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To my daughter Lilya, who has been the one who made the greatest sacrifice. Thank you for being a constant reminder of the most important things in life and to make me strive for the better. I look forward to the next chapter ahead of us.

“When the why is clear, the how becomes easy”

Nivethitha Ilangkovan
October 2017
Aabenraa
Table of contents

Abbreviations .......................................................................................................................................... 7
List of papers ........................................................................................................................................... 9
English summary ................................................................................................................................... 11
Dansk resumé ........................................................................................................................................ 13
Prologue ................................................................................................................................................ 15
Background .......................................................................................................................................... 17
Aims and objectives ............................................................................................................................... 23
Methods and results ............................................................................................................................... 27
  Data sources in general ..................................................................................................................... 27
  Method: Study I ................................................................................................................................. 28
  Summary of results: Study I .............................................................................................................. 30
  Method: Study II and study III ........................................................................................................... 32
  Summary of results: Study II and III ................................................................................................. 36
Discussion .............................................................................................................................................. 39
  Summary of key findings ................................................................................................................ 39
  Comparison with existing literature ............................................................................................... 40
  Methodological considerations ...................................................................................................... 42
  Limitations ...................................................................................................................................... 44
  Generalisability ............................................................................................................................... 45
  Clinical implications ....................................................................................................................... 46
Conclusion ............................................................................................................................................. 47
  Perspectives ................................................................................................................................... 47
Epilogue ................................................................................................................................................. 49
References ............................................................................................................................................ 50
Papers I-III .............................................................................................................................................. 57
  Paper I ........................................................................................................................................... 59
  Paper II .......................................................................................................................................... 81
  Paper III ......................................................................................................................................... 101
Appendices .......................................................................................................................................... 121
# Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AU</td>
<td>Agatston units</td>
</tr>
<tr>
<td>AP</td>
<td>Angina Pectoris</td>
</tr>
<tr>
<td>CAC</td>
<td>Coronary artery calcium</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>DanRisk</td>
<td>The Danish Risk Score study</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>hsTn</td>
<td>High sensitive troponins</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International classification of disease with 10th revision</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
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<tr>
<td>NSCP</td>
<td>Non-specific chest pain</td>
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</table>
List of papers

The thesis is based on the following papers:


English summary

Patients with chest pain of unknown aetiology are a challenge to the emergency departments and the cardiology departments. In spite of great advances within the cardiology field over the last decades, the knowledge of patients with non-specific chest pain (NSCP) and their prognosis is limited. In this thesis, we wanted to describe this patient population, their characteristics, risk stratification and prognosis for a year of follow-up.

In study I, we examined the overall prognosis for NSCP patients before and after high sensitive troponins implementation and compared them to other diagnostic groups as myocardial infarction (MI), other heart-related conditions and stable angina pectoris in a population-based study. Our findings showed that the all-cause one-year mortality and risk of a cardiac related event (myocardial infarction, ventricular arrhythmia, and cardiac arrest) for NSCP was favourable, especially compared to the MI group. The all-cause one year mortality was corresponding to the general population.

In study II, we aimed to investigate risk factors characterising NSCP patients with a clinical endpoint and their prognosis during one year of follow-up. We conducted a prospective cohort study that included NSCP patients and gathered data prospectively. In this study, we demonstrated that NSCP patients have a good prognosis, with few cardiac-related events and one-year all-cause mortality similar to the general population. The risk factors identified were gender, Charlson score >=1, previous known coronary artery disease, hypertension, hypercholesterolemia, diabetes and use of statins (cholesterol lowering medication). However, the few events occurring in this study limits the statistical statements inference.

In study III, we investigated the role of non-contrast cardiac computer tomography in NSCP patients and determined whether there was a relationship between coronary artery calcium and clinical endpoints occurring during one year. This was a double-blinded prospective cohort study. The study population from the Danish Risk score (DanRisk) study represented the asymptomatic general population for comparison. We found no significant difference in the prevalence of coronary artery calcium or occurrence of clinical endpoints for the NSCP population compared to the DanRisk population. We could not make a definite conclusion based on the few events occurring during one-year follow-up.

In general, all three studies have concluded that NSCP patients have a good prognosis compared to the general population and patients with MI. The all-cause mortality for NSCP was comparable with the age and gender-adjusted general population. The occurrence of cardiac-related endpoints were few and associated with risk factors such as male gender, Charlson score >=1, previous coronary artery disease, hypertension, hypercholesterolemia, diabetes and use of
statins. The indication for cardiac computed tomography was not more significant for NSCP patients than for the asymptomatic DanRisk general population.
**Dansk resumé**

Patienter med brystsmerter af ukendt ætiologi udgør en udfordring i vores akutmodtagelser samt kardiologiske afdelinger. Til trods for den udvikling, der har fundet sted indenfor det kardiologiske felt de sidste årtier, er den viden, der eksisterer om patienter med uspecifikke brystsmerter (NSCP), begrænset. I denne afhandling ønskede vi at beskrive patientgruppen af NSCP patienter, deres karakteristika, risikostratifcierung samt prognose for ét år.


I det andet studie, studerede vi risikofaktorer, der karakteriserede NSCP patienter samt deres etårs prognose efter en akut henvendelse for brystsmerter, herunder omfanget af patienter, der blev diagnosticeret med hjertekarsygdom i løbet af et års opfølgningstid, samt risikofaktorer der kunne identificere disse patienter ved første kontakt. Studiet blev udført som et prospektivt kohorte studie. Dette studie viste, at NSCP patienter havde en favorabel prognose med få hjerterelaterede hændelser. Den totale mortalitet var sammenlignelig med baggrundsbefolkningen. De identificerede risikofaktorer var køn, Charlson score ≥1, tidligere kendt hjertekarsygdom, hypertension, hypercholesterolæmi, diabetes samt statin (cholesterolsænkende medicin) forbrug. De få hændelser som fandt sted betød dog, at vi ikke kan drage en sikker konklusion vedrørende disse risikofaktors prædiktive værdi.

Den overordnede konklusion i dette studie er, at prognosen for NSCP patienter er favorabel sammenlignet med baggrundsbefolkningen og MI patienter. Den generelle dødelighed var sammenlignelig med den køns- og aldersjusterede baggrundsbefolkning. De hjertekarrelaterede hændelser som forekom i løbet af opfølgningstiden var få og var associeret med risikofaktorerne mandligt køn, Charlson score >=1, tidligere kendt koronararteriesygdom, hypertension, hypercholesterolæmi, diabetes samt statin forbrug. Hjerte Computer Tomografi var ikke mere indiceret hos NSCP patienter end for den asymptomatiske baggrundsbefolkning.
Imagine this: the setting is an emergency department or cardiology department. You are the physician on call. The department is overcrowded. The time is 3 p.m. Still, three patients with chest pain to assess. The electrocardiograms are normal. The blood test likewise, including the high sensitive troponins measurements. Your clinical judgment tells you these are low-risk patients for cardiac-related chest pain. You do not suspect another diagnosis, which requires treatment. You send them home without subsequent work up.

“I wonder how it will go them.” you reflect while you dictate the discharge note and label it with the discharge diagnosis “Chest pain” or “Observation for myocardial infarction”. Will they come back with a myocardial infarction tomorrow? Possibly in six months? Could I have reassured them that there was no higher risk for such an event for these patients than anyone else? Are the new sensitive troponins so sensitive that they detect everything that should be caught? Can I rely on my clinical judgment that they do not need further follow-up? Are the traditional risk factor assessments enough or should they have been investigated with some of the advanced devices available next to the emergency department? What about a fast computer tomography scan for calcification in the coronary vessels? Takes just 5 minutes on the way home, anyway.

I have found myself in this situation several times and I share your concerns and questions. I would like to search for the answers in this Ph.D., so that we in the future can add a little more knowledge to the discharge situation and counseling. This thesis will provide you with some of the answers.
Background

Cardiovascular disease is a leading cause of death among women and men in Europe. Cardiovascular disease causes 51% of all deaths in women and 42% in men, respectively (1, 2). In Denmark, it is only to be exceeded by cancer-related deaths (1). A subgroup of cardiovascular diseases is coronary artery disease (CAD). The statistics show a decreasing mortality rate of CAD while the hospitalisation and prevalence of CAD are increasing (3).

The acute presentation of CAD is acute myocardial infarction (MI). The handling of MI has gone through a remarkable development. Just a decade ago the treatment for acute ST-elevation MI was fibrinolysis (4, 5) and before that virtually no causal treatment existed. The DANAMI II study established the role of an early invasive strategy with primary percutaneous coronary intervention in ST- elevations MI patients (6). The role of revascularisation in non- ST-segment elevation MI patients was furthermore secured and studies confirmed the improvement in long-term mortality with revascularisation strategies (7, 8).

High sensitive troponins

In the 1960s Lactate dehydrogenase was the preferred biomarker for MI (9). Almost concurrently the creatinine kinase was used for the same purpose (10). Just 20 years ago the evaluation of MI in the emergency departments consisted of history, electrocardiogram (ECG) and blood test; the golden standard being creatinine kinase MB (11, 12). Troponin, a protein complex that serves as a biomarker for cardiac cell death (13), was only safe to use as an exclusion tool for AMI if the diagnosis was made more than 6 hours from the time of emergency department presentation (14). From the year 2000 troponin was included in the definition of MI (15).

Since then several generations of troponin assays have been developed leading to high sensitive troponins (hsTn) (16, 17). The newest assays show very high negative predictive values above 99% when the cut-off is set at undetectable values (18, 19).

Figure 1 illustrates the three studies in this thesis in context with the progress of cardiac marker and treatment strategies.
Chest pain

Chest pain is the cardinal symptom of MI. Only 15-20% of patients with chest pain turn out to have an acute MI (18, 20, 21), while about 50% have chest pain of undetermined cause (22). Chest pain is a symptom that gives rise of suspicion to many differential diagnoses from the more benign disorders with low health impact to the acute and fatal conditions.

According to the consensus document, the definition of MI is based on elevated troponin above the 99th percentile and ischemic symptoms or ECG changes concordant with myocardial ischemia (23). MI was defined as myocardial necrosis, which is myocardial cell death that causes an increase in troponin together with either ischemia symptoms or ECG changes (23). Increased troponin level in the bloodstream indicates myocardial injury, but it does not always mean that the myocardial necrosis is present or caused by myocardial ischemia. Other causes of troponin rise can be due to cardiac surgery, heart failure, and arrhythmia. Of non-cardiac-related causes, renal failure and rhabdomyolysis can be mentioned (24). Hence, the evaluation of acute chest pain patients can lead to the diagnosis of MI, other coronary related chest pain as unstable and stable angina pectoris (AP), cardiac related chest pain, non-cardiac related chest pain with an alternative diagnosis, like pulmonary embolism or gastrointestinal disorders or non-specific chest pain (NSCP) when no obvious explanation is found (25). The possible diagnoses for patients with chest pain presentation are listed in Table 1.

Clinical assessment of chest pain is thus important in the risk stratification of MI. The clinician must distinguish between typical cardiac related chest pain and atypical chest pain. Typical chest pain is in daily terms referred to as angina and is characterised by retrosternal pressure/heaviness, radiation to the left arm, neck or jaw, duration of several minutes or persistent (26). Additional symptoms like sweating, nausea, and dyspnoea may also be present. Atypical chest pain, on the other hand, is characterised by symptoms like epigastric pain, indigestion-like symptoms or the sole presence of dyspnoea (26). Atypical chest pain occurs
more in females and in patients with diabetes or chronic renal disease and dementia (27-29). When chest pain and concomitant symptoms are worsened by physical effort or relieved by rest the likelihood that the chest pain is caused by myocardial ischemia increases.

<table>
<thead>
<tr>
<th>Low likelihood</th>
<th>High likelihood</th>
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</thead>
<tbody>
<tr>
<td><strong>Presentation</strong></td>
<td><strong>Atypical</strong></td>
</tr>
<tr>
<td>ECG</td>
<td>-</td>
</tr>
<tr>
<td>Troponin</td>
<td>-</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Unspecific chest pain</td>
</tr>
<tr>
<td></td>
<td>Stable AP</td>
</tr>
</tbody>
</table>

Table 1
The presentation of chest pain, clinical assessment and diagnosis

The chest pain patient in the emergency departments
Chest pain complaints account for 6% of emergency departments visits (30, 31). One out of three patients with MI diagnosis does not present with typical chest pain symptoms (29). Even with hsTn, it remains a challenge for emergency physicians to be able to identify patients with MI when they do not present with typical chest pain. It can lead to delayed and incorrect diagnosis and treatment. However, admitting and investigating all patients with a minor suspicion of MI means that patients occupy a bed for at least six hours. Newer studies are investigating the prognostic implication of a single hsTn measurement below the detection limit as a rule out for MI in combination with clinical assessment and non-ischemic ECG (18, 32, 33). For the moment no consensus document or guidelines exist regarding this approach.

Risk assessment
An important risk stratification tool for patients with CAD is based on the evaluation of traditional risk factors like hypertension, hypercholesterolemia, diabetes, lifestyle, obesity, smoking and family history. An aggressive prevention and treatment strategy of these risk factors is beneficial for the CAD prognosis. Several algorithms have been developed for the purpose of risk stratification of CAD patients. The systematic Coronary risk evaluation (SCORE) estimates 10-year mortality for cardiovascular disease in Europeans. This risk chart is based on the risk factors sex, age, smoking, systolic, blood pressure and cholesterol levels (34). For assessment of chest pain in a more acute setting the HEART score was developed taking into account history, ECG, age, risk factors including diabetes and troponin (35, 36). The findings by Omstedt et al. (37) supported the use of HEART score in NSCP patients. We do, however, know
that up to 20% of patients with CAD do not have a traditional risk factor (38) and other forms of testing could be useful.

**Non-acute assessment of CAD**

*Coronary angiography* is a reliable test for CAD; however, it is invasive and associated with certain risks of complications like hematoma, arrhythmias, coronary artery dissection and myocardial infarction (39, 40).

Even though several possibilities for cardiac testing exist, pros and cons have to be taken into consideration with the patient’s pre-test possibility of CAD. Current guidelines for management of stable CAD recommends non-invasive testing as the first choice in patients with low to intermediate pre-test probability of CAD (41).

*Stress testing* with bicycle or treadmill using a 12 lead ECG is the most simple and non-invasive test for stable CAD patients with an intermediate pre-test probability (41). The best diagnostic information from this test is obtained in patients with normal ECGs and without the use of anti-ischemic drugs. The interpretation of the results demands an exercise effort where 85% of the maximum heart rate is achieved and can be limited by functional problems, which also may explain, why this test is outdated today.

*Myocardial perfusion scintigraphy* (single photon emission computed tomography and positron emission tomography) produces images of regional tracer uptake in rest and in stress, and shows hypo-perfusion during stress-induced conditions that is diagnostic for stable CAD (41). However, this test is associated with the administration of pharmacological agents and radiation. Recent guidelines recommend *Cardiac Computed Tomography (CT) angiography* as a non-invasive test for ruling out CAD in patients with intermediate pre-test probability (40-42). This test is able to visualise the artery lumen and the narrowing by a contrast agent. The limitation of this test is that it cannot be performed in patients with severe coronary artery calcification, high body mass index or irregular rhythm.

*Coronary CT* with calcium score (CAC) is a non-invasive diagnostic imaging to assess future cardiovascular risk. Coronary calcium scoring CT has a low radiation risk, with a mean exposure of 1 mSv (43), is easy to perform and interpret, cheap and non-invasive. There is a correlation between coronary artery calcification and coronary atherosclerosis which is visualised by cardiac CT and expressed in Agatston unit (AU) (44). Previous studies have shown that a high AU is associated with an increased risk of cardiac event and mortality, while no calcification (0 AU) has a low risk of cardiac event (45-47). In a symptomatic population without previous known CAD, the prevalence of CAC was 79% (48). It has been shown that among an asymptomatic background population 44% had coronary calcification and subclinical
atherosclerosis (49). The higher CAC associated with a worse prognosis in an asymptomatic population is well established (45, 50). However, diagnostic accuracy is lower in patients with previous MI and revascularisations. Other chest pain groups have also been examined which include unstable AP and patients excluded for MI (51, 52). The role of non-contrast cardiac CT in NSCP patients is yet to be investigated.

Prognosis
The 10-year mortality rate for MI patients was 59% in 1991 (53). A decrease in post-discharge mortality has been shown since the beginning of the 21st century (54-56). Sarkisian et al. reported from a patient inclusion from 2010-2011 before hsTn, where a mortality of 39% was found in MI patients in Denmark during a median follow up time of 3.2 years (57). The one-year mortality was respectively 27 %, 14% and 5% for non-ST elevation MI, ST elevation MI and unstable AP before hsTn definition was introduced around 2013 (58). HsTn identifies smaller MI with a lower mortality rate compared to standard troponin assays and therefore a decrease in MI mortality rate can be expected with hsTn (59).

Few studies have investigated the prognosis for NSCP patients. A small study showed a higher frequency of healthcare contact and a higher frequency of drug prescription compared to the general population (60). A declining tendency in one-year mortality rate among patients with NSCP from 1987-2006 was shown by Fagring et al. (61). Another study investigated NSCP patients in the transition period during hsTn implementation and found that 0.8% of NSCP patients experienced an adverse event during 30 days follow-up (37). A recently published study compared NSCP patients before and after hsTn and showed no significant difference in prognosis after hsTn (62). However, the prognosis of NSCP in relation to other higher risk chest pain groups has not been elucidated. The number of NSCP patients has increased and is twice as large as angina patients (61, 63). Although, that the NSCP patients make up such a substantial part of acute chest pain patients seen in the hospitals, very little emphasis has been given to the diagnostic work-out or prognosis of these patients.
Aims and objectives

The overall aim of this thesis was to describe NSCP patients, their risk of future cardiac-related events and prognosis and evaluate clinical risk factors as well as cardiac CT as a risk stratification tool.

Study 1
The purpose of this population-based study was to describe the prognosis of chest pain patients above 18 years old with an acute visit to the emergency departments or cardiology departments for chest pain and specifically for NSCP patients before and after hsTn implementation for routine clinical use in patients with chest pain.

The objectives were to
• describe the change in the proportion of chest pain diagnoses after implementation of hsTn.
• describe one-year mortality in NSCP patients before and after implementation of hsTn compared to the general population.
• describe the prognosis for patients with MI, other heart-related conditions, stable AP and NSCP before and after implementation of hsTn – that included all-cause mortality, future risk of MI, cardiac arrest and ventricular fibrillation during 12 months follow-up.

Study 2
The aim of this clinical prospective cohort study was to describe and identify NSCP patients with increased 12 months risk of CAD-related diseases among patients with acute chest pain seen in the emergency department or cardiology department where MI was subsequently ruled out.

The objectives were to
• determine the rate of cardiac-related events and all-cause mortality among NSCP patients during 12 months follow-up
• identify risk factors among NSCP patients that had a cardiac-related event within 12 months follow-up
Study 3

The aim of this prospective clinical cohort study was through a double-blinded design to determine whether non-contrast CT scan with calcium score could be used to describe the association between calcification and cardiac-related events in a NSCP population compared to the general population.

