UiT The Arctic University of Norway

Faculty of Health Sciences, Department of Clinical Medicine

Clinical characteristics, mortality and pain tolerance in stable versus acute presentation of coronary heart disease

Kristina Fladseth

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Summary

Despite immense progress in the prevention, diagnosis and treatment of coronary heart disease, several challenges remain. In more than half of patients referred to coronary angiography for stable and unstable angina, no obstructive coronary artery disease (CAD) is found. At the same time, some patients present for the first time with already extensive CAD. Further, the management of unstable angina patients after implementing high-sensitivity troponins is uncertain. We investigated if we could improve the selection of unstable angina patients to coronary angiography, the outcomes of unstable angina compared to stable angina and myocardial infarction (MI), and how pain tolerance affects when and how CAD presents.

We applied data from patient hospital records, the local and national coronary angiography registry and the Tromsø Study. Pain tolerance was assessed using a cold pressor test in the Tromsø Study. Paper I is a retrospective cohort study, while papers II and III are prospective cohorts studies. We used logistic regression and Cox proportional hazard regression analyses. In paper I, adding symptom characteristics to cardiovascular risk factors, we created a risk score to predict obstructive CAD in unstable angina patients. This score performed better than guidelines and other risk scores. In paper II, we found that unstable angina patients had a similar risk of cardiovascular events but a higher risk of death than stable angina patients. Unstable angina had a lower 1-year risk of cardiovascular events and death than non-ST segment elevation MI. In paper III, individuals with low pain tolerance had a higher risk of coronary angiography, obstructive CAD and death. Pain tolerance was not associated with the clinical presentation or extent of CAD.

Our findings confirm that unstable angina patients have a better prognosis than MI patients and support the newest guidelines recommending fewer invasive coronary angiographies in unstable angina patients. The discrepancy in when and how CAD presents is still unclear, and further studies are warranted.

Sammendrag

Til tross store framskritt i forebygging, diagnose og behandling av koronarsykdom gjenstår flere utfordringer. Over halvparten av pasientene som henvises til koronar angiografi for stabil og ustabil angina har ingen obstruktiv koronarsykdom. Samtidig er det noen pasienter som fanges opp først når de har utviklet langtkommen koronarsykdom. Implementeringen av høy-sensitive troponiner har endret diagnostikk og behandling for pasienter med ustabil angina. Vi har undersøkt om det er mulig å bedre seleksjonen av pasienter med ustabil angina til koronar angiografi, overlevelsen etter ustabil angina sammenlignet med stabil angina og hjerteinfarkt, og hvordan smertetoleranse påvirker når og hvordan koronarsykdom presenterer seg.

Vi har brukt data fra pasientjournaler, det lokale og nasjonale angiografiregisteret og Tromsøundersøkelsen. Smertetoleranse ble testet med kuldesmertetest i Tromsøundersøkelsen. Artikkel I er en retrospektiv kohortstudie, mens artikkel II og III er prospektive kohortstudier. Analysene er utført med logistisk regresjon og Cox proporsjonal hasard regresjon. I artikkel I utarbeidet vi en risikoskår som benyttet symptomer i tillegg til kardiovaskulære risikofaktorer til å predikere obstruktiv koronar sykdom hos pasienter med ustabil angina. Denne skåren presterte bedre enn retningslinjer og andre etablerte risikoskårer. Videre fant vi i artikkel II at pasienter med pasienter med ustabil angina henvist til koronar angiografi hadde lik risiko for kardiovaskulære hendelser som stabil angina, men høyere risiko for død. Ustabil angina hadde lavere risiko for død og kardiovaskulære hendelser enn pasienter med akutt hjerteinfarkt uten ST-elevasjoner det første året etter koronar angiografi. Artikkel 3 fant at individer med lav smertetoleranse hadde høyere risiko for koronar angiografi, obstruktiv koronarsykdom og død. Smertetoleranse var ikke assosiert med klinisk presentasjon av koronarsykdom eller ikke-obstruktiv koronarsykdom.

Våre funn bekrefter at pasienter med ustabil angina har bedre prognose enn pasienter med hjerteinfarkt. De støtter også nye retningslinjer som anbefaler mindre bruk av invasiv koronar angiografi hos ustabil angina pasienter. Variasjonen i når og hvordan pasienter med koronarsykdom presenterer seg til koronar angiografi er fortsatt uklar og ytterligere studier er nødvendig.

