrealistic to suggest that the decrease in some risk factors for MI might have contributed to incidence decline; cigarette smoking decreased in Denmark for men from 68% to 31% (54.4% decline) and for women from 47% to 25% (46.8% decline) comparing the year 1970 to 2006.[13] Cholesterol levels and blood pressure decreased as well in Denmark's population since the 1960s.[13] These changes in risk factors were also observed in many other countries, for example in Sweden, smoking habit decreased in society by 55.4%, total cholesterol level decreased by 10.4%, and average systolic blood pressure decreased by 1.9% comparing the year 1986 with 2002.[68] Many other studies in different countries confirmed the decrease in these risk factors for MI.[1,69–71] On the other hand, other risk factors are increasing in society like diabetes mellitus and obesity.[13,68] However, the significant decline in MI incidence suggests that the effect of the decreasing risk factors on incidence rate is greater than the effect of the increasing risk factors.

5.2. Gender-specific incidence rate of first myocardial infarction (Study I)

Our results revealed that MI incidence rate was higher among men than women throughout the study period. This was also observed in another study from the UK.[32] This observation confirms that male sex is a risk factor for ischemic heart disease. Moreover, other risk factors like blood pressure and cholesterol levels as well as smoking frequency are higher among men than women.[13,72,73] Nevertheless, incidence decline was more significant among men than women comparing the study year 2012 to 1978. The explanation could partly be that men had a higher incidence rate at study start, and partly because the decline in other risk factors like smoking reduction was more obvious in men than in women since the early 1970s in Denmark.[13]

5.3. Incidence rate of first myocardial infarction for both genders divided into different age groups (Study I)

Incidence decline was more prominent in age groups with a higher incidence rate at study start. The greatest decline was reported in men aged 70–79, followed by men aged 60–69, and then women aged 70–79 years. The most remarkable findings in this study were increasing incidence rate of first MI in younger age groups; women under the age of 50 years and men under the age of 40 years. Moreover, women aged 50–59 years, and men aged 40–49 years experienced an increase in incidence rate since 1996. In addition, the older age groups (men and women ≥90 years) experienced an increase in incidence throughout the study period. The reason behind these findings in younger age groups might be that the change in risk factors for MI was not evenly distributed throughout all age groups. According to another study, LDL-cholesterol levels declined from 2001 to 2008 in society among both genders and all age groups, however, this decline was lowest among younger age groups.[72] Smoking rates declined as well from 1974 to 2012 among all age groups; nevertheless, the decline was less noticed among people less than 60 years of age. Furthermore, the percentage of smokers in society was higher in younger age groups.[14] On the other hand, obesity and diabetes are increasing[15–17] especially among younger people,[18–20] which could have a negative effect on incidence rates among younger age groups.

Another reason for these findings might be immigration. We have a work in progress after this thesis (not published data) which shows that the proportion of non-Danish ethnicity from all patients with first MI increased from 2% in 1978 to 12% in 2012 for patients under the age of 60, and from 2% to 6% for patients older than 60 years.

5.4. One-year mortality after first time myocardial infarction (Study I)

One-year case fatality after admission for first MI decreased tremendously from 1978 to 2012. Other studies have reported similar findings.[74–76] Although there was an increase in incidence rates in early 2000s; this was, however, not accompanied by an increase in one-year case fatality or one-year heart failure complication to the same extent. The reason for this could be the use of cardiac troponin which could have led to the detection of minor injury to the myocardium. This was found in other studies as well.[67,77,78]

Nevertheless, the reduction in one-year mortality was colossal and cannot be solely explained by minor MI's, but an important factor which could have played an important role is the use of evidence-based therapies (e.g. aspirin, beta blockers, lipid-lowering agents, and revascularization) leading to better management and prognosis. This was observed in other studies and registers.[79,80]

5.5. Mechanisms of myocardial injury in non-ST-segment elevation MI with non-obstructive coronary artery disease (Study II)