The objectives were to

- investigate the prevalence of calcification in a NSCP population compared to the DanRisk population (49) (general population).
- describe the rate of cardiac events and the association with CAC within the next 12 months in NSCP and the DanRisk population.
- compare the number of clinical events in NSCP patients during 12 months follow-up with the events that occurred in the DanRisk population and in the patient group who were directly referred for further investigation at index visit.
**Research Aim**
To describe the risk assessment and prognosis for NSCP patients

<table>
<thead>
<tr>
<th>Year</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>To describe the prognosis of chest pain patients and specifically NSCP patients before and after htn implementation</td>
<td>To describe the one year prognosis for NSCP patients and identify risk factors that increases the risk of CAD</td>
<td>To investigate by a non-contrast CT scan the calcification and cardiac related events in a NSCP population compared to the general population.</td>
</tr>
</tbody>
</table>

**Conclusion**

*Figure 2: Research aim and method for all three studies*
Methods and results

The methods and results sections are separated into two sections. Method and results are presented for study I in one section and for study II and III in another section.

Data sources in general

National Patient Register
The Danish hospitals register all discharge diagnoses and procedures in the Danish National Patient Registry. Data from the Danish National Patient Register contains patients’ civil registration number, patients’ municipality, identification of hospital ward, date and time of activity, diagnoses and surgical procedures. The classification of surgical procedures was from 1996 in accordance with the Nordic Classification of Surgical Procedures (64).

We linked this registry with the patient’s civil registration number and received information regarding readmissions and procedures. All visits (in-patient and out-patient visits) are classified by International Classification of Disease codes with the 10th revision (ICD-10). Appendix 1 lists the codes used for study I. MI diagnosis has been validated by clinical comparison between the Danish National Patient Registry and the Danish Monitoring Trends and Determinants in Cardiovascular Disease registry (65). The latter being a multicentre study that registered MI incidence in 21 countries. In this validation, a sensitivity of 97% was shown for MI diagnoses (65).

The Danish Civil Registration System
The Danish civil registration system was established in 1968. It contains information on all persons, who were alive with a permanent residency in Denmark from 1968 and forward and from 1972 for Greenland. All persons are registered by their civil registration number. From the Danish Civil Registration System, it is possible to obtain information on vital status, emigration, immigration and place of residency (66).

The Odense University Pharmaco-epidemiological Database
The Odense University Pharmaco-epidemiological Database was established in 1990 and covered initially the former Funen County, but from January 2007 was expanded to cover the Region of Southern Denmark. All pharmacies in the included area contribute with data to Odense University Pharmaco-epidemiological Database. The register contains information on civil registration number the dispensed package, the pharmacy, quantity, and date of dispensing.
Data from the pharmacies are reported to the Danish Health and Medicines Authority and transferred to Odense University Pharmaco-epidemiological Database (67, 68). From Odense University Pharmaco-epidemiological Database medication use, defined as collected prescriptions for the patient, was identified based on their civil registration number.

**Charlson comorbidity index**

The Charlson comorbidity index is one of the most commonly used indexes in confounder control for patients’ comorbidity in mortality studies (69) and was updated to ICD-10 (70). Comorbidity can be an important confounder for the prognosis for the disease of interest (71). The Charlson index was validated in a Danish study conducted in the Region of Northern Denmark that compared the Danish National Patient Registry diagnoses with the discharge diagnoses and found a positive predictive value of 98% for the overall Charlson conditions (72). In our studies, Charlson comorbidity index was based on the primary discharge diagnosis (A diagnosis) for all visits (In-patient and out-patient visits).

**Method: Study I**

**Study design, setting and population**

This was a prospective register-based cohort study with patient inclusion from eight hospitals (Figure 4) in the Region of Southern Denmark. Patients above the age of 18 and with acute chest pain were included. In this study, we defined acute chest pain as an acute visit to an emergency department or cardiology department with a hsTn measurement within 24 hours of their visit.

Patient inclusion took place from 1 January 2013 to 31 December 2013. During this time the assays for troponin measurement were changed for all departments to hsTn assays.

Patients were stratified into two cohorts, cohort 1 and cohort 2, respectively. Cohort 1 comprised patients before the hsTn implementation and cohort 2 after the implementation. Each cohort was further stratified into four groups depending on the patient’s final discharge diagnoses for the entire index visit and the highest level of troponin at index visit, with consideration to the 99th percentile for the respective troponin assays. The diagnoses codes are listed in Appendix 1.
The four groups defined were a) patients with MI, b) patients with other heart-related conditions, c) patients with stable AP and d) patients with NSCP. Patients were followed until 30th June 2015 or until emigration or clinical endpoints occurred. The results were reported as one-year endpoints. The clinical endpoints consisted of all-cause mortality, new MI, cardiac arrest and ventricular fibrillation. Cardiac-related endpoints were defined as new MI, cardiac arrest, and ventricular fibrillation. Composite endpoints consisted of cardiac-related endpoints and all-cause mortality. Each patient could not contribute with more than one endpoint in the composite endpoint.

![Figure 4](image)

*Figure 4*

*The hospitals included and the Region of Southern Denmark*

**Data collection**

The index visit of interest was the first visit to an emergency department or a cardiology department during 2013, which could be registered as an acute outpatient visit or acute admission. Previous visits to emergency departments or cardiology departments, with the same discharge diagnosis up to six months prior to the index visit, was an exclusion criterion as the two cohorts were included during two different time periods and this approach made them more comparable.

During the course of an admission, the patient receives a diagnosis for every transfer between departments. In this study, we only used the last given primary diagnoses (A diagnosis) during the given visit.

**Statistical analysis study I**
In general, for all three studies, continuous variables were shown as medians and interquartile ranges. Normally distributed variables were compared with Student's t-test, while skewed distributions were compared with Wilcoxon rank sum test. Categorical variables were presented with numbers and percentages and compared with Chi-square test as all our cells included more than five counts. P-values <= 0.05 were interpreted as statistically significant.

The mortality in NSCP group was compared with the mortality in the general population in the same area. The standardised mortality ratio was calculated adjusted for age and gender.

One-year outcomes for all groups after hsTn were shown as categorical with frequency and percentage and their belonging 95% confidence intervals (CI). Univariate Cox regression was used for finding any significant differences between the groups. The Hazard Ratios (HR) were depicted unadjusted and adjusted for sex, age and comorbidities to compare the significance among the groups with myocardial infarction as the reference groups (=1). The total endpoints during total follow-up were depicted as accumulated endpoints.

Ethics
The study was registered at The Danish Data Protection Agency (2008-58-0035 nr. 1085) and approved by the Danish Health Authorities j.nr. 3-3013-862/1/.

Summary of results: Study I
In total 5 352 patients were included in this study, of whom 2 151 patients were before hsTn implementation and 3 200 from after hsTn. Figure 5 shows the study inclusion.

Before hsTn more than half of the cohort was diagnosed with NSCP, one out of four with other heart-related conditions, one out of eight with MI and one out of twenty with stable AP.

After the hsTn implementation, fewer patients were diagnosed with NSCP (8.0 %) and stable AP (42.6 %), while more patients were diagnosed with MI (20.9 %) and other heart-related conditions (13.9 %). All changes were significant.
Figure 5
Patient inclusion for study I. The prognosis for patients with non-specific chest pain compared to other chest pain patients before and after implementation of highly sensitive troponins – a population-based study. Paper I, Figure 1.
The mortality rate in NSCP patients did not change, significantly, compared to the before hsTn group. A mortality rate of respectively 3.1% (95% CI: 2.2%-4.1%) and 1.9% (95% CI: 1.2%-2.5%) were found during one-year follow-up before and after hsTn in NSCP patients. Compared to the general population the standardised mortality ratio was 1.2 (CI: 0.8-1.7) for NSCP patients after hsTn and non-significant.

The crude one-year prognosis for all four groups showed that NSCP patient and other heart-related condition patients had the lowest rate of subsequent MI before and after hsTn. A significant decrease in mortality was seen in MI patients from 18.7% (14.3%-23.2%) before hsTn to 11.3% (8.7%-14%) after hsTn. HR adjusted for age, gender, Charlson score, anti-diabetic, beta-blockers and cholesterol-lowering medication estimated a 5 times decreased risk of future MI in NSCP patients compared to MI group after hsTn. The results are shown in table 2.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Composite endpoints</th>
<th>Death</th>
<th>Future MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadj HR</td>
<td>HR</td>
<td>Unadj HR</td>
</tr>
<tr>
<td>MI</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>SAP</td>
<td>0.3(0.1-0.9)</td>
<td>0.5(0.2-1.3)</td>
<td>0.2(0.1-0.9)</td>
</tr>
<tr>
<td>OHC</td>
<td>0.7(0.5-1.0)</td>
<td>0.6(0.5-0.9)</td>
<td>0.9(0.6-1.2)</td>
</tr>
<tr>
<td>NSCP</td>
<td>0.3(0.1-0.2)</td>
<td>0.3(0.2-0.4)</td>
<td>0.3(0.2-0.5)</td>
</tr>
</tbody>
</table>

*Table 2*


The prognosis for patients with non-specific chest pain compared to other chest pain patients before and after implementation of highly sensitive troponins – a population-based study. Paper I, Table 4.

**Method: Study II and study III**

**Study II: Study design, setting and population**

This was a prospective study. Danish inhabitants between the age of 30 and 70 years with an index acute visit to an emergency department or cardiology department in the Region of Southern Denmark due to chest pain, and who did not have a MI and without obvious cause of their pain were included. Patients were included from September 2014 until June 2015 and followed until June 2016 or emigration.

Clinical endpoints were defined as all-cause mortality, cardiac death, MI, unstable AP and acute and non-acute
revascularisations for study II. The cardiac related endpoint was defined as MI, revascularisations and unstable AP. Composite endpoint was defined as cardiac-related endpoints and all-cause mortality. For study III the endpoints consisted of cardiac death, ventricular tachycardia, MI, revascularisations and unstable AP.

Data collection
Patients with a hsTn measurement within the last 24 hours from an emergency department or cardiology department in any of the six hospitals: Odense University Hospital, Svendborg Hospital, Kolding Hospital, Vejle Hospital, Hospital of Southern Jutland- Sonderborg and Aabenraa were identified by the Central Biochemical database. Patients with a discharge diagnosis code of DR072/DR073/DZ034/DZ035 (unknown causes of chest pain) were afterward contacted for a structured phone interview within three days of discharge. Information concerning the clinical endpoints was gathered from the Danish National Patient Registry and the Danish Civil Registration System at the end of follow up. Both registries are described in further details above.

The questionnaire
This interview was registered in the electronic questionnaire SurveyXact and was composed of questions focusing on the patient’s medical history. The questions were related to the patient’s symptoms at index admission, previously known heart conditions, comorbidities, family history, previous known CAD, risk factors (smoking, alcohol), and work status. Appendix 2 shows the translated questionnaire.
The interview was conducted by the Ph.D. student and two nurses sharing a full-time position for this task. Interviews were mainly conducted during daytime but also during evenings and weekends. If no contacts had been established after three phone calls during different times of the day and week, no further efforts were made to include the patient.
 Patients were sent written information and informed consent to access their chart and to use the interview, which is required by Danish law. If these were returned with the subject’s signature, the patient could be included as a participant.
Prior to the study, the questionnaire was content validated and tested on patients as well as healthcare personnel. The standardised questionnaire was validated for inter-rater validity. Ten questions from the survey regarding the patient's medical history were tested in term of comparability between the interviewers. The average agreement was 72% between the 3 interviewers (range from 55%-100% depending on the question).
Chart review including ECG diagnosis
The aim of the chart review was to obtain information on cholesterol values, ECGs and essential clinical features including blood pressure, pulse, respiratory frequency, saturation, temperature and echocardiography (Appendix 3). All ECGs were analysed by the first author and validated by a cardiologist. The agreement here was 70%. The first taken ECG during index admission was analysed. An abnormal ECG was compared with previous ECGs. If no action was taken on the abnormality according to the chart, it was interpreted as a known abnormality.

Study III: Study design, setting and population
At the end of the telephone interview, we informed the patients that we conducted another study, a cardiac CT with CAC measurement. All patients with one known risk factor for CAD and with no previous invasive or non-invasive cardiac imaging testing the last five years were offered participation in the CT study. The patients were mailed written information and consent. If these were returned, the Ph.D. student called them and gave them information about the study and scheduled an appointment for the CT scan. Patients, who came for the scan, had a lipid profile taken if it had not been done at the index admission.

CAC was assessed by a non-contrast cardiac CT scan. The scan was performed in four hospitals in the Region of Southern Denmark; Vejle Hospital, Aabenraa Hospital, Svendborg, and Odense hospital. CAC was assessed by summing the scores from all foci in the coronary arteries and expressed in AU. The DanRisk study population was used as a representative asymptomatic general population for comparison (49).

This study was conducted double-blinded. The patients were not informed of the result until one year later when they received a letter if their CT scan revealed no or little calcification (CAC<400 AU). Patients with moderate to high calcification (CAC>400 AU) received a letter and a phone call from the Ph.D. student to answer further questions.

The CAC was assessed by radiographers, who were trained by cardiologists. The CAC was reanalysed by the Ph.D. student. The correlation of the CAC analyses between the Ph.D. student and the radiographers was 99%.
Statistical analyses study II and III

Sample size calculations were conducted for both studies and described in paper II and III, respectively.

Study II: Univariate Cox regression analysis was used to analyse HR for the association between risk factors and endpoints. Variables without known values, like information of cholesterol levels, were analysed as missing values.

All endpoints were reported for one-year follow-up in frequencies and percentages of total cohort. Endpoints were furthermore reported as a composite endpoint accounting for one event for each patient which was the first adverse event that occurred during the follow-up period.

In study III, age was presented as mean to be able to compare with DanRisk that consisted of 50-years-old and 60-year-olds. CAC was a continuous not-normally distributed variable and reported as medians with interquartile range (IQR).

Endpoints were reported for a one year follow-up period. Clinical endpoints were reported in percentages. Prevalence of CAC (CAC>0) was reported with percentage and compared in 2x2 tables with Chi-square test. Multiple logistic regression with adjustment for age, sex, hypercholesterolemia, family history and smoking was used to compare prevalence of CAC in NSCP with the DanRisk population.

Ethics

Study II was approved by the Danish Health Authorities j.nr. 3-3013-573/1. No ethical clearance was required for study upon request to the regional scientific ethical committee for Southern Denmark (confirmed by email 18.03.2014) for study II.

Study III was approved by the ethical committee (S-20140055) and was executed in accordance with the Declaration of Helsinki. Study III registered in ClinicalTrials.gov with the number NCT02422316.

The Danish Data Protection Agency registered study II with 2008-58-0035 nr 1086 and study III with 2008-58-0035 nr 1092. Written informed consents to access patient records and for participation for CT scan were obtained from the participants.
Summary of results: Study II and III

Study II
The study sample consisted of 1027 patients. Complete follow-up time was one year; two patients left Denmark before the end of follow-up time and were accounted for until emigration. The median age of the study population was 54 years (IQR: 47-62 years). The majority of patients consisted of women (55%). During one year follow up the composite endpoint was 2.5% (95% CI 1.6%-3.5%). 0.7% (95% CI: 0.2%-1.2%) died. Compared to the general population the standardised mortality ratio was 1.2 (95% CI: 0.5-2.4). 0.2% (95% CI: 0-0.5%) had an MI. 1.7% (95% CI 0.9%-2.4%) were revascularised – acutely and non-acutely, UAP was found in 0.4% (95% CI: 0.01%-0.1%).

Cardiac-related endpoints (without all-cause mortality) isolated composed 1.9%. The majority of the endpoints occurred in males (73%). Male gender was a significant risk factor for a cardiac-related clinical endpoint with HR=4.7 (95% CI: 1.6-14.0) and for the composite endpoint that also included all-cause mortality. Table 3 shows the clinical endpoints for NSCP patients. Other characteristics that identified patients with a cardiac-related endpoint were Charlson score >=1, previous CAD, hypertension, hypercholesterolemia, diabetes and use of statins (cholesterol lowering medication). HR was less significant when all-cause mortality was included.
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All clinical events (n=26)</th>
<th>Cardiac clinical events (n=19)</th>
<th>All-cause mortality (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td>3.4(1.4-8.1)</td>
<td>4.7(1.6-14.0)</td>
<td>1.7(0.4-7.6)</td>
</tr>
<tr>
<td>Age/years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>1.1(0.3-4.0)</td>
<td>1.0(0.3-3.5)</td>
<td>1</td>
</tr>
<tr>
<td>60+</td>
<td>2.8(0.9-8.4)</td>
<td>1.8(0.6-5.6)</td>
<td>5.6(0.7-46.7)</td>
</tr>
<tr>
<td>BMI&lt;25 kg/m2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>BMI&gt;25 kg/m2</td>
<td>3.0(1.0-7.6)</td>
<td>4.6(1.1-19.7)</td>
<td>1.4(0.3-7.0)</td>
</tr>
<tr>
<td>Charlsons score=0</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Charlsons score&gt;=1</td>
<td>3.2(1.5-6.9)</td>
<td>1.9(0.7-4.8)</td>
<td>19.5(2.4-162.3)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12 package years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;12 package years</td>
<td>1.9(0.8-4.3)</td>
<td>2.1(0.8-5.3)</td>
<td>1.6(0.4-7.2)</td>
</tr>
<tr>
<td>Alcohol 0-2 U/week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol &gt;2 U/week</td>
<td>0.8(0.4-1.7)</td>
<td>0.9(0.3-2.1)</td>
<td>0.7(0.2-3.1)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not known coronary artery disease</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3.3(1.5-7.3)</td>
<td>3.8(1.5-9.5)</td>
<td>2.1(0.4-11.0)</td>
</tr>
<tr>
<td>Not known ischemic cerebral disease</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ischemic cerebral disease</td>
<td>1.7(0.4-7.0)</td>
<td>1.1(0.2-8.3)</td>
<td>3.4(0.4-27.8)</td>
</tr>
<tr>
<td>Not known with extremity ischemia</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ektremity ischemia</td>
<td>7.4(2.2-24.5)</td>
<td>3.1(0.4-23)</td>
<td>23.5(4.6-121.0)</td>
</tr>
<tr>
<td>Not known supraventricular tachycardia</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>1.5(0.4-6.4)</td>
<td>1.0(0.2-7.6)</td>
<td>3.0(0.4-25.2)</td>
</tr>
<tr>
<td>None of the above mentioned comorbidity</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Combined ischemic comorbidity</td>
<td>4.0(1.9-8.7)</td>
<td>3.6(1.5-8.9)</td>
<td>5.5(1.2-24.4)</td>
</tr>
<tr>
<td>Not known hypertension</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Known hypertension</td>
<td>5.2(2.1-12.8)</td>
<td>5.8(1.9-17.5)</td>
<td>3.9(0.8-20.2)</td>
</tr>
<tr>
<td>Not known hypercholesterolemia</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Known hypercholesterolemia</td>
<td>2.5(1.1-5.9)</td>
<td>6.0(1.7-20.6)</td>
<td>0.5(0.1-2.5)</td>
</tr>
<tr>
<td>Not known diabetes</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Known diabetes</td>
<td>5.0(2.2-11.6)</td>
<td>5.2(2.0-13.7)</td>
<td>4.7(0.9-24.1)</td>
</tr>
<tr>
<td>No family history of CVD</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>1.7(0.7-3.8)</td>
<td>1.6(0.6-4.0)</td>
<td>2.3(0.4-11.8)</td>
</tr>
<tr>
<td>Triglycerides&lt;1 mmol/L</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Triglycerides&gt;=1 mmol/L</td>
<td>1.4(0.5-3.8)</td>
<td>1.0(0.4-2.7)</td>
<td>n.c</td>
</tr>
<tr>
<td>Total cholesterol&lt;5 mmol/L</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total cholesterol&gt;=5 mmol/L</td>
<td>0.5(2-1.2)</td>
<td>0.4(0.2-1.1)</td>
<td>1.1(0.2-5.2)</td>
</tr>
<tr>
<td>LDL&lt;3 mmol/L</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>LDL&gt;=3 mmol/L</td>
<td>0.5(0.2-1.1)</td>
<td>0.3(0.1-1.0)</td>
<td>1.1(0.2-5.4)</td>
</tr>
<tr>
<td>HDL&lt;1 mmol/L</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HDL&gt;=1 mmol/L</td>
<td>2.1(0.8-5.5)</td>
<td>3.0(1.1-8.5)</td>
<td>n.c</td>
</tr>
<tr>
<td>No statins</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Statins</td>
<td>2.8(1.3-6.2)</td>
<td>4.3(1.8-10.6)</td>
<td>0.7 (0.1-5.5)</td>
</tr>
</tbody>
</table>

*Combined ischemic comorbidity consists of coronary artery disease, ischemic cerebral disease and extremity ischemia.

n.c: not calculated, CVD: cardiovascular disease, LDL: Low density lipoprotein, HDL: High density lipoprotein

Table 3
Hazard ratio for exposure variables and endpoints during 1 year of follow up
Clinical features and prognosis in patients with non-specific chest pain after the introduction of highly sensitive troponins. Paper II, Table 3.
Study III

The study population consisted of 229 patients. The DanRisk population represented the general population and contributed with 722 patients for comparison. Our population consisted of 30-70 years old, while DanRisk was 50 and 60 years old. The mean age of our population was 52 years and 55 years in DanRisk, respectively. Significantly more patients were known with hypercholesterolemia and had a family history of cardiovascular disease in the study population, while significantly more people were smoking in the DanRisk population.