List of papers

I. Pre-test characteristics of unstable angina patients with obstructive coronary artery disease confirmed by coronary angiography
Open Heart 2018;5:e000888

II. Outcomes after coronary angiography for unstable angina compared to stable angina, myocardial infarction and an asymptomatic general population
Under revision

III. Low pain tolerance is associated with coronary angiography, coronary artery disease and mortality: The Tromsø Study
Journal of the American Heart Association 2021;0:e021291

Abbreviations

ACS	Acute coronary syndrome
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CI	Confidence interval
CHD	Coronary heart disease
ESC	European Society of Cardiology
FFR	Fractional flow reserve
GRACE	Global Registry of Acute Coronary Events
HR	Hazard ratio
hs-cTn	High-sensitivity cardiac troponin
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
MINOCA	Myocardial infarction with non-obstructive coronary arteries
NORIC	Norwegian Registry of Invasive Cardiology
NPV	Negative predictive value
NSTE-ACS	Non-ST-segment elevation acute coronary syndrome
NSTEMI	Non-ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
RCT	Randomised controlled trial
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction
UNN	University Hospital of North Norway

1 Introduction

Coronary heart disease (CHD), also known as ischemic heart disease, remains one of the leading causes of mortality and morbidity in Norway and the rest of the world (1). There have been tremendous advances in the prevention, diagnosis and treatment of CHD, but several challenges remain. In clinical practice, over half of elective invasive coronary angiographies and up to 80% of coronary computed tomography angiography (CCTA) reveal no obstructive coronary artery disease (CAD) (2-6). At the same time, over one-third of myocardial infarctions (MI) are unrecognised, and up to 15% of CHD presents with sudden cardiac death (7-10). Studies have also demonstrated that non-obstructive CAD is not as benign as previously thought but is associated with increased mortality and morbidity (11-13). The management and prognosis of unstable angina in the high-sensitivity cardiac troponin (hs-cTn) era are unsure. Appropriate identification and management of high-risk individuals are essential to improve prognosis. In contrast, low-risk individuals should be deferred to prevent adverse effects from unnecessary testing and treatment and contribute to better resource utilisation. This thesis explored the association between the clinical presentation, findings on coronary angiography, pain tolerance, and outcomes of different clinical presentations of CHD.

1.1 Epidemiology

1.1.1 Mortality

Over the past four decades, there has been a marked reduction in age-adjusted CHD death in most high-income countries, with well over 50% reduction in many countries (1, 14, 15). In Norway, the age-adjusted mortality has fallen from 431 per 100 000 in 1972 to 74 per 100 000 in 2018. This is among the lowest rate of high-income countries (1, 16, 17). The decline in CHD mortality is caused by lower incidence and improved survival of CHD, with a distinct shift towards higher age at the time of death (9, 18-21). The largest contributor is the lower burden of cardiovascular risk factors in the population, followed by improvements in preventive therapy, initial treatment of acute coronary syndrome (ACS) including revascularisation, and better heart failure treatment (9, 21-23). Nevertheless, despite the tremendous progress, CHD causes 15% of deaths in Norway and remains a leading death

cause globally (1, 16, 17, 24). Further, many low and middle-income countries experience rising CHD mortality (1, 24).

1.1.2 Incidence

The annual incidence of an incident hospitalised MI in Norway is estimated to be around 400 per 100,000 individuals overall and 250 per 100,000 individuals age-standardised, and has declined around 3% annually for the last three decades (9, 16, 21, 25). This is comparable to other high-income countries (20, 26-28). The incidence of unstable angina and stable angina is more uncertain due to the lack of objective criteria and definitions. In Finland, the annual incidence of stable angina was 465 per 100,000 individuals aged 45 years or older (29). According to the Norwegian Patient Registry data, around 300 per 100,000 individuals aged 30 years or older were treated for stable angina per year in Norway's secondary health care system (30). Unstable angina had an annual incidence of 64 per 100,000 individuals in another Finnish study, comparable to the 54 per 100,000 individuals per year in the Norwegian patient registry (30, 31). A younger Danish population aged 30 to 69 years old found a lower annual incidence of 39 per 100 000 individuals (32).

The incidence of chest pain and suspected CHD is much higher than the confirmed cases of CHD. Around 5-20% of patients presenting to the emergency department with acute chest pain have a final diagnosis of MI or unstable angina (33-36). In Norway, the annual incidence of a visit to an emergency department is 1,200 per 100,000 individuals, and 11% have chest pain as the main symptom (36, 37). Around 1.5% of visits in primary care are due to chest pain (38). The annual incidence of first-time nitrate prescription in Finland was 1,960 per 100,000 individuals aged 45 years or older (29).