Previous research led to the discovery of several possible mechanisms for myocardial injury in patients with NSTEMI without obstructive coronary arteries. Some of these mechanisms cause ischemia by for example a rupture in an athermanous plaque without the plaque causing significant stenosis and where clot has already dissolved before the angiography.[37] Other studies which used provocation tests reported coronary artery spasm as a possible mechanism.[34,35,81,82] In addition, there were reports of microvascular disease,[36] or thrombophilias whether congenital or acquired, as causes for NSTEMI with non-obstructive coronary artery disease.[34] The abovementioned mechanisms are related to ischemia, however, a non-ischemic mechanism like myocarditis was also reported in 7% of patients diagnosed with NSTEMI when cardiac MRI was used,[9] this is because myocarditis can resemble MI and fulfill the universal diagnostic criteria for MI.[12] Finely, other conditions can cause a demand-supply mismatch leading to type 2 MI, such as severe anemia, severe respiratory failure, tachy-brady arrhythmias or severe aortic valve disease.[12]

5.6. Prevalence of NSTEMI with non-obstructive coronary artery disease (Study II)

The proportion of NSTEMI with non-obstructive coronary arteries from all NSTEMI patients increased gradually to 18% in 2011 in our data. This can eventually be explained by the use of different generations and cutoffs of cardiac

troponin assay which became a high sensitive assay in the last years of the study. This development led to the detection of minor injury to the myocardium.[67,77,78] Other studies have reported a varied prevalence of MI with non-obstructive coronary arteries from 4-13%, depending on the type of acute coronary syndrome used (STEMI, NSTEMI, and/or unstable angina).[8–10,83]

5.7. Characteristics of patients with NSTEMI and non-obstructive coronary artery disease (Study II)

There were significantly more females in both the 0-vessel and the atherosclerosis groups than all other groups. This finding confirms other studies,[8,38–40,43,83,84] however, some of these studies reported that NSTEMI patients with non-obstructive coronary artery disease are generally younger and have less risk factors for ischemic heart disease than patients with obstructive coronary artery disease. These studies, nevertheless, did not divide patients with non-obstructive or obstructive coronary artery disease into subgroups. Our study illustrates that patients have different characteristics within both non-obstructive and obstructive coronary artery disease large groups. Thus in our study patients with 0-vesel disease were younger, more likely to be females and have less risk profile than those with diffuse atherosclerosis. This was also observed in another study.[40] Moreover, patients in the 0-vessel group had generally a comparable profile to the1-vessel group and those in the atherosclerosis group were comparable to the 2-vessel group. The 3-vessel group had higher risk profile than all other groups, which might have contributed to the generally higher risk profile in obstructive coronary artery disease group compared with non-obstructive group in studies which compared these broad groups.

5.8. Long-term mortality for patients with NSTEMI according to their coronary pathology (Study II)

Our study illustrated that mortality risk was higher in patients with 0-vessel disease (if they were non-diabetic) and diffuse atherosclerosis compared with patients with 1-vessel disease, and not significantly different than patients with 2-vessel disease. Another study reported that NSTEMI patients with normal coronaries had no difference in mortality than both atherosclerosis, 1-vessel, and 2-vessel disease not involving proximal LAD,[44] while other studies which compared obstructive versus non-obstructive coronary arteries in NSTEMI patients without sub-differentiation of these two groups demonstrated that mortality risk was similar in these broad groups.[39,40,43,84] Moreover, mortality risk of type 2 MI was reported before to be comparable to type 1 MI,[85,86] and our study did not distinguish between type 1 and type 2 MI, if the latter was coded as NSTEMI as the primary diagnosis in the register.