The prevalence of CAC was 54% in NSCP population and 52% in DanRisk, respectively. No significant difference was found in the prevalence of CAC (CAC>0 AU) between NSCP and DanRisk patients. The odds ratio for presence of CAC was 1.3 (95% CI: 0.9-1.9) for NSCP compared to DanRisk. In the NSCP group 0.9% (95% CI: 0.2%-2.9%) were re-vascularised during one year follow up. Cardiac death, future MI, unstable AP or ventricular tachycardia did not occur in the study population. In DanRisk clinical endpoints occurred in 4/ 772, 0.6% (95% CI: 0.2%-1.3%). One cardiac-related death, two with MI, and one with ventricular tachycardia. No significant difference between the study population and the DanRisk population was demonstrated in the association of CAC with clinical endpoints.

A group of NSCP patients from the main study (Study II) were referred for further cardiac imaging at index admission (n=211). The group referred at index admission had an event rate of 5.2% (2.8%-8.9%) vs. 0.9% (0.1%-2.9%) in our study sample during one year follow up. A significant difference between the outcome in patients referred directly for further investigations and DanRisk patients, 0.6% (95% CI: 0.2%-1.3%) could be shown. Table 4.

<table>
<thead>
<tr>
<th>Referred for cardiac testing</th>
<th>Study population</th>
<th>DanRisk population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number(n)</td>
<td>211</td>
<td>229</td>
</tr>
<tr>
<td>Event (n)</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>% (95% CI)</td>
<td>5.2 (2.8-8.9)</td>
<td>0.9 (0.1-2.9)</td>
</tr>
</tbody>
</table>

Table 4
Clinical event rate for patients referred for cardiac investigation at index, NSCP, and the DanRisk population.
Non-contrast cardiac CT scan as a risk stratification tool in non-specific chest pain patients. Paper III, table 5.


**Discussion**

**Summary of key findings**

In these cohort studies that addressed patients with chest pain and with an acute visit to the emergency department and cardiology department, we found the following:

i. Fewer patients are diagnosed with NSCP and more patients with MI after the hsTn implementation

ii. The risk of future MI within one year is five times lower in NSCP patients compared to MI patients after the hsTn implementation.

iii. No significance in mortality was shown in NSCP patients before and after the hsTn implementation.

iv. The all-cause mortality for NSCP patients after hsTn was 1.9% (study I) and 0.7% (Study II) and comparable with the standardised mortality rate adjusted for gender and age in the general population.

v. The one-year cardiac-related events were 1.9% and occurred primarily in males.

i. Risk factors associated with clinical endpoints were male gender, Charlson score >=1, previous CAD, hypertension, hypercholesterolemia, diabetes and use of statins.

ii. The prevalence of coronary artery calcification in NSCP patients did not differ from the DanRisk population.

iii. The rate of cardiac-related events in NSCP patients did not differ from the DanRisk population.

iv. No significant difference in the rate of clinical endpoints was shown for patients with CAC=0 AU and CAC>=0 AU.

i. Patients who were referred for cardiac imaging testing at index visit had a less favourable prognosis than the DanRisk population.

The major clinical endpoints are further listed in Table 5.

<table>
<thead>
<tr>
<th></th>
<th>Study I (Cohort 1 and 2)</th>
<th>Study II</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Median 65 and 62</td>
<td>Median 54</td>
<td>Mean 52</td>
</tr>
<tr>
<td>Mortality</td>
<td>3.1% and 1.9%</td>
<td>0.7%</td>
<td>-</td>
</tr>
<tr>
<td>Cardiac-related endpoints</td>
<td>0.9% and 0.4%</td>
<td>1.9%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

*Table 5*

The endpoints for the NSCP population in the three studies


**Comparison with existing literature**

**Chest pain groups**

In all three studies, we chose to identify chest pain patients by discharge diagnosis and troponin measurements. In addition, in study II and III we excluded everyone with a coronary angiography performed during index visit as they, at one point, must have been suspected for CAD. In the mentioned criteria there is an implicit selection criterion, as it is a clinician dependent assessment, which patients are chosen to be sent home without a troponin measurement. These criteria also imply that patients with atypical chest pain and without troponin measurement are at risk of not being represented in this study as one out of three patients with MI do not present with chest pain (29).

In study I, we showed that about half of the chest pain population consisted of NSCP patients. This is consistent with a previous study (22). The decline in NSCP patients (study I) after hsTn is consistent with more patients were diagnosed with MI and other heart-related conditions as even minor myocardial necrosis is diagnosed (59). Our results are in concordance with other studies that show an increase in MI diagnoses (59, 73). We did not include unstable AP patients in study I. There were very few patients with this discharge diagnosis. However, these findings support that unstable AP is a diminishing diagnosis (73), as previous unstable AP patients are now diagnosed with MI. This implies that the future approach for distinguishing between acute and non-acute chest pain diagnoses composes two groups: stable AP that is non-acute and MI (74).

**Characteristics and risk factors for NSCP patients**

In study I, we showed that NSCP patients were younger and included a higher proportion of females compared to MI, stable AP, and other heart-related conditions patients. Even further the comorbidity (Charlson index \(\geq 1\), use of beta-blockers/antidiabetic and cholesterol-lowering medication) was lowest in NSCP patients. In Study II we also found that women comprise the majority of NSCP patients. The median age for study II was 54 years (IQR: 47-62 years). Considering the lower age limitation in study II it is comparable with study I age with a median of 56 years (IQR: 45-67 years). Our results correlate with Durand et al. (22) who, before hsTn implementation found a lower mean age, more women and fewer with a known risk factor in NSCP patients compared to patients with acute MI.

In our study male gender was significant and associated with a worse endpoint. The measured cholesterol levels showed no significant association with the outcome. In contrary, increased LDL values and total cholesterol values seemed to have a protecting effect on future CAD. A confounder here could be that patients were already treated with statins which means that
Several risk score tools have been developed for the purpose of risk stratification of chest pain patients and especially the HEART score has been proposed as a tool for predicting MI, the need for revascularisation and death among chest pain patients in the Emergency Department (75). The HEART score is based on history, ECG, age, risk factors and troponin results (35). The Systematic COronary Risk Evaluation (SCORE) algorithm, that also considers country of origin and gender in its risk stratification, was developed for the estimation of 10-year cardiovascular risk. However, it is intended as a tool for primary prevention of cardiovascular disease (34) and not for acute assessment. Omstedt et al. (37) investigating HEART score in NSCP patients showed that age, previous MI, hypertension, stroke, hyperlipidemia, diabetes mellitus and male gender are important risk factors among NSCP patients. We found the same risk factors to be of significance in our study. The modified Goldman risk score, on the other hand, is mainly based on chest pain characteristics (76, 77). These characteristics were not found to be of significance in our cohort. The established risk scores, however, differ in performance depending on the hsTn assays; hence the use for rapid rule out is for the present limited (76).

**Non-contrast cardiac CT and NSCP patients**

Our study is the first study to evaluate non-contrast cardiac CT in acute patients with NSCP. No difference in CAC prevalence and CAC associated prognosis was demonstrated between NSCP patients and the general population represented by the DanRisk population (49) in this study. The role of CAC in asymptomatic individuals is established and shows an increased risk of CAD with increased CAC (45, 49, 50, 78). We found no association between CAC and CAD prognosis for NSCP patients. These findings and results from previous studies imply that similar indications as for the asymptomatic population could be applicable for NSCP patients.

It has been shown that a single hsTn in combination with clinical judgment and admission ECG has a sensitivity of 100% for ruling out ACS (79). This corroborates with our study where patients referred for cardiac investigation at index visit had significantly higher clinical endpoints than the general population in study III. Hence, neither clinical risk stratification nor cardiac CT can stand alone, the clinical judgment is important for this patient group.

**Prognosis for NSCP patients**

Study I and II investigated the one-year prognosis in NSCP patients and found 1.9% (95% CI: 1.2%-2.5%) and 0.7% (95% CI: 0.2%-1.2%) all-cause mortality after hsTn, respectively. The 95% CI showed no significant difference. The studies differed in study design, population-based
design and clinical design, respectively. The age criterion also differs with study I including all patients above 18, while study II has an age limitation set at 30-70 years old. The only recent study (62) that addresses the 30-day prognosis of NSCP patients found similar results with an all-cause mortality of 0.2%-1.1% in patients directly discharged from emergency department and patients admitted briefly in emergency departments before discharge, respectively. Nejatian et al similar to study I found no significant difference in mortality rate for NSCP before and after hsTn. However, the risk factors for cardiovascular disease differed for the two time periods in their study. We tried to avoid this by exclusion of patients with similar visits to emergency departments and cardiology departments six months prior to index visit.

Previous studies (61, 80, 81) that investigated patients excluded for acute MI have shown a mortality rate of 1.9 %-11 % before hsTn. The patient group of interests in these studies were patients excluded for acute MI and consisted of a more heterogeneous group (other diagnoses for chest pain) than our patient group that focused on patients without a diagnosis.

Cardiac-related endpoints differed for the three studies, but the definitions were not alike. In study I, we did not include revascularisations as a cardiac endpoint. Study III consisted of a selected cohort in which all patients with previous known CAD were excluded. This could explain the differences found in the endpoints. Our results are consistent with Nejatian et al. (62) when consideration is given to weight the endpoints according to the cohort sizes (directly discharged vs. briefly admitted) that differ.

NSCP patients compared to stable AP patients show a similar prognosis in mortality (82-84). The explanation might be improvement in prevention and treatment of stable AP patients (85, 86) and one contributory factor could be that the hsTn allocate lower risk patients with even small troponin increase to the MI group which leave patients with a lower risk profile in the stable AP group. This was probably also the plausible explanation for the lower mortality rate found in MI patients after hsTn, as more low-risk patients are diagnosed with MI after hsTn (59).

Comparison of NSCP patients with the general population showed that the mortality did not differ, neither in study I or study II when adjusted for age and gender distribution after hsTn. This corroborates with Fagring et al. that demonstrated that the mortality in NSCP before hsTn was similar to the general population(61).

**Methodological considerations**

**Selection bias**

Written informed consent had to be returned by postal mail or email for participation in study II and III. However, less than 50 % returned the written informed consent primarily. A second contact and reminder were necessary for us to be able to obtain 85% acceptance. We do not
know the reason for why the remaining did not return the informed consent and thereby participation. It could be related to health issues, pure forgetfulness, or lack of involvement. It could also be logistic reasons as wrong addresses or wrong delivery from postal service. Nonetheless, it means that the included patients could represent a selected population. Previous studies have showed that patients who participate in clinical studies are healthier than those who do not and this could have underestimated the clinical endpoints in study II and III (87). However, we tried to account for comorbidity by a comparative analysis with the general population adjusted for age and gender. Furthermore, our population-based study (study I) shows similar results as the clinical study (study II) regarding prognosis. Even though study I was not dependent on consent it was based on discharge diagnosis which is dependent on the responsible clinician. In study III only four hospitals had a cardiac CT scanner Distance to the hospital could have influenced and demotivated the non-participants in this study and hence caused the lack of recruitment.

**Information bias**

*Misclassification of exposure*

Study II was based on telephone interview with a structured questionnaire. Hence, majority of the data in this study were self-reported. Patients might have -either unintentionally or intentionally- underestimated their cigarette or alcohol consumption due to social stigmatisation (88). Furthermore, patients with an excessive use could have been less prone to participate in this study.

The family history of cardiovascular disease was defined without age limitation in study II and III. In study III, The DanRisk (49) definition of family history was known cardiovascular disease for a first degree relative male < 55 years and female < 65 years. In our study, we did not include the age limitation which could mean that this risk factor is overestimated in our study cohort.

We tried to minimize recall bias by conducting the interview within three days of discharge.

*Misclassification of clinical endpoints*

MI ICD-10 discharge diagnoses have previously been validated with medical records and had a positive predictive value of 93% (65, 89). Mortality data were complete (90). The validity of NSCP diagnoses is unknown.

The hospitals get financial reimbursement from the government as health care is free in Denmark. The amount of reimbursement is determined by the diagnosis. This can cause some
diagnoses to be preferable compared to others and can lead to a misclassified incidence and prevalence of the diagnosis of interest.

**Limitations**

All three studies focus on patients with chest pain and a troponin measurement and find patients diagnosed with NSCP to be of low risk. However, the group of patients with chest pain and who by the attending physician is assessed to be at low risk of cardiac event and thus do not have a troponin measurement were not accounted for in this thesis. Hence, we do not know their prognosis and the extent of missed diagnosis, which is also highly important knowledge and therefore limits the generalisability. A previous study that used a less sensitive assay showed that less than 1% of patients discharged without acute coronary syndrome diagnosis have an adverse outcome within 30 days (91).

In study I, one of the main limitations was that we did not have the time to validate the final diagnoses used for stratification of the groups. We also chose not to include unstable AP in study I. This group consisted of very few patients which corroborate with other findings that unstable AP is a decreasing and small group (73).

In Study II and III, few endpoints occurred during follow up. A larger study population could have been more confirmative of the results, but the findings we believe would be the same. However, a larger study could have allowed us to conduct a prognostic aspect for risk stratification of NSCP patients in study II. Due to the few events, it was not possible to perform a multivariate analysis.

Both study II and III had upper limits of 70 years old. This is probably why we find a difference in the one-year mortality between study I and II. By exclusion of patients over 70 years, we excluded a higher risk group of CAD. However, our rationale for this was that it is well known that coronary calcification and thereby CAC was higher with increased age and that CAC was thus not useful in the elderly (35, 75). However, the mortality rates in study I and II, respectively 1.9% and 0.7%, were comparable with the general population adjusted for age and gender and thereby demonstrate that NSCP patients do not have an increased mortality rate compared to the general population.

In Study II revascularisations composed the majority of the endpoints. Some of these revascularisations could have been derived from the index visit and could thereby reflect a higher event rate than the actual.

**Non-participants**

In study II and III, we recruited fewer patients than expected. In study II we were able to recruit 1027 patients who fulfilled the criteria for inclusion. Approximately 50% of all patients with a
normal troponin were eligible for participation. In Study III we included 229 out of 441 patients who were assessed to be eligible. As study III recruited from study II, more patients could have been eligible if more patients had been recruited for study II. We could possibly have recruited more patients by study inclusion before discharge in the departments by direct approach. However, due to resources, we were not able to have covered all departments and all visits (day and night).

A previous study has demonstrated that patients who did not participate in clinical trials were at risk for worse outcome (87). This could imply we are underestimating the adverse prognosis for NSCP patients. For study II and III detailed information of those who were not included could not be reported. We were not able to report on the patients who we could not contact, and for those who declined participation by not returning their informed consent, we were not allowed to use their information from the telephone interview.

For a complete information and data for NSCP patients, register-based studies would be more appropriate, as they are not dependent on patient inclusion and consent. However, we would not have been able to gather the same detailed information (family history of cardiovascular disease, smoking status, and detailed medical history) from register-based studies. Neither would we be able to control the validity of the discharge diagnoses for NSCP.

**Generalisability**

All three studies involved the patients in the southern part of Denmark from several hospitals. We tried to consider the demographic differences by this approach. The number of participants in study II and III compared to eligible patients, and lack of information besides age and gender limits the external validity. However, the combination of the clinical studies and population-based study confirming the same results adds validity to our results.

We believe the results are applicable to countries where the health care system is comparable to the Danish health care system. The number of acute chest pain patients is around 6000 patients yearly in the Region of Southern Denmark. We included hospitals that serve as an invasive centre for the acute treatment of acute MI and hospitals, from where patients had to be transferred to the invasive centre, representing a broad patient population.

Certain eastern European countries have shown higher mortality rates regarding CAD compared to the rest of Europe (1, 2). Based on this, the generalisability of our studies would apply to Western Europa and especially the Nordic countries.
Clinical implications

All three studies showed that the prognosis for NSCP patients was good regarding mortality and clinical cardiac-related events during one year follow up. The few clinical endpoints showed that the risk assessment taking place during the hospital visits identify those at risk for future CAD. Our studies showed that even with hsTn, clinical assessment is important and allows us to identify patients with a higher event rate (study III). Physician-based assessment is also important in the discrimination between unstable AP and NSCP patients in the emergency departments and cardiology departments. The diagnosis given is of high importance for the further investigation and visitation. These studies make us able to reassure NSCP patients of their good prognosis compared to other chest pain patients. We know from other findings that NSCP patients have more frequent contact with the health care system (60). Being able to reassure the patient might have an implication for the re-admission rate for this patient group.
Conclusion

Based on the findings in the three papers the following conclusions were made:

The implications of hsTn implementation were that fewer patients were diagnosed with NSCP as even minor hsTn increases were identified and stratified into other diagnosis groups as MI and other heart-related conditions. The risk of future MI was 1/5 in NSCP patients compared to MI patients. The mortality for NSCP patients was not significantly different from the MI group. The mortality after the hsTn implementation compared to before the hsTn for NSCP patients did not differ. The causal explanation is that more low-risk patients were now allocated into other diagnoses groups due to hsTn, and there for the prognosis for these groups were more beneficial than previously.

The NSCP patients had, during a year of follow-up period, a favourable prognosis for all-cause mortality that was comparable with the general population. Very few cardiac related endpoints occurred during one year follow up. The majority of the events were revascularisations and their initial association with the index visit is undetermined. Only 0.2% had a MI during one year. The identified risk factors were male gender, Charlson score >=1, previous CAD, hypertension, hypercholesterolemia, diabetes and use of statins. Especially male gender was associated with a higher risk of clinical endpoints.

The number of clinical events during one-year follow-up was also low in study III for the NSCP patients and the DanRisk population. Significantly more events occurred in the group of patients who were referred directly for further investigations from the index visit. No significance was found between the number of events occurring in patients with CAC=0 and CAC>=0.

Perspectives

Even though, the implementation of hsTn has led to a better prognosis among all patients groups regarding all-cause mortality and cardiac-related death, the clinical evaluation of the patients is still crucial - especially, in the discrimination between unstable AP and NSCP. More patients are admitted with MI due to hsTn which means more patients are acutely admitted and acutely examined; this puts a larger workload on our departments receiving these patients and requires additional resources to meet the demands.

Risk stratification among NSCP patients is, on one hand, important due to the seriousness of a cardiac-related event. On the other hand, the numbers of events are very few and the balance
between the resources used on this low-risk patient group and their future risk of adverse event has to be taken into consideration. Especially regarding cardiac-CT, we showed that this was not further indicated in NSCP patients compared to the general population. Nonetheless, the role of non-contrast cardiac CT for asymptomatic individuals with a higher CAC is of relevance and we did not demonstrate that the indication was smaller in NSCP patients than in asymptomatic individuals.

The main endpoints found in this study were revascularisations - acute and non-acute. This implies that an important part of the clinical assessment of NSCP patients was to evaluate whether the patient should be seen in an outpatient clinic for further non-acute cardiac investigations based on the risk factors discussed above.
Epilogue

After completing these three studies my answers for the initially asked questions are:

To my patient, I would tell them not to be concerned. Their risk of future MI is much lower than for patients with an index MI. And their future risk of coronary disease or death is not higher than for anyone else of same gender and age.

To my fellow colleague, I would say; "No worries. You can send this patient home with a good consciousness. This patient's risk of future CAD is comparable to the general population. The new hsTn do not catch everything, but close to. Your clinical judgment is reliable and essential in this setting. The CT scan does not seem more useful for these patients than anyone else because you are able to identify patients, who need it by your own clinical assessment."
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Papers I-III
Paper I
The Prognosis for Patients with non-specific Chest Pain compared to other Chest Pain Patients before and after implementation of highly sensitive Troponins – a Population-based Study.

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Abstract

Aim: Among patients with acute chest pain we wanted to determine the frequency and prognosis of non-specific chest pain (NSCP) compared to different chest pain diagnoses before and after implementation of highly sensitive troponins (hsTn).

Methods: A population-based study involving chest pain patients from departments of Emergency Medicine and Cardiology in the Region of Southern Denmark before and after implementation of hsTn. All patients above 18 years with an acute chest pain visit, troponin measurement and with discharge diagnoses of MI, stable angina pectoris (AP), other heart-related conditions or NSCP. Primary endpoints were all-cause mortality, MI, cardiac arrest and ventricular fibrillation.

Results: 5353 patients (2152 before and 3200 after implementation of hsTn). There was a 8% (CI 5.9%-10.6%) relative decrease in patients who were diagnosed with NSCP after implementation of hsTn, and a 42.6% (28.3%-57.8%) relative decrease in stable AP patients, while the number of patients with MI and other heart-related conditions increased with 20.9% (CI: 14.4%-28.6%) and 13.9% (CI 9.8%-18.7%), respectively. The risk of future MI was decreased by a factor 5 in NSCP patients compared to patients with a discharge diagnosis of MI. The mortality for NSCP patients declined non-significantly from 3.1% (CI: 2.2%-4.1%) to 1.9% (CI:1.2%-2.5%) after implementation of hsTn. The standardised mortality rate for NSCP patients was comparable to the general population: 1.2 (CI: 0.8-1.7). The mortality rate was significantly decreased for MI group from 18.7% (95%CI: 14.3%-23.2%) before hsTn to 11.3% (95% CI: 8.7%-14.0%) after hsTn.

Conclusion: The prognosis for patients with non-specific chest pain is good and the mortality is low and comparable to the general population.
Introduction

Chest pain evaluation in the emergency departments and cardiology departments consists of clinical judgment, ECG assessment and troponin measurements (1). While nearly one out of five patients with chest pain have an acute myocardial infarction (MI) (2), a group of patients with acute chest pain, normal ECG and troponin does not get a discharge diagnosis explaining the cause of their chest pain and these patients are categorised as non-specific chest pain (NSCP). Previous studies before the implementation of highly sensitive troponins (hsTn) in clinical practice showed that NSCP patients have more contacts to the health care system and a higher use of medication compared to the general population (3).

In the era of hsTn, where even minor myocardial damages causes a rise in hsTn, recent studies have demonstrated that use of hsTn has changed the distribution of cardiac causes of chest pain, with a decrease in unstable angina pectoris (AP) and an increase in non-ST-elevation myocardial infarction diagnosis (4, 5). In this light, it may be expected that the prevalence and prognosis of NSCP patients also have changed – but this issue has only been scarcely described so far. A recent Swedish study (6) compared the time period prior to and after the routine use of hsTn and did not find any significant difference in the 30 days clinical endpoints for NSCP. Another study (7) demonstrated that 0.5% of NSCP patients were diagnosed with MI within 30 days from index contact for chest pain in the Emergency Department. A longer follows up time for NSCP patients is required to assess the need for further diagnostic efforts for this patient group as well as for the patient's information and concern for their future risk of cardiac-related events.

The aim of this study was to investigate if there has been a change after the implementation of hsTn in the relative distribution for patients diagnosed with NSCP, MI, stable AP and other heart-related conditions, and to compare the cardiac-related events and all-cause mortality for NSCP patients with patients with MI, stable AP and other heart related conditions and the general population.

Method

Study population

This study included all citizens in the Region of Southern Denmark (1.201.955 inhabitants in 2013), aged 18 years or older with an acute contact to an Emergency Department or Cardiology Department during 2013 and who had at least one troponin measurement done within 24 hours of their admission together with a discharge diagnosis of MI (non-ST elevation MI or ST elevations MI), stable AP, other heart related conditions (like aortic dissection, pulmonary embolus, pericardial diseases, endocardial diseases, supraventricular arrhythmia) or NSCP (chest pain and no obvious reason). The International classification of diseases diagnosis codes with 10th revision (ICD-10) are specified in appendix 1.
Study design

The study was a population-based cohort study involving patients from all hospitals in the Region of Southern Denmark (Sonderborg, Aabenraa, Haderslev, Kolding, Vejle, Esbjerg, Odense and Svendborg). In Denmark, every inhabitant is entitled to free healthcare. Patients with a measurement of troponin in any of these hospitals from 1st January 2013 to 31st December 2013 were included in the study and followed to 30th June 2015 or until emigration or a clinical endpoint occurred, whichever came first. Patients were referred to the emergency department or cardiology department by their general practitioner, emergency services, or arrived directly to the hospital without any pre-hospital visitation. Patients highly suspected of coronary causes of chest pain were referred directly to the cardiology department while others were first seen in the emergency department.

All patients with at least one troponin measurement were identified through the electronic central laboratory system in the region. The assays for troponin were changed during the course of this study. Departments using contemporary troponin I changed to hsTn I on the 11th May 2013 and departments using contemporary troponin T changed to hsTn T on the 26th of June 2013. The total cohort was split into a pre-hsTn cohort (cohort 1) and a post-hsTn cohort (cohort 2) according to these dates.

All admissions were classified by International Classification of Disease codes using the 10th revision (Appendix 1). Based on troponin levels and discharge codes, four patient groups were defined:

a) MI: Troponin elevation and discharge by a diagnosis of acute non-ST elevation MI or ST elevation MI.

b) Stable AP: Normal troponins and the diagnosis stable angina pectoris.

c) Other heart-related conditions: Normal or elevated troponin but diagnosed with serious cardiac disorders other than acute MI (Diagnoses are listed in Appendix 1).

d) NSCP: Normal troponins and no serious cardiac disease and discharged with an unspecified diagnosis.

Patients with a discharge diagnosis of other aetiology were not included.

The first contact to an emergency department or cardiology department during 2013 for chest pain with the defined discharge diagnoses was defined as the index contact. Patients with a visit and any of the above discharge diagnosis six months prior to the index visit were excluded. This was due to different inclusion periods for the two cohorts, January to May (troponin I), January to June (troponin T) for cohort 1 and May to December (troponin I) and June to December (troponin T) for cohort 2, respectively. By this exclusion, we avoided that cohort 1 could potentially have a more frequent admission rate with the same diagnosis prior to the index contact.
All Danish inhabitants have a unique civil personal registration number that can be used to identify a subject in all registers (8). Patients without a valid personal identification number were excluded in the study. The identification number was used to combine the level of troponin with the final discharge diagnosis. From the Danish civil registration system information on vital status, emigration, immigration, and place of residence were obtained (9). The Danish National Patient Registry register at individual level all hospital contacts, discharge diagnosis and hospital-based procedures (10). Odense University Pharmaco-epidemiological Database register information on an individual level on redeemed medications (11). Prescribed medications collected at any pharmacy up to three months before index admission was included. Medications including anti-diabetic medicine, beta blockers, and cholesterol-lowering medication were identified by ATC codes. The applied ATC codes are listed in Appendix 2.

The Charlson comorbidity index was used to describe the patient’s comorbidity (12, 13). In this study, Charlson comorbidity index was based on the primary discharge diagnosis for all admissions 10 years back.

**Troponins**

Before the implementation of hsTn (cohort 1), troponin I was analyzed by use of Architect c16000 (Abbott Diagnostics, Lake Forest, Ill). Upper reference limit was the 99th percentile of 28 ng/mL. The 10% coefficient of variation was 32 ng/mL. The decision limit was at 30 ng/mL for MI. After the hsTn implementation (cohort 2) troponin I was analyzed by Abbot Diagnostics Architect with upper reference limit of the 99th percentile of 25 ng/L. The 10% coefficient of variation was at 5 ng/L. The decision limit for MI was set at >= 25 ng/L. Concerning troponin T, this was in cohort 1 analysed by Roche Diagnostic Elecsys 2010, modular analytics E170, Cobas e411, cobas e601. The 99th percentile cut off was 14 ng/L. The 10% coefficient variation was 13 ng/L. The decision limit was set > 50 ng/L for MI. In cohort 2 the hsTn T decision limit was changed from 50 to 14 ng/mL.

**Endpoints**

All-cause mortality was accounted for from index admission. Readmission with MI, ventricular fibrillation or cardiac arrest was from ≥ 8 days from the date of discharge after the index visit. Appendix 3.

The following visits after the index visit accounted as a clinical endpoint. An endpoint was the first defined endpoint occurring during the follow-up period.
Statistical analysis

Continuous variables are presented as medians and interquartile range (IQR). Significance was tested with rank sum test. Categorical variables are listed as frequencies and percentages and tested by Chi-square test.

All events were pooled to a combined endpoint. Time to event was reported by accumulated plots. Cox regression was used to calculate the hazard ratios (HR) for the risk of an event. Results were reported unadjusted and adjusted for age, sex, Charlson score, use of beta-blocker, anti-diabetes and cholesterol-lowering medication.

Mortality was compared with the mortality in the general population. From Statistics Denmark (14) we found the regional population number and deaths in 2013. Based on this we calculated the age (10 year age band) and gender-adjusted standardised mortality rate for the general population and compared it with the observed death rate (including 95% confidence interval (CI)) for the NSCP group.

This study was reported according to the STROBE guidelines for cohort studies (15). Analyses were performed with STATA 14.2 0 (StataCorp, College Station, Texas).

Ethics

The study was registered with The Danish Data Protection Agency (2008-58-0035 nr 1085) and approved by the Danish Health Authorities (j.nr. 3-3013-862/1). According to Danish law patient consent is not acquired for register-based studies.

Results

16 135 patients had a troponin measurement in an Emergency Department or Cardiology Department. 6 656 had a relevant diagnose and a troponin measurement was taken within 24 hours of the initial visit time. After the relevant exclusion the final cohort for analysis consisted of 5 352 patients (Figure 1).
Figure 1: Patient inclusion

Population
Patients above 18 years old with one of the defined
Discharge diagnoses and a first contact to an ED or CD and
a troponin measurement (n=6656)

Not living in the region of southern
Denmark (n=369)
Not residing in Denmark at admission
(n=1)
Without Danish personal registration
number (n=208)

Eligible
(n=6078)

Excluded (n=726)
Chest pain contact within 6 months
and discharged with a diagnosis
belonging to the four defined groups

For analysis
(n=5352)

Pre hsTn
(n=2,152)

Post hsTn
(n=3,200)
**Changes in the relative distribution of diagnosis after hsTn**

The patients were stratified into two cohorts. A cohort with index admission before implementation of hsTn including 2,152 patients (Cohort 1) and another after implementation of hsTn with 3,200 patients (cohort 2). Cohort 1 patients were slightly older and had a higher use of beta-blockers (Table 1). The frequencies of the four predefined patient groups changed after the introduction of hsTn. The change was significant for all groups; MI with a 20.9%(CI: 14.4%-28.6%) relative increase, other heart-related conditions also increased with 13.9%(CI 9.8%-18.7%) while Stable AP had a 42.6%(28.3%-57.8%) relative decrease and an 8% (CI 5.9%-10.6%) decrease among NSCP.

**Table 1: Baseline characteristics of the cohorts including the frequency of the discharge diagnosis before and after hsTn implementation.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Total</td>
<td>2,152</td>
<td>3,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,215</td>
<td>1,794</td>
<td>56.5(54.4-58.6)</td>
<td>56.1(54.3-57.8)</td>
</tr>
<tr>
<td>Median age /years (IQR)</td>
<td>65(52-76)</td>
<td>62(50-74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlson’s index&gt;= 1</td>
<td>723</td>
<td>965</td>
<td>33.6(31.6-35.6)</td>
<td>30.2(28.6-31.8)</td>
</tr>
<tr>
<td>Medications last 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-diabetic</td>
<td>207</td>
<td>286</td>
<td>9.6(8.4-10.9)</td>
<td>8.9(8.0-9.9)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>512</td>
<td>617</td>
<td>23.8(22.0-25.6)</td>
<td>19.3(17.9-20.7)</td>
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<td>Cholesterol lowering medication</td>
<td>527</td>
<td>736</td>
<td>24.5(22.7-26.3)</td>
<td>23.0(21.5-24.5)</td>
</tr>
<tr>
<td>Discharge diagnosis</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>299</td>
<td>538</td>
<td>13.9(12.4-15.4)</td>
<td>16.8(15.5-18.1)</td>
</tr>
<tr>
<td>SAP</td>
<td>100</td>
<td>86</td>
<td>4.7(3.8-5.5)</td>
<td>2.7(2.1-3.3)</td>
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<tr>
<td>OHC</td>
<td>544</td>
<td>922</td>
<td>25.3(23.4-27.1)</td>
<td>28.8(27.2-30.4)</td>
</tr>
<tr>
<td>NSCP</td>
<td>1,209</td>
<td>1,654</td>
<td>56.2(54.1-58.3)</td>
<td>51.7(50.0-53.4)</td>
</tr>
</tbody>
</table>


In general for all groups in cohort 2 (after hsTn) compared to cohort 1 (before hsTn), the median age was lower, fewer patients with a Charlson >1, and fewer patients used medication (Table 2). The NSCP groups were younger, had a larger proportion of women, less comorbidity and the smallest use of medication compared to MI, SAP and OHC patients in both cohorts.
Cardiac-related events and all-cause mortality after hsTn implementation

Table 3 lists the number of endpoints during the first year follow-up for all four diagnosis groups. The median follow up time was 688 days (IQR: 598-797 days), while the median time to an endpoint was 78 days (IQR: 13-212 days).

There was a trend towards fewer composite endpoints for NSCP patients after hsTn implementation with 3.7% (95% CI: 2.7%-4.8%) before and 2.2% (95% CI: 1.5%-2.9%) after hsTn respectively, however, this was not significant. The only significant change was seen in the MI group for the change in mortality which was 18.7% (95% CI: 14.3%-23.2%) before hsTn and 11.3% (95% CI: 8.7%-14.0%) after hsTn, respectively.
Composite endpoints consist of MI, cardiac arrest, ventricular fibrillation and all-cause mortality.

The mortality for the NSCP patients in cohort 1 and 2 are illustrated in Figure 2. No significant difference is shown between the cohorts during total follow up time. The crude one-year mortality rate in the NSCP group before hsTn was 3.1 % (CI: 2.2%-4.1%) and after 1.9 % (CI:1.2%-2.5%), ie. no significant difference, but a trend towards lower mortality in the NSCP group after the implementation of the hsTn.

NSCP patients’ mortality compared with the general population’s mortality after hsTn implementation showed that the standardised mortality ratio for the NSCP group adjusted for age and gender was 1.2 (95% CI: 0.8-1.7).

Table 3: One year endpoints before and after hsTn

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n)</td>
<td>MI (n)</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>% (CI)</td>
</tr>
<tr>
<td>Death</td>
<td>164</td>
<td>7.6 (6.5-8.7)</td>
</tr>
<tr>
<td>Cardiac arrest/VF</td>
<td>7</td>
<td>0.3 (0.1-0.6)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>21</td>
<td>1.0 (0.6-1.4)</td>
</tr>
<tr>
<td>Composite endpoints*</td>
<td>182</td>
<td>8.3 (7.2-9.5)</td>
</tr>
<tr>
<td></td>
<td>186</td>
<td>5.8 (5.0-6.6)</td>
</tr>
<tr>
<td>Cardiac arrest/VF</td>
<td>9</td>
<td>0.3 (0.1-0.5)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>32</td>
<td>1.0 (0.7-1.3)</td>
</tr>
<tr>
<td>Composite endpoints*</td>
<td>214</td>
<td>6.6 (5.8-7.5)</td>
</tr>
</tbody>
</table>

*Composite endpoints consist of MI, cardiac arrest, ventricular fibrillation and all-cause mortality.