The reason for our findings can only be speculated upon, but it is not unreasonable to assume that patients in the 0-vessel group are different from those in the atherosclerosis group. The 0-vessel group is most likely to be very heterogeneous and includes a variety of underlying conditions which may not have been investigated in detail during the admission. Some of these conditions could cause fatality and morbidity without directly involving coronary artery disease, while the atherosclerosis group patients could have the same underlying ischemic heart disease as NSTEMI patients with obstructive coronary arteries, but these patients are less likely to receive evidence-based medical treatment after MI and more likely to discontinue platelet inhibition treatment if this was started.[39,43]

5.10. Long-term risk of recurrent MI after first NSTEMI (Study II)

The risk of recurrent MI was similar between patients with diffuse atherosclerosis and patients with 1-vessel disease, and both groups had a higher risk than patients with 0-vessel disease.

A possible explanation can be that atherosclerotic plaque burden could be similar among atherosclerosis and 1-vessel patients, but higher than 0-vessel patients. Yamagishi and collogues examined 106 patients with no stenosis >50% but atherosclerosis with intra vascular ultrasound system and reported within a mean follow up period of 21 months, that 11.3% were admitted for acute coronary syndrome with culprit lesion in the previously examined plaque, and 3.7% with culprit lesion in a previously normal coronary artery.[87] Maehara and collogues reported that with the use of intra vascular ultrasound system, 11.6% of ruptured plaques were not detected by angiography.[88] Moreover, acute coronary syndrome with high grade stenosis (>75%) can occur in about 50% of lesions, which previously found not significant, and treated medically.[89] On a 3 years follow-up, 12.9% of major adverse cardiovascular events were related to culprit lesion and 11.6% were related to non-culprit lesion, most of non-culprit lesions were angiographically mild lesions at base-line.[90]

Other studies have shown that patients with non-obstructive coronary artery disease have lower risk of MI than obstructive coronary artery disease,[39,40] however, these studies did not perform sub classification of obstructive coronary artery disease patients.

5.9. Long-term heart failure complication after first NSTEMI (Study II)

Our results demonstrated that heart failure risk was higher among patients in the with 0-vessel or atherosclerosis groups than those in the 1-vessel, and similar to those in the 2-vessel group. There was a study that reported the risk of heart failure to be the same among patients with acute coronary syndrome with or without

obstructive coronary artery disease.[84] This study was, however, among patients ≥ 75 years, and did not differentiate between subgroups of obstructive or non-obstructive coronary artery disease.

One explanation of these findings could be that, although we excluded patients known with heart failure from our study, some of the patients in the normal 0-vessel or atherosclerosis group of the study could have been admitted with acute heart failure with signs, symptoms, and cardiac markers that resembled MI. Therefore they received the diagnosis NSTEMI upon discharge. It is well known that acute heart failure can cause myocardial injury resembling myocardial infarction.[12] Other patients could have also suffered from some type of non-ischemic cardiomyopathy or hypertensive heart disease which became manifest at a later stage.

5.11. Long-term stroke risk after first NSTEMI according to coronary pathology (Study II)

There was no significant difference in stroke risk among NSTEMI patients across coronary pathology subgroups. This finding supports other studies,[39,43] however, these studies did not differentiate between different subtypes of obstructive coronary artery disease.

5.12. Overall explanation for outcomes differences between NSTEMI patients accroding to coronary artery pathology on the angiography (Study II)

An overall explanation for the differences in outcomes maybe hypothesized as 0-vessel disease patients might have a non-ischemic basis for their MI, such as acute heart failure, myocarditis, arrhythmias, or other causes which predispose them to higher future heart failure and higher or comparable mortality compared with 1-vessel patients. While diffuse atherosclerosis patients have an extended atherosclerotic disease without focal significant stenosis, nevertheless, they are less likely to receive the recommended medical therapy,[39,43] therefore their prognosis is worse than 1-vessel and comparable to 2-vessel patients.