Table 4 shows the HR for the endpoints in the different groups with and without adjustment for age, sex, Charlson score, use of Beta-blockers, diabetes, and cholesterol-lowering medication for cohort 2 (after hsTn). The MI group was baseline with HR=1. Compared to MI, NSCP patients had an HR of 0.3 for combined endpoints primarily due to a much-reduced risk of MI, whereas the risk of death did not significantly differ between the groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Composite endpoints</th>
<th>Death</th>
<th>Future MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadj HR</td>
<td>HR</td>
<td>Unadj HR</td>
</tr>
<tr>
<td>MI</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>SAP</td>
<td>0.3(0.1-0.9)</td>
<td>0.5(0.2-1.3)</td>
<td>0.2(0.1-0.9)</td>
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<tr>
<td>OHC</td>
<td>0.7(0.5-1.0)</td>
<td>0.6(0.5-0.9)</td>
<td>0.9(0.6-1.2)</td>
</tr>
<tr>
<td>NSCP</td>
<td>0.3(0.1-0.2)</td>
<td>0.3(0.2-0.4)</td>
<td>0.3(0.2-0.5)</td>
</tr>
</tbody>
</table>

Figure 3 shows the risk of a combined endpoint, death or future MI, during a median follow up of 688 days. The lowest risk of a combined endpoint was found in NSCP patients. Stable AP has a wide CI interval due to few patients and few endpoints in this group.

Figure 3: Accumulated endpoints for the four diagnosis groups.

Discussion

In this population-based study, we compared chest pain patients before and after hsTn implementation and found that the prevalence had changed with less proportion diagnosed with NSCP and stable AP, and more patients were diagnosed with MI and other heart-related conditions.

The NSCP patients in this study had very few cardiac endpoints and no significant difference was found after hsTn was introduced. NSCP patients experienced a five times smaller risk of future MI compared to patients with an index MI. The first year mortality for NSCP patients were respectively

MI: Myocardial infarction. OHC: other heart-related conditions, SAP: stable angina pectoris, NSCP: non-specific chest pain
3.1% and 1.9% before and after implementation of hsTn, but no significant difference was found. Of significant importance, the mortality in NSCP group was comparable with the general population.

**Prognosis for NSCP patients**

This is the first study to report the prognosis of NSCP patients compared to other patients with acute chest pain. Out of 16 135 patients with a troponin measurement in an emergency department or cardiology department 2 863 were diagnosed with NSCP, comprising 18%.

The findings in our study are supported by the works by Reichlin et al and Nejatian et al (5, 6). Reichlin et al. showed that in patients without MI the cumulative 30-month mortality was 4.8%. The troponin assay used by Reichlin’s study was a hsTn assay. The average annual mortality rate in this study would approximately be 1.9% which is very consistent with our results (5). Similar to our study Nejatian found no difference in the 30 days mortality for NSCP patients before and after hsTn implementation, respectively.

Other studies to be mentioned are Fagring et al(16), Ravn-Fischer et al (17) and Kelly et al (18). These studies are older (16) and included patients excluded for acute MI, however not specifically NSCP patients (17, 18). Patients excluded for acute MI could have other serious disorder for their chest pain explaining a different prognosis. The first two mentioned (16, 17) showed a higher mortality rate of 3-11% depending on age and gender. Fagring et al.’s study (16) reported from chest pain patients from 2002-2006 and before the use of hsTn. The mortality rate for NSCP patients was higher in Fagring et al’s study, however, the mortality rate was not significantly different from the age-matched general population. A contributory reason for the decreased mortality in our study compared to Fagring’s could be the overall improvements in prevention and treatment strategies between Fagring’s study (2006) and ours (2013). Ravn-Fischer et al from 2011 found the average one-year mortality was 3.2-9.4% among patients without acute MI. Patients were included in 2008 before hsTn in this study.

Kelly et al showed a lower mortality rate of 3% in non-MI patients during a median follow up time of 48 months(18) using an assay that was one generation older than ours. Kelly’s study has a longer follow up time and consisted of patients without known CAD and therefore a lower risk patient group than ours.

**Comparison of other chest pain diagnoses**

The crude one year mortality for NSCP patients was not significantly different from stable AP, 1.9% (CI:1.2%-2.5%) and 2.3% (95% CI: 0%-5.6%) respectively. In patients with stable AP, Madsen et al (19) and Douglas et al (20) found an average annual mortality of less than 1%. Opposed to our study, both studies included outpatients with suspected AP. Furthermore, Madsen et al excluded patients with a previous CAD. Thus, these studies included a lower risk population compared to our acutely admitted AP patients.
A recent study by D’Souza et al. (4) showed that the one-year mortality in non-ST elevations MI patients was 27% vs 14% in ST elevations MI patients. The one-year mortality for unstable AP, ST elevation MI and Non-ST elevation patients in total was 22%. Our MI group had a one-year mortality of respectively 18.7% (14.3%-23.2%) before implementation of hsTn and 11% (8.7%-14.0%) after. D’Souza et al used the Architect C16000 troponin assay which is an assay that is a generation older than our hsTn. An explanation for the improved mortality in our MI group after hsTn could be the better treatment and secondary prevention of CAD patients. The decreased mortality in MI patients is in concordance with the increasing prevalence of CAD patients in Denmark (21). However, we know from previous studies that patients, who were not diagnosed with MI, are now diagnosed with MI due to a lower threshold for MI diagnosis with hsTn (5). This could implicate that healthier patients with a better risk profile are stratified into MI groups, which can explain the better prognosis of MI patients found in our study. Patients with other heart-related conditions had the highest risk of death that could be caused by some of the high-risk conditions in this group like aortic dissection and pulmonic embolus.

**Limitations and strengths**

The national registries in Denmark, used for data gathering, are validated and documented (9-11). The diagnosis codes used for identifications of the patients were the final discharges diagnose code for the entire visit. These are clinician dependent and individual variation might be present and could be a limitation. We did not include secondary diagnoses that might have given us more information, as secondary diagnoses may reflect previous comorbidities instead of the cause of index visits leading to an overestimation of the diagnoses. This study accounted for total mortality from index visit and thereby reflecting the real morbidity associated with the diagnoses. To avoid overestimation of the risk of a cardiac-related event in cohort 1 (before hsTn) compared to cohort 2 (after hsTn), we excluded everyone with a previous admission with chest pain up to 6 months before the index visit. Selection bias can be present. There may be patients with chest pain that do not have a hsTn measurement, i.e. if it is assessed that the chest pain is not related to ischemic heart disease, and accordingly these patients cannot be accounted for. However, this should not affect the results before and after hsTn.

Furthermore, it was difficult to differentiate between index admission related procedures and new acute procedures as some procedures can be conducted both acutely or subacutely after index discharge (i.e admitted at a secondary hospital and referred to a tertiary hospital for coronary angiography). We chose not to include revascularisation as an endpoint for the same reason. It can also be difficult to differentiate between a re-admission and a continuous admission if several visits are registered with only one day apart.
In this study, we did not include patients with unstable AP, as the number of these was very few and composed an even smaller group than stable AP patients. We decided that the statistical conclusions based upon this would be too inaccurate.

**Clinical implications**

Our study has important clinical implications. With the very sensitive hsTn, more patients will be identified with MI and treated accordingly. Even though the absolute number was not that high, the relative increase in MI patients was 21%, which means 21% more patients have acute investigations and treatment. Patients that previously would have been diagnosed as stable AP and NSCP and referred for non-acute out-patient investigations may now have a prolonged hospitalization until an invasive coronary angiography has been conducted. Accordingly, the prognosis and outcome for MI are expected to improve, as more patients with less extensive MI are diagnosed. However it also demands more resources from emergency departments and cardiology departments allocated to acute treatment, follow-up, and controls.

In clinical practice, the NSCP patients presently have a frequent contact with the health care system and a higher use of medication compared to the general population (3), but with the knowledge from our results we might be able to change this. The good cardiac related prognosis for NSCP patients makes physicians in an emergency department or a cardiology department able to reassure, and this might decrease the subsequent admission of these patients. This is significant since this group composes more than half of the chest pain population (Table 1).

**Conclusion**

After implementation of hsTn an increasing number of patients with increased risk are identified. The mortality rate in patients with NSCP was low and comparable with the general population. The risk of future MI among NSCP patient was five times lower than among patients with new diagnosed MI.
References


### Appendix 1  ICD-10 diagnoses for the four groups

<table>
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<tr>
<th>Chest pain groups</th>
<th>Diagnosis</th>
<th>ICD codes</th>
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<tr>
<td>MI</td>
<td>STEMI</td>
<td>D210B D211B D213B D210A D211A D447 D446</td>
</tr>
<tr>
<td></td>
<td>NSTEMI</td>
<td>D219 D210 D210A D2111 D211A D214 D248 D249 D256</td>
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<tr>
<td>Stable AP</td>
<td>AP</td>
<td>D201 D208 D208D D209 D251 D251B D208E D208E1</td>
</tr>
<tr>
<td>NSCP</td>
<td>NSCP</td>
<td>D8073 D8074 DZ035 D8072 DZ034</td>
</tr>
<tr>
<td>Other hear related</td>
<td>Pulmonary embolus</td>
<td>D260 D260A D269 D269A</td>
</tr>
<tr>
<td></td>
<td>Cor pulmonale</td>
<td>D279</td>
</tr>
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<td></td>
<td>Pericardial diseases</td>
<td>D318 D319 D319A D313 D300 D301A D301 D308 D309 D311</td>
</tr>
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<td>Endocarditis</td>
<td>D330 D339 D389</td>
</tr>
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<td></td>
<td>Myocardial disease</td>
<td>D409 D429 D428 D428B D428A D420 D421 D422 D426</td>
</tr>
<tr>
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<td>Mitral valve diseases</td>
<td>D340 D341</td>
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<td>Aortic valve diseases</td>
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<td></td>
<td>Supraventricular Arrhythmia</td>
<td>D456C D471 D441A-E D441 D498 D499 D499A D440 D480 D484</td>
</tr>
<tr>
<td></td>
<td>Block</td>
<td>D446 D447 D451 D451A D452 D459 D459A D455 D455B D455G</td>
</tr>
<tr>
<td></td>
<td>Ventricular arrhythmia</td>
<td>D472 D472A-E D472M D470 D471</td>
</tr>
<tr>
<td></td>
<td>Aortic dissection/aneurism</td>
<td>D710 D710A D710B D711 D712 D713 D715 D718 D719</td>
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Appendix 2: ATC codes for redeemed medication

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<th>Anti-diabetic</th>
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<th>A10AD</th>
<th>A10AE</th>
<th>A10BA</th>
<th>A10BB</th>
<th>A10BH</th>
<th>A10BX</th>
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<tbody>
<tr>
<td>Betablocker</td>
<td>C07AB</td>
<td>C07AA</td>
<td>C07AB</td>
<td>C07AG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>C10AA</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>
Appendix 3: ICD-10 diagnoses for the clinical endpoints

<table>
<thead>
<tr>
<th>MI</th>
<th>DI210</th>
<th>DI211</th>
<th>DI213</th>
<th>DI210A</th>
<th>DI213</th>
<th>DI211A</th>
<th>DI447</th>
<th>DI446</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DI219</td>
<td>DI210</td>
<td>DI210A</td>
<td>DI211</td>
<td>DI211A</td>
<td>DI214</td>
<td>DI248</td>
<td>DI249</td>
</tr>
<tr>
<td>Cardiac arrest / Ventricular</td>
<td>DI460</td>
<td>DI461</td>
<td>DI469</td>
<td>DI490</td>
<td>DI490A</td>
<td>DI490B</td>
<td>DI490BA</td>
<td>DI470A</td>
</tr>
</tbody>
</table>
Paper II
Clinical Features and Prognosis in Patients with Non-Specific Chest Pain after the Introduction of highly sensitive Troponins.


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6. Emergency Department, Hospital of Southern Denmark, Aabenraa.

Abstract

Objectives: To determine the extent of clinical cardiac related endpoints and mortality among patients with non-specific chest pain (NSCP) and an acute contact to the hospital after the implementation of highly sensitive troponins and to identify risk factors among these patients during 12 months follow-up.

Design: A prospective multicentre study.

Setting: Emergency departments and Cardiology departments in Southern Denmark.

Subjects: 1027 patients with an acute hospital contact due to chest pain, in whom a myocardial infarction or other obvious reasons for chest pain had been ruled out. Patients were included from September 2014 to June 2015 and followed for one year.

Main outcome measures: All-cause mortality and coronary related clinical endpoints (acute myocardial infarction, unstable angina, and coronary revascularisation.)

Results: Clinical cardiac related endpoints during one year were found in 19 patients (1.9%); two (0.2%) had a myocardial infarction, four (0.4%) had unstable angina pectoris and 17 (1.7%) underwent coronary revascularisation. All-cause mortality was observed in seven patients (0.7%). Compared to the general population the standardised mortality ratio did not differ. The risk factors associated with a clinical endpoint were male gender, BMI >25 kg/m2, previous known CAD, hypertension, hypercholesterolemia, diabetes mellitus and use of statins. 73% of the composite endpoints occurred in males. The estimated Hazard ratio for a cardiac-related clinical event was 4.7 for the male gender.

Conclusion: The prognosis for NSCP patients is good. The mortality is comparable with the background population. Very few endpoints took place during follow up and occurred mainly in males. Gender was an important prognostic factor for cardiac-related clinical endpoints.
Introduction

Patients with acute chest pain or chest discomfort represent a large proportion of acute referrals to emergency departments and cardiology departments. Only 14-17% ends up with the diagnosis of an acute myocardial infarction (MI) (1, 2). Even though an MI is excluded, coronary artery disease (CAD) may still be present. CAD is associated with 20% of all deaths in Europe (3). Discharge diagnoses after admission because of acute chest pain includes different clinical manifestations of CAD (Acute MI, unstable angina pectoris (UAP)), other cardiac-related diagnoses (aortic dissection, pulmonary embolus), non-cardiac disorders (gastro-oesophageal diseases, lower airway infection, musculoskeletal disorders) and non-specific chest pain (NSCP). The latter group is represented by patients discharged without a plausible diagnosis explaining the cause of the chest pain. After the implementation of high sensitive troponins (hsTn), where the detection limit for MI has been lowered, a relative increase in the frequency of acute MI has been observed (4). Furthermore, the increased focus on cardiac diseases with primary and secondary prevention seems to have lowered the mortality in patients with cardiovascular disease (5-7). While the former groups are well described in the literature (8, 9), very little attention has been given to the NSCP group, except that it is well known that NSCP patients have frequent contacts to the health care system and high use of medication (10). It has been shown that at least 0.6%-0.8% of NSCP patients discharged from emergency departments had an adverse major cardiac event within 30 days (11, 12). Hence, chest pain evaluation in these departments is thus a professional challenge as the best diagnostic and treatment plan is not obvious for the NSCP patients.

In this multicentre study, we addressed patients discharged from emergency or cardiology departments with the diagnosis of NSCP after the implementation of hsTn for routine clinical use. The study objectives were first to describe the outcome of NSCP patients in terms of all-cause mortality and clinical cardiac-related events during a follow-up period of at least 12 months. Second, we wanted to identify risk factors that may be helpful in predicting the occurrence of clinical ischemic events within 12 months of follow-up.

Methods

Design and settings

This study was conducted as a prospective multicentre cohort study. Six hospitals in the Region of Southern Denmark (Aabenraa Hospital, Sonderborg hospital, Odense University Hospital, Svendborg hospital, Vejle Hospital and Kolding Hospital) were involved and contributed with consecutive acutely admitted chest pain patients from emergency departments and cardiology departments. All patients
were acutely evaluated by a physician based on clinical history, physical examination, ECGs and biochemical biomarkers and included hsTn measurements. The criterion of the third universal definition of MI was used (13).

**Study population**
All patients aged 30-70 years referred to the emergency department or cardiology department and with at least one hsTn measurement during the first 24 hours after admission were identified through daily screening in the central biochemical database. This database included all biochemical laboratory results from all patients in the Region of Southern Denmark. A hsTn T value <14 ng/L or a hsTn I value <25 ng/L was required for inclusion. The diagnosis at discharge given by the attending physicians were traced for each patient, and in this study patients were considered to have NSCP if any of the following international diagnosis code (ICD 10 codes) were given: DR072 (precordial chest pains), DR073 (other chest pains), DZ034 (observation for myocardial infarction) and DZ035 (observation for coronary disease).

A structured interview within 3 days of discharge was completed by telephone calls to each of the patients. Patients were excluded from the study if no contact with the patient was established after 3 calls during different times of the day and week, if they did not understand Danish/English, were intoxicated, pregnant, had an obvious other cause for the chest pain/discomfort, or if they had a coronary angiography performed during the index admission regardless of the results. Patients were also excluded if they declined informed consent to follow-up or if the medical records regarding the index admission were not available.

Patients were prospectively included during a 9 month period from September 2014 to June 2015 and followed until June 2016. Thus, the patients were followed for at least 12 months or until emigration or death.

**Material/Data**
The interview was conducted by the first author or one of two nurses, dedicated to this task only. The patients were asked to answer standardised questions regarding symptoms at their index contact, medical history, and risk factors for cardiovascular disease. The standardised questionnaire was validated for inter-observer validity, where 10 questions from the survey regarding the patient’s medical history were tested in terms of comparability. The agreement was 72% between the 3 interviewers.

After the interview, a written informed consent was signed by the patient giving permission to access the patient records, in which laboratory results, ECGs, basic essential clinical features, blood
pressure, heart rate, respiratory frequency, saturation, temperature and results of echocardiography were registered.

**Definitions**
Smoking was registered as package years. 20 cigarettes per day for a year was one package year. Hypertension, hypercholesterolemia, and diabetes were self-reported. Family history included cardiovascular disease in a first degree relative regardless of age. Statins were defined according to ATC code (C10AA) for cholesterol-lowering medication.
The patient’s history of diseases was on ICD diagnoses from previous admissions for up to 10 years from index visit Prior CAD included known acute and chronic ischemic heart disease diagnoses up 10 years before the index visit. Peripheral artery disease included diagnoses codes for intermittent claudication and atherosclerotic disease. Ischemic cerebral diseases included apoplexy and transitory cerebral ischemia. Supraventricular tachycardia was atrial fibrillation or atrial flutter.
Data on use of redeemed medication was based on information from Odense Pharmaco-epidemiologic Database (14). Lipid-lowering medication was defined as redeemed medication for up to 3 months before index admission.

**Clinical outcome**
A clinical cardiac related endpoint at 12-month follow-up was present if the patient had suffered one or more of the following clinical manifestations: cardiac death, acute MI, UAP or coronary revascularisation.
Clinical endpoints were obtained from the National Patient Register (15) and from the Civil Registration System (16). The main outcome was a composite endpoint consisting of all-cause mortality and clinical cardiac related endpoints.

**HsTn assays**
The troponin assays used in this study were hsTn I or T with 99th percentile cut-off points. In Odense University Hospital the hsTn I was analysed by Abbot Diagnostics Architect with upper reference limit of the 99th percentile of 25 ng/L. The 10% coefficient of variation was at 5 ng/L, The decision limit for myocardial infarction was set at >= 25 ng/L(17). hsTn T was used in all other participating hospitals and was analysed by Roche Diagnostic Elecsys 2010, modular analytics E170, Cobas e411, Cobas e601. The 99th percentile cut off value was 14 ng/L with a 10% coefficient variation at 13 ng/L. The decision limit for MI was >= 14 ng/L (18).
Sample size calculations
By inclusion of 1 298 patients, the study had a power of 80% and a two-sided confidence interval of 95% to identify risk factors that occurred 20% more frequent in patients with a clinical endpoint compared to patients without a clinical endpoint. We assumed that clinical endpoints in unexposed to be 2% and in exposed to be 5%.

Statistics
Continuous variables were categorised in categorical subgroups except for age that was reported in medians with interquartile ranges. Receiver-operator curves (ROC) were made for each variable to identify reasonable cut off points. Categorical variables were reported in frequency and percentages. Pearson's chi-square test was used for intergroup comparison of categorical variables. Laboratory data that was not obtained were analysed as missing data.
Patients were followed until the first upcoming clinical endpoint that was shown for the total cohort and according to gender. Unadjusted event data was shown as Kaplan Meier plot according to gender. The prognostic effect of variables on the clinical endpoints was analysed by univariates cox regression. More variables were tested than reported but all significant variables are reported along with some clinical relevant non-significant variables. P value < 0.05 was considered significant.
From Statistics Denmark we obtained the population number and mortality for the general population 30-70 years old in the region of Southern Denmark for 2015. The expected mortality ratio for our study population was calculated from this information. The observed mortality ratio in the NSCP study population was compared with the expected mortality ration to estimate the standardised mortality ratio compared to the general population.
Data were analysed using STATA version STATA 14.2 0 (StataCorp, College Station, Texas).

Ethics
After a request to the Regional Scientific Ethical Committees for Southern Denmark, no ethical clearance was required (confirmed by email 18.03.2014). The study was registered with The Danish Data Protection Agency (2008-58-0035 number 1086). The study was approved by the Danish Health Authorities j.nr. 3-3013-573/1 allowing access to discharge diagnosis from the charts.
A written informed consent to access patient records was obtained from the participants.

Results
Among 1 213 eligible patients, 1 027 returned an informed consent and were included. Figure 1 shows the flowchart for patient inclusion and exclusion. Non-participants consisted of patients that
were eligible, and completed the interview, but did not return informed consent for participation. Comparison between participants (n=1,027) and non-participants (n=186) showed a significant difference in median age of 54 years (IQR: 47:62) in participants vs 47 years (IQR: 39:56) in non-participants, p=0.001. Females accounted for 568 (55%) of the participants and 90 (48%) of the non-participants, p=0.081. Two patients left Denmark before the end of the follow-up time.

Baseline characteristics of the participants are shown in table 1. Patients with a clinical endpoint were significantly older with a median age of 61 (IQR: 47-62), consisted of more men (73%), had a Charlson score >=1 and used cholesterol-lowering medication and had more vascular comorbidity at baseline than patients who did not experience a clinical endpoint.
Patients attending ED and CD with troponin measurement and age between 30-70 years in the study period (n=4289)

Not assessed for eligibility (n=1857)
hsTn T >= 14 ng/ml
hsTn I > 25ng/ml
Discharged >8 days from index admission

Patients with normal troponin
(n=2423)

Ineligible (1210)
No contact established
Denied participation
The cause of the chest pain was identified
Did not speak Danish
Not from the catchment area
Interview lost/not completed
Coronary angiography during index admission or referred for coronary angiography connected to index admission
Chart information not found

Eligible (n=1213)
Completed the interview

Eligible, but not recruited (n=186)
Did not return consent form for participation

Recruited study population
(n=1027)

*Figure 1 shows the patient inclusion and exclusion. ED: emergency departments, CD: cardiology departments.*
During 30 days follow-up the all-cause mortality was zero (0%, 95% CI: 0%-0.3%), two had a MI (0.2%, 95% CI: 0%-0.5%), zero (0%, 95% CI: 0%-0.3%) had UAP and four (0.4%, 95% CI: 0.01%-0.8%) were revascularised. The 30 day composite endpoint was experienced by five patients (0.5%, 95% CI: 0.1%-0.9%).

Table 1: Descriptive baseline characteristics

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Total n=1027</th>
<th>Without clinical endpoint n=1001</th>
<th>With clinical endpoint n=26</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aabenraa</td>
<td>164 (16%)</td>
<td>156 (15%)</td>
<td>8 (31%)</td>
<td></td>
</tr>
<tr>
<td>Kolding</td>
<td>210 (20%)</td>
<td>206 (21%)</td>
<td>4 (15%)</td>
<td></td>
</tr>
<tr>
<td>Odense</td>
<td>318 (31%)</td>
<td>309 (31%)</td>
<td>9 (35%)</td>
<td>0.268</td>
</tr>
<tr>
<td>Svendborg</td>
<td>180 (17%)</td>
<td>177 (18%)</td>
<td>3 (11%)</td>
<td></td>
</tr>
<tr>
<td>Sonderborg</td>
<td>67 (7%)</td>
<td>67 (7%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Vejle</td>
<td>88 (9%)</td>
<td>86 (8%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>Female 568 (55%)</th>
<th>Male 459 (45%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>561 (56%)</td>
<td>440 (44%)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>7 (7%)</td>
<td>19 (19%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27 (27%)</td>
<td>73 (73%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median age(IQR)/years</th>
<th>Total 54(47-62)</th>
<th>Without clinical endpoint 54(47-62)</th>
<th>With clinical endpoint 61(53-66)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>102 (10%)</td>
<td>102 (10%)</td>
<td>0 (0%)</td>
<td>0.010</td>
</tr>
<tr>
<td>40-49</td>
<td>247 (24%)</td>
<td>243 (24%)</td>
<td>4 (15%)</td>
<td>0.020</td>
</tr>
<tr>
<td>50-59</td>
<td>325 (32%)</td>
<td>319 (32%)</td>
<td>6 (23%)</td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>353 (34%)</td>
<td>337 (34%)</td>
<td>16 (62%)</td>
<td></td>
</tr>
</tbody>
</table>

| Charlson score | 0 783 (76%) | 770 (77%) | 13 (50%) | 0.001 |
|                | 244 (24%)   | 231 (23%) | 13 (50%) |       |

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Previous smoker 338 (33%)</th>
<th>Current smoker 257 (25%)</th>
<th>Never- smoker 432 (42%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>334 (33%)</td>
<td>243 (24%)</td>
<td>424 (43%)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>33 (33%)</td>
<td>24 (24%)</td>
<td>8 (31%)</td>
<td></td>
</tr>
</tbody>
</table>

| Statins       | 213 (21%) | 202 (20%) | 11 (42%) | 0.006 |
|              | 21 (21%)  | 23 (23%)  | 13 (50%) |       |

<table>
<thead>
<tr>
<th>Cardiovascular comorbidity</th>
<th>Total 166 (16%)</th>
<th>Without clinical endpoint 156 (16%)</th>
<th>With clinical endpoint 10 (39%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
<td>156 (16%)</td>
<td>156 (16%)</td>
<td>10 (39%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>19 (2%)</td>
<td>16 (2%)</td>
<td>3 (12%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ischemic cerebral disease</td>
<td>49 (5%)</td>
<td>47 (5%)</td>
<td>2 (8%)</td>
<td>0.479</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>53 (5%)</td>
<td>51 (5%)</td>
<td>2 (8%)</td>
<td>0.554</td>
</tr>
</tbody>
</table>

Table 1 shows the baseline characteristics. P values for Chi square test between patients with and without a clinical endpoint.

Table 2 lists the clinical endpoints during 12 months follow-up for the total cohort and according to gender. During one year follow up we found that in the total cohort seven patients died (0.7%, 95% CI: 0.2%-1.2%). Compared to the general population the standardised mortality ratio was 1.2 (95% CI: 0.5-2.4). No cardiac related death was observed, 0 (0%, 95% CI: 0%-0.3%) while two (0.2%, 95%
CI: 0-0.5%) had a MI, four (0.4%, 95% CI: 0.01%-0.1%) experienced UAP and 17 (1.7%; 95% CI 0.9%-2.4%) patients underwent coronary revascularisation. In total the number of patients with clinical cardiac related endpoints during one year follow up was 19 (1.9%; 95% CI 1.0%-2.7%).

In total, 26 patients had 30 events which made the composite endpoint 26/1027 (2.5%, 95% CI 1.6%-3.5%).

Accounting for one year follow up, 19 (73%) of the total composite endpoints occurred in male patients. The difference is even more distinct with time, which is demonstrated in the accumulated endpoints plot (Figure 2) and further stratified by gender (figure 3). Both figures are depicted for the total follow up time of 1.4 years.

<p>| Table 2: Endpoints during 1 year follow up |</p>
<table>
<thead>
<tr>
<th>Total</th>
<th>Male</th>
<th>Female</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=26</td>
<td>%</td>
<td>n=19</td>
</tr>
<tr>
<td>Death</td>
<td>7</td>
<td>0.7(0.2-1.2)</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac related death</td>
<td>0</td>
<td>0.0(0.0-0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2</td>
<td>0.2(0.0-0.5)</td>
<td>2</td>
</tr>
<tr>
<td>Unstable Angina Pectoris</td>
<td>4</td>
<td>0.4(0.0-0.8)</td>
<td>3</td>
</tr>
<tr>
<td>Revascularisation</td>
<td>17</td>
<td>1.7(0.9-2.4)</td>
<td>13</td>
</tr>
<tr>
<td>Composite endpoint</td>
<td>26</td>
<td>2.5(1.6-3.5)</td>
<td>19</td>
</tr>
</tbody>
</table>
Figure 2: Failure plot for combined clinical endpoints and the total cohort.

Figure 3: Failure plot for clinical endpoints according to gender
Table 3 shows the hazard ratio (HR) for risk factors and outcome during a follow-up time of one year. This table shows HR with the confidence interval for all clinical events, cardiac-related events, and all-cause mortality. A univariate analysis was conducted. Due to few clinical events, multivariate analysis was omitted. Significant characteristics associated with clinical events were gender, BMI>25 kg/m2, Charlson score >1, previous known CAD and combined ischaemic co-morbidity, hypertension, hypercholesterolemia, diabetes and use of statins. It was not possible to obtain cholesterol and statin values from 15% of the patients.
### Table 3: Hazard ratio for exposure variables and endpoints during 1 year of follow up

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All clinical events (n=26)</th>
<th>Cardiac clinical events (n=19)</th>
<th>All-cause mortality (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td>3.4(1.4-8.1)</td>
<td>4.7(1.6-14.0)</td>
<td>1.7(0.4-7.6)</td>
</tr>
<tr>
<td>Age/years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50+</td>
<td>1.1(0.3-4.0)</td>
<td>1.0(0.3-3.5)</td>
<td>1</td>
</tr>
<tr>
<td>60+</td>
<td>2.8(0.9-8.4)</td>
<td>1.8(0.6-5.6)</td>
<td>5.6(0.7-46.7)</td>
</tr>
<tr>
<td>BMI&lt;25 kg/m²</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>BMI&gt;25 kg/m²</td>
<td>3.0(1.0-7.6)</td>
<td>4.6(1.1-19.7)</td>
<td>1.4(0.3-7.0)</td>
</tr>
<tr>
<td>Charlsons score=0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charlsons score&gt;=1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-12 package years</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt;12 package years</td>
<td>1.9(0.8-4.3)</td>
<td>2.1(0.8-5.3)</td>
<td>1.6(0.4-7.2)</td>
</tr>
<tr>
<td>Alcohol 0-2 U/week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol &gt;2 U/week</td>
<td>0.8(0.4-1.7)</td>
<td>0.9(0.3-2.1)</td>
<td>0.7(0.2-3.1)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not known coronary artery disease</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3.3(1.5-7.3)</td>
<td>3.8(1.5-9.5)</td>
<td>2.1(0.4-11.0)</td>
</tr>
<tr>
<td>Not known ischemic cerebral disease</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ischemic cerebral disease</td>
<td>1.7(0.4-7.0)</td>
<td>1.1(0.2-8.3)</td>
<td>3.4(0.4-27.8)</td>
</tr>
<tr>
<td>Not known with extremity ischemia</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ekstremit ischemia</td>
<td>7.4(2.2-24.5)</td>
<td>3.1(0.4-23)</td>
<td>23.5(4.6-121.0)</td>
</tr>
<tr>
<td>Not known supraventricular tachycardia</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>1.5(0.4-6.4)</td>
<td>1.0(0.2-7.6)</td>
<td>3.0(0.4-25.2)</td>
</tr>
<tr>
<td>None of the above mentioned comorbidity</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Combined ischemic comorbidity*</td>
<td>4.0(1.9-8.7)</td>
<td>3.6(1.5-8.9)</td>
<td>5.5(1.2-24.4)</td>
</tr>
<tr>
<td>Not known hypertension</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Known hypertension</td>
<td>5.2(2.1-12.8)</td>
<td>5.8(1.9-17.5)</td>
<td>3.9(0.8-20.2)</td>
</tr>
<tr>
<td>Not known hypercholesterolemia</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Known hypercholesterolemia</td>
<td>2.5(1.1-5.9)</td>
<td>6.0(1.7-20.6)</td>
<td>0.5(0.1-2.5)</td>
</tr>
<tr>
<td>Not known diabetes</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Known diabetes</td>
<td>5.0(2.2-11.6)</td>
<td>5.2(2.0-13.7)</td>
<td>4.7(0.9-24.1)</td>
</tr>
<tr>
<td>No family history of CVD</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>1.7(0.7-3.8)</td>
<td>1.6(0.6-4.0)</td>
<td>2.3(0.4-11.8)</td>
</tr>
<tr>
<td>Triglycerides&lt;1 mmol/L</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Triglycerides&gt;=1 mmol/L</td>
<td>1.4(0.5-3.8)</td>
<td>1.0(0.4-2.7)</td>
<td>n.c</td>
</tr>
<tr>
<td>Total cholesterol&lt;5 mmol/L</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total cholesterol&gt;5 mmol/L</td>
<td>0.5(2.1-1.2)</td>
<td>0.4(0.2-1.1)</td>
<td>1.1(0.2-5.2)</td>
</tr>
<tr>
<td>LDL&lt;3 mmol/L</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>LDL&gt;3 mmol/L</td>
<td>0.5(2.1-1.1)</td>
<td>0.3(0.1-1.0)</td>
<td>1.1(0.2-5.4)</td>
</tr>
<tr>
<td>HDL&gt;=1 mmol/L</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HDL&lt;1 mmol/L</td>
<td>2.1(0.8-5.5)</td>
<td>3.0(1.1-8.5)</td>
<td>n.c</td>
</tr>
<tr>
<td>No statins</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Statins</td>
<td>2.8(1.3-6.2)</td>
<td>4.3(1.8-10.6)</td>
<td>0.7(0.1-5.5)</td>
</tr>
</tbody>
</table>

*Combined ischemic comorbidity consists of coronary artery disease, ischemic cerebral disease and ektremity ischemia.

n.c.: not calculated, CVD: cardiovascular disease, LDL: Low density lipoprotein, HDL: High density lipoprotein
Discussion

Prognosis for NSCP patients

In general patients with NSCP have gained little attention. However, as shown in this study out of a cohort of 4,289 patients with a hsTn measurement in the emergency departments or cardiology departments, NSCP patients compose roughly 25% and thereby a substantial and unneglectable proportion of the chest pain patients.

The prognosis for NSCP patients, when it comes to one-year all-cause mortality was 0.7 %, not different from the age and gender-adjusted background population. The risk for a clinical cardiac related endpoint was 1.9% in 12 months.

Comparing NSCP patients with the Danish general population from the same demographic area during 2015 the standardised mortality rate was 1.2(CI: 0.5-2.4)(19) without significant difference, which confirms the favourable prognosis for NSCP patients.

Fagring et al showed a one-year mortality rate of 0.9% and 1.5 % in respectively women and men aged 25-74 years with NSCP in 2006, which was before hsTn (20). This is almost twice as high as the mortality rate in our study conducted after the hsTn implementation.

The results of our study are confirmed by two other studies (11, 12). The first one regardless of troponin assay showed that NSCP patients during 30 days follow up had an MI rate of 0.5%, 0.3% experienced unplanned revascularisation and 0.2% died during 30 days follow up in NSCP Patients(11).

In a recent population-based study from Sweden, the 30-day mortality for NSCP patients after the implementation of hsTn (12) was 0.2%, MI 0.3 %) and revascularisation rate 0.3% for patients directly discharged from emergency departments after chest pain. Hence, the prognosis for directly discharged patients was much more benign than for the briefly admitted patients, respectively 1.1%, 5.0% and 4.0% for mortality, MI, and revascularisation within 30 days. Our results were comparable with patients directly discharged. These rates are similar to our findings and underline that most clinical events occur during early follow-up (12).

Other studies have looked into the prognosis of patients with excluded MI. Excluded MI also includes patients with other cardiac-related diseases and non-cardiac related chest pain. Our results confirm previous studies showing a low event rate among patients with a first hsTn below the detection limit for acute MI (21-23). Bandstein et al. demonstrated that in a cohort of patients >25 years presenting to the ED with chest pain and one hsTn T <14 1.2 % (146/12033) patients experienced an MI during one year follow up (22). Even though we looked at overall ischemic heart disease and not just acute
MI, our event rate was lower. This could be explained by the age difference between the cohorts (24).
Kelly et al. (23) found in a cohort with chest pain presentation in an ED, normal ECG and normal troponins a mortality rate of 3%, MI of 0.6% and revascularization 3.1% during a median follow up time of 48 months. The patient group in this sub-study was younger, preselected without previous known CAD and consisted of 55% men. Furthermore, the troponin assay used in this study, even though with a cutoff point at 99 percentile was a previous generation of troponin assay than the hsTn used in our study. Furthermore, this study was a single centre study and could reflect a demographic higher risk group in contrast to our multicentre study and that could explain why our results differ.
Comparing the NSCP population with stable CAD patients, several studies have demonstrated a one-year NSCP annual mortality < 1% (25, 26). These studies in combination with ours, shows that stable CAD and NSCP have similar prognosis probably caused by better prevention and treatment strategies in CAD patients.
The prognosis for the NSCP patients regarding clinical manifestations of CAD is good. The few clinical events taking place during follow up imply that the risk stratification taking place in the routine clinical setting is sufficient. The endpoints shown in this study makes the clinician capable of reassuring the patients of their good prognosis and might reduce the re-admission rate for this patient group.

**Risk factors for future cardiac-related events among the NSCP patients**

This is the first study of our knowledge to assess risk factors in non-specific chest pain patients after hsTn implementation. We showed that the risk factors characterizing patients with a one year risk of cardiac events are male gender, BMI >25 kg/m2, previous known CAD or other vascular co-morbidity, hypertension, hypercholesterolemia, diabetes mellitus and use of statins.
Omstedt et al (11) showed that the risk of a future MI, unplanned revascularisation and death in NSCP patients is associated with age, previous MI, heart failure, hypertension, stroke, hyperlipidemia, diabetes mellitus and male gender. These risk factors were recognised in our study. Nejatian et al. study (12) showed that admitted patients had a worse prognosis than the directly discharged patients. However, the admitted patients had more cardiovascular risk factors demonstrating the clinical assessment is a crucial part of chest pain assessment and even with hsTn, a blood test cannot stand alone. Especially in the clinical evaluation of unstable angina, risk profile assessment is crucial for further decision making.
Strength and limitations

The strength of our study is that it was a multicentre study with a prospective data collection. All outcome data were obtained from national registration systems linked to individual civil registration numbers, which results in no loss to follow up (15, 16).