5.13. Cost-effectiveness of the third blood sample of cardiac troponin (Study III)

Although the value of cardiac troponin I and T for risk stratification in non–ST-segment elevation acute coronary syndrome is well established,[91–97] and their use in patients with suspected acute coronary syndrome is cost-effective, [98–100] the cost effectiveness of the routine withdrawing of three or more blood samples of troponin has not been examined. The strategy of serial measurement of troponin has been

used over a long time to increase safety for the patients in ruling out MI diagnosis.[48,49]

This study affirmed that the third measurement of cardiac troponin is not cost effective because it costs our department Euro 575,555 per year without adding important information regarding the management of patients. Thus, it is safe to reevaluate patients after the second blood sample of troponin and make a decision on further management or discharge. Other studies have also reported the safety of discharge from the hospital after a few hours of observation and negative troponin levels.[101,102] On applying the European Society of Cardiology guidelines on the management of non-ST-elevation acute coronary syndrome,[52] the four patients with normal first two troponin levels in our study, would all have been referred to early coronary angiography due to either ST-segment changes in the ECG (patient 1), previous CABG with typical crescendo angina over 1 month (patient 2), diabetes mellitus with high risk profile (patient 3); or to an urgent invasive strategy due to refractory angina (patient 4). Moreover our data showed 58 patients who were referred to an early (in hospital) coronary angiography based on a risk profile and/or ECG changes. This would have been applied for the four patients with elevated third sample of cTnT even before the results of this sample became available.

Besides reducing expenses, the prospective of withdrawing two troponin blood samples instead of three will lead to earlier re-evaluation of patients as soon as the second troponin results becomes available without delay.

6. STRENGTHS AND LIMITATIONS

The strengths of our study include the large number of unselected patient populations including men and women, different age groups, and patients of both Danish origin as well as immigrants; this helps generalize our findings.

However, our studies do have some limitations. In Study I different thresholds for cardiac biomarkers throughout study years might have affected the incidence rates, and some patients who were considered as having first MI during the early years of the study might have suffered a MI prior to the introduction of national registers. That is why we did a sensitivity analysis using all MIs.

In both Study I and II we had no access to clinical data as symptoms, signs, ECG changes, and results of blood tests. Moreover, like all other register-based studies, the validity of these studies depends much on the validity of MI diagnosis in the Danish National Patient Register, which was estimated to be 92-93%.

In Study II, patients with MI type 2 might have been included if the primary discharge diagnosis was NSTEMI. Moreover, a core-lab for coronary angiography assessment was not used, thus inter-operator variation might exist. Only patients who underwent coronary angiography were included which might make generalizations of the results limited. Finally there was no adjudication committee to verify clinical events. In angiography database the definitions of 0-vessel disease and diffuse atherosclerosis were subject for inter- and intra-hospital different interpretations, thus some of the patients with diffuse atherosclerosis might have been coded as 0-vessel disease. However, this misclassification would lead to minimize the differences between 0-vessel and atherosclerosis groups, thus the real differences between these groups in outcome may be larger than that reported in our article.

In Study III, a limitation of this study might be that the study was conducted using 4^{th} generation cTnT, while many institutions nowadays are using high sensitive cTnT. However, the use of high sensitive cTnT with its even lower threshold leads to the detection of troponin in the blood with less time from symptoms start than 4^{th} generation cTnT, thus the observation period for suspected coronary artery syndrome might become even shorter with these high sensitive assays.

7. CONCLUSION

Myocardial infarction is decreasing in incidence and patients' prognosis is improving but there are still challenges in specific age groups and subgroups of myocardial infarction with non-obstructive coronary artery disease.

More detailed conclusions are based on our studies:

Study I: The results of this nation-wide population-based 35-year study with 316,790 patients demonstrate that the incidence rates of first myocardial infarction has generally decreased through the study period until 2012 in the majority of age groups for both genders, nevertheless, younger age groups (women less than 60 years and men less than 50 years of age) have experienced an increase in incidence rates at least since 1996. Moreover, incidence rates increased in the oldest age group (men and women 90 years and older) throughout the study period. These findings require further investigation to confirm age-specific incidence changes which might lead to focus more preventive measurements to target the affected age groups. Study results emphasize the remarkable decline in one-year case fatality after admission for first MI in all age groups of either gender.