Our study has a number of limitations. The cohort was selected as all patients with a coronary angiography performed during index contact were excluded and we cannot account for the endpoints in those patients. We chose to exclude these patients as they were evaluated by a physician to be suspected for CAD during index visit since a coronary angiography was performed acutely during this visit.

Our study participation was dependent on the written informed consent. Even though they participated in the interview, 186 patients did not return this consent. We do not know the reasons for not returning the informed consent. Some of these patients may have been ill, not capable to return the consent, hospitalised or they might just not want to participate.

We only included patients up to 70 years old. We know from previously developed risk models that age is an important factor for assessment of cardiovascular risk. This could partially explain the differences between our study and other studies describes above as many studies include patients above 18 years old (11, 12, 22). Our study cohort consisted of more women than men; however male gender is associated with increased risk of a CAD. An increasing tendency of female among NSCP patients has been shown by Fagring et al(20). Health care systems have during the last couple of years conveyed that females show other symptoms than men in relation to heart attack and could encourage more females to seek medical attention.

Nearly 15% of the patients were missing information on their cholesterol levels and this might have had an impact on that sub analysis.

The main limitation is the few events occurring during follow up, which restricted our possibility to search for risk factors for the events. A sample size was calculated before study start and based on outcome rates from existing literature. However, the calculation was overestimating the outcome rate. A larger study cohort would have resulted in more events which would have allowed multivariate analysis of the risk factors for adverse outcomes.

This study has shown that the prognosis for NSCP patients is good. Very few patients, who were not identified during the index visit, had a clinical endpoint. However, to be able to predict patients at risk requires a much larger study due to the few events observed in this patient group. Future research could focus on NSCP patients with the identified risk factors from this study. Future area of
research may even focus on how to reduce the frequency of visits from NSCP patients in our emergency and cardiology departments.

**Conclusion**

Our study demonstrates that the prognosis for patients with NSCP is good. Among NSCP patients with cardiac related endpoints, male gender is a significant risk factor for an adverse outcome among with BMI >25 kg/m2, previous known CAD or other vascular co-morbidity, hypertension, hypercholesterolemia, diabetes mellitus and use of statins.

Patients who are discharged from the hospital after an initial assessment for acute chest pain and without further investigations are evaluated correctly and can be assured of their good prognosis.

**Acknowledgement**

We are indebted to Jens Haastrup (Biochemical department, Kolding Hospital) for the daily search of troponin values.

We want to thank the below-mentioned hospitals for our collaboration during this study:

Emergency Department and Cardiology Department- Hospital of Southern Denmark

Emergency Department and Cardiology Department- Kolding and Vejle Hospital

Emergency Department and Cardiology Department - Odense University Hospital Odense and Svendborg.
References


Non-contrast Cardiac CT scan as a risk stratification Tool in non-specific Chest Pain Patients

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⁴ Emergency Department, Odense University Hospital, Odense, Denmark.
⁵ Medical Department, Svendborg Hospital, Svendborg, Denmark.
⁶ Cardiology Department, Esbjerg Hospital, Esbjerg, Denmark.
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Abstract

Objectives: To examine the prevalence of coronary artery calcification and frequency of cardiac events in a cohort of non-specific chest pain (NSCP) patients (an acute admission for chest pain and discharged without an obvious reason for the chest pain) and compare with the background population.

Design: A double-blinded prospective cohort study examined with non-contrast CT scan and measurement of the coronary artery calcium (CAC) score.

Setting: Departments of Emergency and Cardiology in the Southern Region of Denmark.

Subjects: The study population consists of 229 NSCP patients and was compared with 722 patients from the background population. The patients were included from September 2014 until June 2015 and followed for a year.

Main outcomes measures: Prevalence of CAC. Cardiac-related mortality, acute myocardial infarction (MI), ventricular tachycardia (VT), unstable angina (UAP) and coronary revascularisation.

Results: No significant difference in prevalence of CAC was found. During one year follow-up, two (0.9%) NSCP patients were revascularised, while no one died experienced MI, VT or had UAP. In the background population, four (0.6%) experienced a clinical endpoint; one cardiac-related death, two with MI, one had VT.

Conclusion: The prevalence of CAC is comparable with the background population, and the prognosis for NSCP patients during one-year follow-up is excellent.
Introduction

Cardiovascular disease remains a major public health problem and causes half of all deaths in Europe, while coronary artery disease (CAD) accounts for 20% of all deaths in Europe (1). One of five patients with chest pain in the emergency departments turns out to fulfill the diagnostic criteria of acute myocardial infarction (MI) (2, 3). Other causes of acute chest pain may be of cardiovascular origin (aneurysm, aortic dissection pulmonary embolism), but can also be non-cardiac related (gastrointestinal disorders, musculoskeletal disorders) while in a significant number of patients the cause of symptoms remains unknown, and these patients are defined as having non-Specific Chest Pain (NSCP).

However, even if acute MI is definitely excluded, CAD may be present with an inherent risk of future cardiac events. Hence, 0.8% of NSCP patients experienced an adverse outcome during 30 days follows up after discharge from an emergency department (4). It has been shown that up to 20% of patients with CAD do not have any traditional risk factors such as hypertension, hyperlipidemia, diabetes or smoking (5), thus a non-contrast cardiac CT might serve as a tool in risk stratification by measuring the presence and extent of coronary artery calcium (CAC). The advantages of non-contrast cardiac CT are that the method is easy to perform and interpret, the reproducibility is high and the radiation exposure is low (3, 6-8). The role of a non-contrast cardiac CT as a risk stratification tool has been established in asymptomatic persons (9). The prevalence of CAC in an asymptomatic background population without known prior CVD has been shown to be 44%-50% (10, 11). The Multi-Ethnic Study of Atherosclerosis (MESA) demonstrated that an increased CAC score was associated with a higher risk of CAD during a 10 year follow up period (12). However, the clinical importance of CAC in patients with acute chest pain, in whom an acute MI has been ruled out, remains to be investigated.

In order to evaluate the non-contrast cardiac CT as a potential risk stratification tool for patients with NSCP, the aim of the present study was twofold. First, we wanted to investigate the prevalence of CAC among NSCP patients and to compare the findings with observations from an asymptomatic background population. Second, we wished to examine the frequency of clinical cardiac events related to CAC in NSCP patients during a 12 months follow-up period, and compare these data with the results from the asymptomatic background population but also those directly referred for a further cardiac test from index contact.
Method and materials

Study design
This study was a double-blinded prospective cohort study that included patients from the emergency and cardiology departments in the Region of Southern Denmark. All patients with an acute visit for chest pain to the hospitals in Odense, Svendborg, Vejle, Kolding, Aabenraa or Sonderborg, and at least one troponin measurement during the contact were included. The inclusion period was from September 2014 until May 2015. The patients were invited for this study if they were discharged without any obvious reason for the chest pain (NSCP diagnosis (ICD codes: DR072/DR073/DR034/DR035)).

Study population
Through the central biochemical laboratory for all hospitals in the region of Southern Denmark, all patients with measurement of troponin in the emergency and cardiology departments were identified on a daily basis. Electronic patient files were scrutinized in all patients with normal troponin values, as defined below.
Patients had to complete a structured questionnaire by a telephone interview within three days of discharge from the index admission.
Afterwards written information and a consent form for participation were sent to the patient. Patients who returned the consent form were scheduled for the CT scan. The participant and the physicians were blinded for the result of the non-contrast CT.

The inclusion and exclusion criteria for the study are defined below

Inclusion criteria:
- Normal troponin (troponin T <14 ng/mL or troponin I< 30 ng/mL’
- Age 30-70 years
- Known as one risk factor for CAD (hypertension, hypercholesterolemia, familiar disposition, and diabetes mellitus, present or former smoker).

Exclusions criteria:
- Living outside the catchment area of Region of Southern Denmark
- Refusing participation in the telephone interview and or CT scan
• Percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) and cardiac imaging test within the last 5 years
• Not Danish-speaking,

We used the Danish Risk Score study (DanRisk) population (11) as a control group representing the background population. The DanRisk study population consisted of 1 257 asymptomatic subjects aged 50 and 60 years old, who in 2009 had been examined in one of four cardiac computed tomography (CT) centres (Odense, Esbjerg, Vejle or Svendborg) in the Region of Southern Denmark. The inclusion criteria in this study were at least one risk factor for CAD (hypertension, hypercholesterolemia, familiar disposition, known smoker and diabetes mellitus), and exclusion criteria were known, CAD. Patients missing CAC were excluded. The patient selection procedure used in the DanRisk study is described in details elsewhere (11).

Definitions
In the NSCP population, comorbidity was self-reported. Diabetes Mellitus was defined as the use of antidiabetic medication or a diagnosis given by their general practitioner. Hypertension and hypercholesterolemia were present if the patients stated to be in relevant medical treatment or had received the diagnoses by the general practitioner. Family history was defined as a first degree relative with cardiovascular disease without consideration of age. Smoking was defined as a current smoker. Systolic and diastolic blood pressure and heart rate were retrieved from the patient files, as the first measured value during the index admission. Cholesterol values were collected up to three months before and three months after the index admission. The value closest to the index date was used. BMI was calculated based on self-reported height and weight.

For the DanRisk subjects in this study Diabetes Mellitus was defined as the use of anti-diabetic medication that included any oral antidiabetic drug and/or insulin. Hypertension was defined as the use of antihypertensive medical treatment. Antihypertensive therapy included angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonist, calcium channel blockers, diuretics, beta-blockers, alpha-blockers, and centrally acting antihypertensive drugs. Hypercholesterolemia was defined as the use of lipid-lowering medication. Family history was defined as first degree relative with a cardiovascular disease, male<55 years and female <65 years. Smoking was defined as a current smoker. Blood pressure, heart rate, BMI and cholesterol values were measured at baseline examination.
Troponins
The troponin assays used for this study were high sensitive troponins with a 99th percentile upper reference limit.

The cardiac troponin I, used by Odense University Hospital, was analyzed by use of the Abbot Diagnostics Architect with an upper reference limit of the 99th percentile of 25 ng/L and a coefficient of variation < 10% at 5 ng/L. The decision limit for MI was set at >= 25 ng/L.

Troponin T, used by all other participating hospitals, was analysed by Roche Diagnostic Elecsys 2010, modular analytics E170, Cobas e411, Cobas e601. The 99th percentile upper reference limit was 14 ng/L and a coefficient variation <10% at 13 ng/L. The decision limit was set >= 14 ng/L for MI.

Cardiac CT protocol
CAC was assessed by summing the scores from all foci in the coronary arteries and expressed in Agatston unit (AU) (6). CAC was assessed by trained radiographers and reanalyzed by the first author. The correlation was 99%.

Two centres used dual-source CT scanner (SOMATOM Definition Flash, Siemens Healthcare, Forchheim, Germany) with prospective ECG triggering. In persons with a heart rate <75 beats/minute the ECG triggering was set in diastolic phase at 65-75% of the cardiac R-R interval. In persons with heart rate ≥75 beats/min the ECG triggering was set in systolic phase at 250-400 ms. Additional settings: slice thickness 3 mm, collimation 128 x 0.6 mm, gantry rotation time 0.28ms, 120 kV tube voltage, 90mAs/rotation. One centre used a GE 64-slice CT-scanner (Discovery 750 HD; GE Healthcare). In persons with a heart rate <75 beats/minute the ECG triggering was set in diastolic phase at 75% of the cardiac R-R interval. In persons with heart rate ≥75 beats/min the ECG triggering was set in systolic phase at 40% of the cardiac R-R interval. Additional settings: slice thickness 2.5 mm, collimation 64 x 0.625 mm, gantry rotation time 0.35ms, 120 kV tube voltage and 200 mA tube current. The last centre used a Toshiba Aquilion Next Generation CT scanner with prospective ECG triggering. If heart rate was <75 bpm the ECG triggering was in the diastole phase at 65%-75% of the R-R interval. In persons with heart rates ≥75 beats/min, the ECG triggering was set in systolic phase at 40%. Slice Thickness was 0.5 mm, collimation after scan range 0.5 mm x 240 – 320, gantry rotation time 0.275 ms and 120 kV tube voltage.

Follow-up
The study was conducted as a double-blinded study with a 12 month follow-up time. Neither the participants nor the investigators knew the results of the CAC score before the end of follow-up. By
then the participants and their general practitioner received a letter with the results of the CAC score.

The clinical endpoints in the follow-up study were cardiac death, ventricular tachycardia (VT), non-fatal MI, coronary revascularization and unstable angina. The endpoints were compared with DanRisk participants. Furthermore, we did a comparison with NSCP patients who were referred for cardiac imaging testing at the index admission and thus did not participate in our study. These patients were referred for further diagnostic testing by the physician on call that evaluated these patients to have a higher risk of CAD.

Sample size
A sample size calculation was performed based on the prevalence of elevated CAC score (CAC>0 AU), and we knew that 44% of the background population represented by DanRisk had coronary calcifications (CAC>0 AU) (11). In a symptomatic population referred for coronary angiography 79% had a CAC>0 AU (13). We assumed in a symptomatic low-risk population, the NSCP group, 62% would have CAC>0 AU. The confidence interval was set to 95%, and with an expected power of 80% using the Fleiss method gave us a sample size of 238 patients.

Statistical analyses
Categorical variables were presented as frequency tables and percentages, and continuous variables with mean and medians. Fischer’s exact test and Chi-square test were used for categorical variables. The t-test was used for comparison of normally distributed variables, while the Wilcoxon’s rank sum test was used for not normally distributed continuous variables. The odds ratio was calculated with multi-logistic regression.

Exclusion analyses (table 1) were performed between participants and non-participants. Non-participants were those who fulfilled the eligibility criteria but were not recruited. The variables were categorical variables and the inference was estimated with Fishers exact and chi-square test. Age was non-parametric and reported with medians and inference estimated with Wilcoxon’s rank-sum test. Descriptive characteristics of the DanRisk and the NSCP patients (Table 2) consisted of a categorical and continuous variable. The characteristics were reported with frequency and means. Statistics estimates were conducted with Fishers exact test and Chi-square test for categorical and t-test for continuous variables.

The amount of CAC and its association with risk factors were reported with medians for each risk factor in NSCP patients and DanRisk patients (Table 3). P values estimates are based on Wilcoxon’s rank-sum test.
Comparison between coronary calcification (CAC>0 AU) in NSCP patients and the DanRisk population was performed with 2x2 tables and Chi-square test, and the relationship between calcification in the NSCP and DanRisk patients adjusted for risk factors that were significant in Table 2. Statistics were calculated by multivariate logistic regression on coronary calcification status (CAC=0 AU vs CAC >0 AU). The analyses were performed with STATA 14.20 (StataCorp, College Station, Texas). A P-value <0.05 was considered to be significant.

**Ethics**

The protocol was approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20140055) and conducted in accordance with the Declaration of Helsinki. The study was registered in Clinical.Trial.gov with number NCT02422316. The study was registered with The Danish Data Protection Agency (2008-58-0035 nr 1092). Written informed consent was obtained from each participant.

The DanRisk protocol was approved by the Regional Scientific Ethical Committee for Southern Denmark (S-20080140) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

**Results**

In total 4 289 patients aged 30 to 70 years old attended an Emergency or Cardiology Department and had at least one troponin measurement done. After exclusion of 3 047 patients (i.e. elevated troponin, identified a cause of the chest pain, no consent, see Figure 1), 1 241 were left for study eligibility. However, further 800 of these for different reasons (i.e. no risk factors, referred for coronary imaging) had to be excluded from participation in a cardiac CT scan examination. Of the remaining 441 patients with NSCP 229 patients (participants) accepted the invitation, and to undergo cardiac CT scan, while 212 patients (non-participants) either declined the invitation or did not show up at the time of cardiac CT-scan. The non-participants represented individuals that were eligible but not recruited. The mean age was 52 (IQR 44;60) and 57 (IQR 50;64) years in participants and in non-participants, respectively, p=0.001. Significantly more were known with hypercholesterolemia and a family history of CVD among participants compared to non-participants. No significant difference was found in gender, diabetes, hypertension or smoking status. Table 1 lists the comparison between participants and non-participants.
Figure 1: Flowchart for the inclusion of the NSCP population

Patient attending EDs and CDs with at least one troponin measurement and age between 30-70 years old. (n=4289)

Not assessed for eligibility (n=3047)
- Elevated troponin: TnT >14 ng/mL or TnT>25 ng/mL
- The cause of the chest pain was identified
- Living outside the catchment area
- No contact established within 3 days of discharge
- Denied participation in the interview/main study
- Coronary angiography performed during index admission
- Did not speak Danish

Assessed for eligibility (n=1241)
by participating in the main study

Excluded
1. Ineligible (n=800)
   Did not return consent form for the main study (n=185)
   Missing information in the charts (n=2)
   No risk factors/known CAD (n=402)
   Referred to cardiac imaging test at discharge
   - Referred for cardiac CT/Coronary (n=152)
   - Referred for coronary angiography (n=26)
   - Referred for myocardial perfusion scintigraphy (n=33)

Eligible (n=441)
Known with ≥ 1 risk factor

Eligible, but not recruited (n=212)
Declined invitation for the CT study (n=152)
Could not find time for participation or did not turn up for the CT scan (n=59)

For analysis (n=229)
Figure 2 shows the inclusion of the patients in the DanRisk study. 1,825 random individuals 50 or 60 years old were invited for study participation. 1,257 accepted the invitation. In total 535 patients were excluded, six did not have a CAC score performed, 16 patients were known with CAD, and 513 did not fulfill the criteria of having at least one risk factor. In total 722 persons from the Danrisk study served as controls for NSCP patients.