Study II: Non-ST-segment elevation myocardial infarction patients with a non-obstructive coronary artery disease on coronary angiography, both normal coronaries and atherosclerosis with stenosis <50%, have a non negligible risk of adverse long term outcomes. Patients with zero-vessel disease have a higher risk of mortality than the one-vessel disease group if they were non-diabetics, and similar risk if they were diabetics. They have, in addition, a higher risk of heart failure than one-vessel disease, and similar risk of stroke to all subgroups of obstructive coronary artery disease.

Patients with diffuse atherosclerosis have a higher risk of mortality and heart failure than one-vessel disease, similar to two-vessel disease and three-vessel disease groups. Moreover, they are similar to all other groups in terms of stroke risk, and have a similar risk of recurrent MI to one-vessel disease.

Finally, patients with zero-vessel disease have better prognosis than those with diffuse atherosclerosis with less recurrent MI and mortality (for mortality if patients were diabetic), but similar risk of heart failure and stroke.

Thus these two NSTEMI groups with non-obstructive coronary arteries should probably be considered separately in future research and further investigation is needed to illuminate both the mechanism of myocardial injury and the optimal management and follow-up plan for each of these two subgroups of patients.

Study III: This study confirms that the third cardiac troponin T blood sample is not cost-effective as it does not add further important information to be used in patients' management and investigations plan. On the contrary, it leads to an unnecessary extended length of stay in the hospital which leads to increased health care costs.

8. CLINICAL IMPLICATIONS AND FUTURE RESEARCH

As a consequence of Study III, our department dropped the routine use of the third blood sample of troponin, and encouraged the practice of re-evaluation as soon as the result of the second sample is available.

Future research:

1- Focus studies on age groups were we found increasing MI incidence rates, especially men less than 50 years, and women less than 60 years of age for better understanding of this phenomenon and focus preventive measures.

2- Developing an algorithm to try to predict which patients admitted with acute NSTEMI might have non-obstructive coronary artery disease, and might be referred to a non-invasive modality to investigate their atherosclerotic burden.

3- Investigate medical treatment differences between NSTEMI patients with and without obstructive coronary artery disease in different subgroups.

4- Design a study with extensive investigation program to find out the cause for myocardial injury in MI patients with non-obstructive coronary artery disease.

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APPENDICES

Appendix A. Study I

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ORIGINAL ARTICLE

Incidence and outcome of first myocardial infarction according to gender and age in Denmark over a 35-year period (1978–2012)†

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Aims To examine temporal changes in incidence and 1-year mortality of first myocardial infarction (MI) in different age groups for both genders in Denmark over a 35-year period (1978–2012).

Methods and results Patients aged 30 years or older admitted with first MI in Denmark from 1978 to 2012 were included ($n = 316\,790$). Overall, first MI incidence per 100 000 person-years (/10^5 p.y.) decreased significantly from 500 to 297/10^5 p.y. for males and from 229 to 156/10^5 p.y. for females. The decline was greatest among men aged 70–79 from 1460 to 643/10^5 p.y. (−56%). The majority of age groups also experienced declining incidence. However, men aged 30–39 and ≥ 90 years as well as females aged 30–49 and ≥ 90 years had increasing incidence during the study period. Moreover, the incidence decreased from 1978 to 1996 among males aged 40–49 and females aged 50–59 years, but increased in the remainder of the study period. One-year case-fatality declined significantly from 50 to 9% of MI male patients, and from 53 to 15% of MI female patients when comparing 1978 to 2012. Statistical analysis with Poisson models demonstrated that the mortality rate increased with age and decreased with time and indicated no significant difference between genders.

Conclusions During the period from 1978 to 2012, there was a significant decline in MI incidence among most age groups for both genders; however, an incidence increase was observed in men under 50 and women under 60 years, and ≥ 90 years for both genders. One-year case-fatality decreased constantly during the study period.