**Figure 2: Flowchart for DanRisk**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Participants</th>
<th>Non-participants</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (years/IQR)</td>
<td>57(50-64)</td>
<td>52 (44-60)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male</td>
<td>98 43%</td>
<td>89 42%</td>
<td>0.863</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 10%</td>
<td>10 5%</td>
<td>0.048</td>
</tr>
<tr>
<td>Hypertension</td>
<td>91 40%</td>
<td>70 33%</td>
<td>0.143</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>97 42%</td>
<td>67 32%</td>
<td>0.020</td>
</tr>
<tr>
<td>Family history</td>
<td>124 54%</td>
<td>93 44%</td>
<td>0.031</td>
</tr>
<tr>
<td>Smoking</td>
<td>58 25%</td>
<td>57 27%</td>
<td>0.709</td>
</tr>
</tbody>
</table>

P values compares the proportions of participants and non-participants that are known with the specific variable.
Table 2 lists the baseline characteristics of the NSCP patients and the DanRisk patients. Mean age for the NSCP population was 57 years and 55 years for DanRisk population (p=0.007). A significantly higher proportion of NSCP patients had known hypercholesterolemia and family history of CVD, while more participants in DanRisk were smoking. Furthermore, a significant difference between the populations regarding blood pressure, heart rate and total cholesterol was found.
Table 2: Descriptive characteristics of NSCP and background population.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NSCP population</th>
<th>Background population</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=229</td>
<td>n=722</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>131 (57)</td>
<td>327 (55)</td>
<td>0.476</td>
</tr>
<tr>
<td>Male</td>
<td>98 (43)</td>
<td>295 (45)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>30-39</td>
<td>7 (3)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>46 (20)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>76 (33)</td>
<td>316 (44)</td>
<td></td>
</tr>
<tr>
<td>60-70</td>
<td>100 (44)</td>
<td>406 (56)</td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Odense</td>
<td>70 (31)</td>
<td>175 (24)</td>
<td></td>
</tr>
<tr>
<td>Vejle</td>
<td>63 (27)</td>
<td>171 (24)</td>
<td></td>
</tr>
<tr>
<td>Aabenraa</td>
<td>58 (25)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Svendborg</td>
<td>38 (17)</td>
<td>180 (25)</td>
<td></td>
</tr>
<tr>
<td>Esbjerg</td>
<td>-</td>
<td>196 (27)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>91 (40)</td>
<td>266 (37)</td>
<td>0.458</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>97 (42)</td>
<td>126 (18)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22 (10)</td>
<td>59 (8)</td>
<td>0.509</td>
</tr>
<tr>
<td>Family history</td>
<td>124 (54)</td>
<td>287 (40)</td>
<td>0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>58 (25)</td>
<td>314 (44)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>144</td>
<td>137</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>97</td>
<td>83</td>
<td>0.002</td>
</tr>
<tr>
<td>Pulse (rate/min)</td>
<td>74</td>
<td>71</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol mmol/L</td>
<td>5.2</td>
<td>5.5</td>
<td>0.005</td>
</tr>
<tr>
<td>LDL cholesterol mmol/L</td>
<td>3.1</td>
<td>3.2</td>
<td>0.067</td>
</tr>
<tr>
<td>HDL cholesterol mmol/L</td>
<td>1.4</td>
<td>1.5</td>
<td>0.088</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>27</td>
<td>27</td>
<td>0.715</td>
</tr>
</tbody>
</table>

*P-values estimates for comparison of mean values
The median CAC score for each variable is listed in Table 3. A significant difference was found between patients ≥ 60 years in the NSCP population and the asymptomatic 60 years old patients in DanRisk cohort. Patients with hypertension in the NSCP population also had significantly more CAC than hypertensive DanRisk patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>NSCP Median CAC (IQR) AU</th>
<th>Background population Median CAC (IQR) AU</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>0(0;67)</td>
<td>0(0;18)</td>
<td>0.736</td>
</tr>
<tr>
<td>Male</td>
<td>18(0;83)</td>
<td>9(0;116)</td>
<td>0.117</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>0(0;1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>0(0;5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>0(0;33)</td>
<td>0(0;12.5)</td>
<td>0.247</td>
</tr>
<tr>
<td>60-70</td>
<td>47(0;147)</td>
<td>7(0;110)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odense</td>
<td>0(0;26)</td>
<td>1(0;69)</td>
<td>0.019</td>
</tr>
<tr>
<td>Vejle</td>
<td>8(0;104)</td>
<td>4(0;28)</td>
<td>0.109</td>
</tr>
<tr>
<td>Aabenraa</td>
<td>10(0;120)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Svendborg</td>
<td>16(0;65)</td>
<td>0(0;61)</td>
<td>0.083</td>
</tr>
<tr>
<td>Esbjerg</td>
<td>-</td>
<td>0(0;66)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>30(0;251)</td>
<td>4(0;96)</td>
<td>0.022</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>6(0;94)</td>
<td>14(0;127)</td>
<td>0.878</td>
</tr>
<tr>
<td>Diabetes</td>
<td>61(0;253)</td>
<td>11(0;129)</td>
<td>0.251</td>
</tr>
<tr>
<td>Familiar history of CVD</td>
<td>3(0;72)</td>
<td>1(0;36)</td>
<td>0.198</td>
</tr>
<tr>
<td>Smoking</td>
<td>4(0;133)</td>
<td>5(0;73)</td>
<td>0.607</td>
</tr>
</tbody>
</table>

* P value compares median value of CAC (AU) between NSCP and background population.

The prevalence of CAC score >0 AU was 54 % in the NSCP population and 52 % in the DanRisk cohort (p=0.605). When adjusted for sex, age, hypercholesterolemia, smoking status and family history in a multi-logistic regression analysis no significant difference was found between the presences of CAC in the NSCP population vs the DanRisk cohort (Odds ratio (OR) 1.3 (95%: 0.9-1.9), p=0.126).

During one year follow-up 2/ 229 (0.9%) NSCP patients were revascularised, while no one died from cardiac-related causes, or had an MI, VT or UAP. The two patients with events were a female aged 64 and a male aged 60 years with a CAC score of 349 AU and 2595 AU, respectively. Both were known as hypertension, hypercholesterolemia and a family history of CVD. Fisher’s exact test showed no
statistical difference in endpoints p=0.636 between NSCP and DanRisk. The event rate in the DanRisk population was 4/722 (0.6%) one cardiac-related death, two had MI, and one had VT. All four patients were males. The patient with VT was 50 years and had a CAC=0, but also a family history of CVD. The three other persons in the DanRisk cohort were 60 years old with a CAC score of 166 AU, 832 AU, and 1326 AU respectively. One was a smoker, one had hypertension and hypercholesterolemia, while the last was smoking, had diabetes and a family history of CVD.

Table 4: The distribution of CAC and endpoints for NSCP and background population.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>CAC=0 AU</th>
<th>CAC&gt;0 AU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% (CI)</td>
<td>n</td>
</tr>
<tr>
<td>NSCP</td>
<td>2/229</td>
<td>0.9(0.2-2.9)</td>
<td>0/106</td>
</tr>
<tr>
<td>Background population</td>
<td>4/722</td>
<td>0.6(0.2-1.3)</td>
<td>1/350</td>
</tr>
</tbody>
</table>

Table 4 shows how the clinical endpoints are associated with the prevalence of CAC. No significant difference was found between the numbers of endpoints related to CAC between the groups.

211 patients were referred for further work up from the index contact and not included in this study. 152 went through a cardiac CT, 26 were referred for coronary angiography and 33 for myocardial perfusion scintigraphy. The combined clinical endpoints in this study were 11/211 (5.2%). Two patients had UAP, two had MI and nine had coronary revascularization performed during one year of follow-up. No one had VT or died from cardiac-related causes. Table 5 shows the event rate in those referred directly for cardiac testing is significantly higher compared to the background population and to the NSCP group.

Table 5: number of events in the patients referred directly for cardiac testing, the study population and Background population.

<table>
<thead>
<tr>
<th></th>
<th>Referred for cardiac testing</th>
<th>Study population</th>
<th>Background population</th>
</tr>
</thead>
<tbody>
<tr>
<td>number (n)</td>
<td>211</td>
<td>229</td>
<td>722</td>
</tr>
<tr>
<td>event (n)</td>
<td>11</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>%</td>
<td>5.2</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>CI %</td>
<td>2.8-8.9</td>
<td>0.1-2.9</td>
<td>0.2-1.3</td>
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Discussion

This is the first study to our knowledge to evaluate the role of non-contrast CT in a NSCP population. We showed that CAC can be detected in roughly half of patients with NSCP, and the occurrence does not differ significantly from what can be found in the background population. Furthermore, the CAC prevalence and prognosis for NSCP patients does not differ from the prognosis in the asymptomatic background population. However comparing NSCP patients and background population with those referred for cardiac investigation at index contact showed the latter to have a significantly higher rate of clinical events. Our study demonstrated that results of non-contrast cardiac CT in NSCP patients does not differ from the background population, and we thus do not consider the results of this examination as a potential stratification tool for NSCP patients compared to use of cardiac CT in the background population. The use of cardiac CT scan for CAC appears to be of limited value in the setting of patients with NSCP, and will in the worst case scenario lead to more downstream test utilization.

Laudon et al. (14) showed that in non-cardiac chest pain patients presenting to the ED and fulfilling the criteria for UAP, the prevalence of CAC was 49%, which is consistent with our findings in NSCP patients. Non-cardiac chest pain patients, all though excluded for MI, represent a heterogeneous group and also include patients with other causes of chest pain than cardiac related. In Laudon’s study non-cardiac chest pain patients with a CAC=0 had a 5-year probability of event-free survival of 100%. This was significantly better than the cardiac-related chest pain group, implying that a non-contrast CT scan may be useful in the discrimination between non-cardiac related and cardiac related chest pain. However, the study by Laudon et al included patients fulfilling the criteria for unstable angina, who were scanned during index contact, which makes their patient population a higher risk than our patients. NSCP patients in our study were scanned after discharge and exclusion for high-risk patients that were referred for further investigation at index contact.

The Society of Cardiovascular Computed Tomography Guidelines recommends (15) that patients in the emergency department with acute chest pain, a negative ECG, normal biomarkers and low to intermediate pretest likelihood by risk stratification and in whom a non-coronary cause of the chest pain has been excluded, should be referred for a coronary CT angiography. In the present study we found that patients referred for early further workup, had a one-year event rate of 5 %, as opposed to the approximately 1 % demonstrated in NSCP patients, who from a clinical point of view did not require additional early diagnostic workup. Thus, the current clinical assessment when it comes to risk stratification that distinguishes the patients who need further investigations from the NSCP
patients seems to be efficient. The differences in characteristics between those referred for further investigations and those included in our study (without referral at index contact) is however not further elucidated in this study.

It is not possible to conclude on the prognostic value of CAC in predicting adverse cardiac event due to the low number of event in our study, the short follow up time and a small number of participants. However, the two patients in the NSCP study population experiencing a clinical event had a high CAC score, respectively 349 and 2595, and were known with three risk factors for CVD (hypertension, hypercholesterolemia and a family history of CVD). This may suggest a benefit from combining traditional risk factors with the presence of severe CAC. In concordance with previous studies that found a pooled event rate of 0.3-0.6%/year with CAC=0, the risk of cardiac events is very low when CAC=0 (16). In the NSCP population no events among patients with a CAC=0 was observed, while one person in DanRisk with CAC=0 experienced VT.

The NSCP population consisted of more patients with hypercholesterolemia vs DanRisk (43% vs 18%). We know from previous studies that NSCP is associated with more frequent contacts to the health care system and use of medication than the background population (17). This could partially explain that more patients in this group could have been diagnosed with hypercholesterolemia. However, the higher prevalence of CAC in the NSCP population might be explained by more patients having hypercholesterolemia compared to the DanRisk population. The effect of statins on coronary calcification has also demonstrated conflicting results with a previous study showing a trend toward increasing atheroma calcification with statin use (18).

**Strengths /Limitations**

The outcome data collected from the Danish registries are well documented and validated, which adds strength to this study (19, 20). The patients included in this study are low-risk patients. It cannot be excluded that the participating patients included in this study and DanRisk are healthier as it is known that non-participants in clinical trials are at higher risk and have worse outcomes than participants (21). NSCP and background population were pre-selected and excluded for known CAD and revascularisation or coronary angiography within the last five years, and this excludes the higher risk patients. Conversely, both NSCP and DanRisk participants had to have one risk factor for CAD to fulfill inclusion criteria excluding very low-risk patients without risk factors. Patients who at index admission were referred for further investigations were not included in this study. They could have a higher prevalence of CAC which cannot be accounted for in this study.
Age was also a selection criterion in both studies, focusing on 30-70 years old among NSCP patients and 50 and 60 years old in DanRisk. Both studies are most useful in evaluating the middle age patients. However, we do know that increasing age leads to increased calcification and the use of CAC in an older population is hence not useful. The low age among both populations in contrary could be a causal explanation for the few events taking place.

The definitions of risk factors were not similar. Family history was limited by age in the DanRisk study while no age limitation existed in NSCP patients, and that could explain the higher proportion of patients with family history of CAD among NSCP patients. The data gathering furthermore differed, as NSCP patients were acutely admitted and values were extracted from an acute setting, while DanRisk patients were investigated in a baseline examination. E.g the blood pressures were not obtained uniformly and thus not comparable.

**Conclusion**

Based on the results of this study the occurrence of CAC patients with NSCP does not differ significantly from what is found in the background population when adjusted for established risk factors. Thus, a little more than half of the NSCP patients have detectable CAC on a cardiac CT scan.

Of notice, the prognosis in these patients is excellent with an overall clinical event rate of less than 1%. The results of the present study indicate that patients at increased risk of future clinical events already are being taken care of during the index hospital contact.

**Acknowledgement**

We are indebted to the staff involved in the project at the Department of Cardiology and Nuclear medicine, Odense University Hospital, the Department of Cardiology, Vejle Hospital, the Department of Cardiology and Radiology, Svendborg Hospital and the Department of Cardiology, Hospital of Southern Denmark.
References


## Appendices

### Appendix 1: ICD codes diagnoses

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<tr>
<th>Chest pain groups</th>
<th>Diagnosis</th>
<th>ICD codes</th>
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<td>MI</td>
<td>ST EMI</td>
<td>DI210B DI211B</td>
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<tr>
<td></td>
<td></td>
<td>DI213B DI210A</td>
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<tr>
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<td>DI213 DI211A</td>
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<td>DI249 DI256</td>
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<td>NST EMI</td>
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<td>DI219 DI210</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
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<td>NSCP</td>
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<td>Other hear related conditions</td>
<td>Pulmonary embolus</td>
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<td>Pericardial diseases</td>
<td>DI318 DI319 DI319A DI313 DI300 DI301A-E DI301 DI308 DI309 DI311</td>
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<td>Aortic valve diseases</td>
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<td>Block</td>
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<td>Ventricular arrhythmia</td>
<td>DI472 DI472A-E DI472M DI470 DI471</td>
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<td></td>
<td>Aortic dissection/aneurism</td>
<td>DI710 DI710A DI710B DI711 DI712 DI713 DI715 DI718 DI719</td>
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Appendix 2

The questionnaire used for the phone interview
–translated from Danish to English

**Patients with non-specific chest pain**
- risk stratification and prognosis

The accentuated text is the questions, and the italic is the possible answers

**The patient agrees to participate in the project?**
Yes / No / not participating

**Symptoms**
Did chest pain cause your visit to the hospital?
Yes / No

**How would you describe your chest pain?**
*Stinging, Burning, crushing, pressing, other, please specify __________, Do not know*

**Where did you could feel the pain?**
*Left breast, Right Breast, behind the sternum, The back, The shoulder blades, Belt-shaped at the chest, The right arm, Left arm, The jaw, The stomach, the collarbones, The neck, Other, please specify _____, don't know*

**What were your symptoms?**
*Optional answer*

**When did your pain start?**
*Date/Time*

**How strong were your pains on a scale from 1-10, when it was at its worst, and where 10 is the worst pain you can imagine?**
*1-10*

**Did you have other symptoms related to your pain?**
*Fatigue, dizziness, shortness of breath, palpitations, Headache, Nausea, cough, Abdominal Pain, No other symptoms, other?*

**Was the pain constant or intermittent?**
*Constant / Intermittent*

**How did you arrive at the hospital?**
*Called the emergency service/Out of hours medical service/Own request/referral by GP/ Other:___________*

**What exacerbated the symptoms?**
*Physical activity/Cold/mental stress/other*

**What relieved the symptoms?**
*Nitroglycerin/Rest/Oxygen/Other:*
Previous Angina Pectoris
Have you previously experienced chest pain
Yes/No

Have you previously visited a physician due to chest pain?
Yes/No

What was the cause of the pain?
Free text

Have you previously been told you have heart failure or coronary calcification?
Yes/No

If yes

CCS classification
I: do you have pain with strenuous work?
II Do you experience chest pain related to fast stair walk and walk?
III: do you experience chest pain at walking shorter distance than 200 m on regular terrain?
IV: Do you experience pain at the least activity?
V: No discomfort at all?

NYHA classification
Do you experience dyspnoea in everyday life and how much?
I: No limitation at all
II: Normal physical activity gives short breathe
III: Less strenuous activity gives shortage of breath
IV: Inconvenience at the least activity, also in rest

Do you have other heart conditions?
Yes/no

Do you have
Diabetes/ hypertension/ hypercholesterolemia?
If yes, for how many years

Other known diseases?
Optional answer

Did your parents have calcification or thrombus in the heart or brain?
One parent/both parents/no parents

Are your siblings known with calcification or thrombus?
Yes/No

How many siblings?
Optional answer

Are you previous or current smoker?
Occasional smoker: less than 30 cigarettes in a month. Previous smoker: smoking ended more than a month ago.
Previous/current/never smoker/occasional smoker

How old were you when you started smoking?
Optional answer
How many cigarettes in average do you smoke a day?  
Optional answer

How old were you when you quit smoking?  
Optional answer

How many items of alcohol in average do you drink per week?  
Optional answer

What is your weight?  
Optional answer

What is your height?  
Optional answer

What do you do for a living?  
Working, pension, flex job, not working, partial sick leave, full-time sick leave, working part-time, student

Describe your job?  
Unskilled worker/shorter higher education/Medium length higher education/Longer higher education/ self-employed/Vocational education

Have you been referred for further investigation of your heart after your visit?  
Yes/No

Have you previously had any cardiac investigation done like a scan?  
Yes/No

If yes which investigation?  
Optional answer

Some of you would be candidates for another study with a non- contrast CT scan. Can I send you some information if you are eligible for this study?  
Yes/No

Can I get access to your patient chart for this study regarding information on admission, medication and blood test?  
Yes/No

We also need to written permission to access your chart. I will send you some written information and consent to sign. What is your address?  
Optional answer

The reason patient didn't participate in the study?  
Not at home/Pt not capable to participate/Did not speak Danish/ Phone number was not working/other reason.
Appendix 3: Chart review

The accentuated text is the questions, and the italic is the possible answers

Did the patient?
Fulfil the inclusion criteria
Have a coronary angiography during admission
Have an obvious cause of the chest pain
Been treated for UAP
Not relevant cause of admission
Other

What was the cause for the visit?
Chest pain
Radiation
Other?

Was the patient referred for other examination at the discharge? If so which one?
Cardiac CT
Myocardial scintigraphy
Coronary angiography
Holter monitoring
Coronary artery bypass grafting
Stress test
Echocardiography
Outpatient clinic
Other

Did the patient have an echocardiography during index admission?
Yes normal EF
Yes, abnormal EF (<55%)
No

Clinical values
- associated with the index admission. The first measured
Temperature
Pulse
Saturation with and without oxygen
Respiratory frequency
Systolic blood pressure
Diastolic blood pressure

ECG
Heart rate on the ECG
ECG diagnosis
Sinus rhythm
Sinus arrhythmia
Sinus bradycardia
Sinus tachycardia
Supraventricular tachycardia
ST elevation
ST depression
T wave inversion
Left bundle branch block
Right bundle branch block
Ventricular tachycardia
First degree AV nodal block
Second or third degree AV nodal block
Sinus atrial block
Q waves

If abnormal ECG:

ST elevation
New / previous known / no previous ECG to compare

ST depression
New / previous known / no previous ECG to compare

T wave inversion
New / previous known / no previous ECG to compare

Bundle branch block
New / previous known / no previous ECG to compare

Q wave in which derivations?
Free text