Keywords Acute myocardial infarction • Incidence • Prognosis • Community-wide trends

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†The research was carried out in the Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark.

Appendix B. Study II

Long-term prognosis of patients with non-ST-segment elevation myocardial infarction according to coronary artery pathology on coronary angiography

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Abstract:

Aims: To examine the long-term prognosis of patients with non-ST-segment elevation myocardial infarction (NSTEMI) according to the degree of coronary artery disease (CAD).

Methods and results: We examined 8.889 consecutive patients admitted for first time NSTEMI during 2000-2011, to whom coronary angiography was performed. Patients were classified by coronary angiography: 0-vessel disease (0VD), diffuse atherosclerosis (DA) (0% < stenosis <50%), 1-vessel disease (1VD), 2VD, and 3VD with stenosis ≥50%. Follow-up period: 13 years (median 4.5).

One-year mortality for NSTEMI patients with 0VD was 3.7%, DA 5.7%, 1VD 2.5%, 2VD 4.8 %, and 3VD 11.5%. Non-diabetic 0VD patients had higher risk of mortality than 1VD patients (HR:1.59; 95% CI:1.21-2.02; *P*<0.001), while those with diabetes mellitus (DM) had not significantly different risk. In addition 0VD group had higher risk of heart failure (HF) (HR 1.61; 95% CI: 1.39-1.88; *P* <0.001), and lower risk of recurrent MI (HR:0.55; 95% CI:0.39-0.77; *P* <0.001) compared with 1VD. For patients with DA; mortality and HF risks were higher than 1VD and not different than 2VD, while recurrent MI risk was not different than 1VD and lower than 2VD.

Finally, the DA group had higher risk of mortality if they had DM, higher risk of recurrent MI, and not different risk of HF and stroke compared with the 0VD group patients.

Conclusion: Patients with NSTEMI and non-obstructive CAD (both normal coronaries and atherosclerosis) have a comparable prognosis to patients with one- or two-vessel disease. Patients with atherosclerosis have worse prognosis than those with angiographically normal coronary arteries.

Key words: Myocardial infarction, prognosis, non-obstructive coronary artery disease

Appendix C. Study III

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healthcare

ORIGINAL ARTICLE

A third troponin T blood sample is not cost-effective in patients with suspected non-ST segment elevation acute coronary syndrome

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Abstract

Background. The diagnosis of acute myocardial infarction requires troponin assessment in at least two blood samples 6–9 hours apart, with an optional third sample 12–24 hours after admission if suspicion is high. Yet, in many institutions, this third sample is routinely drawn. This study aimed to evaluate cost-effectiveness of this third sample of troponin. ***Methods.*** A total of 534 patients with possible Non ST-Elevation Acute Coronary Syndrome (NSTE-ACS) were included. Blood samples for cardiac TroponinT (cTnT) were obtained on arrival, after 6–9 hours, and 12–24 hours after admission. The costs of cTnT analysis, and hospital stay were calculated. ***Results.*** Of the 534 patients, 124 had at least one elevated cTnT value. Among these, four patients (3.2%) had cTnT values increased only in the third sample. Based on their risk profile and/or ECG changes, these four patients were eligible for referral to coronary angiography even before the result of the third sample became available. The number of patients whose length of stay was extended solely because of the third sample was 275. Incremental cost of the third blood sample: [534 patients × Euro (EUR) 12 per cTnT analysis] + [275 patients × 0.5 day × EUR 1,550] = EUR 219,533. Approximately 1400 patients with suspected NSTE-ACS are admitted to our department each year. Thus, the total cost per year is: (1,400/534) × EUR 219,533 = EUR 575,555. ***Conclusion.*** A third troponin sample adds no vital information regarding patients' treatment or investigations plan. On the contrary, it may lead to an unnecessary extension of the admission period and increased costs.

Key Words: *Acute coronary syndrome, health care economics and organisations, hospital costs, myocardial infarction, troponin*

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