1.1.3 Prevalence

The CHD prevalence is around 4-6%, with an age-dependent increase from <1% in adults under 40 years to around 25% in individuals aged 80 years and older (39-41). One-fifth of the population in Norway are prescribed at least one drug for cardiovascular diseases (42). Despite the falling incidence of CHD, the prevalence of CHD is expected to rise over the next decades due to the ageing population and improved survival of CHD (42-44). Combined with more advanced diagnostic and treatment options, health care expenditures for CHD are expected to rise (42, 43).

1.1.4 Outcomes

The risk of adverse outcomes after CHD depends on the clinical presentation, the extent of CAD and underlying comorbidities, including age and chronic kidney failure (45-47). Therefore, the outcomes rates vary considerably between studies based on study population selection and inclusion and exclusion criteria. The 1-year incidence of death and MI varies from 1-2% and 1-4% in stable angina patients, 1-7% and 5% in unstable angina patients, and 5-23% and 6-11% in MI patients, respectively (46-56). The Norwegian Myocardial Infarction Registry reports an age-adjusted 30-day and 1-year incidence of death in hospitalised MI patients under 80 years of 6% and 10%, respectively (25). Heart failure is a common complication that worsens the outcome after CHD (57). A study from Norway found that 20% of patients with acute MI had evidence of heart failure at initial presentation or during hospital admission. An additional 10% developed heart failure during the first years after discharge (57). This was similar to a study from Sweden (48). Other prevalent outcomes include angina, repeat coronary angiography and revascularisation, stroke, major bleeding and arrhythmia. Reduced quality of life, depression and anxiety are also more frequent (58). In addition to declining CHD mortality, recurrent MI and heart failure rates are likely also decreasing (59, 60).

Patients with stable angina with angiographically no CAD or non-obstructive CAD have a higher risk of death and major cardiovascular events compared to a general population, as well as high prevalence of persisting angina, low quality of health and high rate of repeat cardiovascular hospitalisation (3, 11-13, 61, 62). Further, MI with no obstructive coronary atherosclerosis (MINOCA) have lower mortality than MI with obstructive CAD, but similar rates of major cardiovascular events as MI with 1-vessel disease or 2-vessel disease (63, 64).

1.1.5 Risk factors

The main risk factors of CHD are well established, including the non-modifiable risk factors of age, sex, family history of CHD and ethnicity, and the modifiable risk factors of smoke, hypertension, hypercholesterolemia, diabetes, obesity, physical inactivity and diet (65, 66). Other known CHD risk factors include chronic kidney disease and inflammation (67, 68). Studies estimate that smoking, hypertension, hypercholesterolemia, diabetes and obesity account for 50% of deaths due to cardiovascular disease. Further adding physical inactivity, psychosocial burden, low consumption of fruits and vegetables, and high alcohol consumption account for 90% of MIs (65, 69). Another study demonstrated that 90% of CHD

events occur in individuals who either smoke, have diabetes, hypertension or dyslipidaemia (70). The population prevalence of smoking, hypertension and hyperlipidaemia is declining and greatly contributes to the lower incidence and mortality of CHD (9, 71). The prevalence of obesity and diabetes is increasing, but the accompanying increased risk of CHD is still being outweighed by the reduced prevalence of the other risk factors (9, 71, 72).

1.2 Pathogenesis and pathophysiology

Coronary artery disease is the pathological process affecting the coronary arteries leading to CHD. It may also be used synonymously with CHD. The main substrate of CAD is atherosclerosis forming plaques in the artery walls (73, 74). Multiple factors contribute to atherosclerosis, including endothelial dysfunction, inflammation, immunological factors, dyslipidaemia, and other traditional CHD risk factors (73, 74). Autopsy reports and newer imaging techniques of the coronary arteries demonstrate that the build-up of fibrofatty lesions begin in early life and advance with age (75-77). A process of inflammation, necrosis and fibrosis evolve the lesions into atherosclerotic plaques with a fibrous cap around a lipid-rich, necrotic core (74). Plaque rupture or erosion may further complicate the lesions with thrombosis and subsequent healing and remodelling of the plaque (78-80). These processes may obstruct coronary blood flow, causing myocardial ischemia with the myocardial oxygen demand exceeding the myocardial oxygen supply, leading to a supply-demand imbalance (81, 82). Unstable angina and MI are usually caused by plaque rupture or erosion causing luminal thrombosis, while stable angina is most often caused by large plaques causing luminal narrowing and stenosis (74, 78, 79, 83). However, since the implementation of coronary angiography, it has been evident that not all patients with CHD had obstructive CAD in the epicardial coronary arteries explaining their clinical presentation (84). Potential mechanisms include plaque rupture or erosion from non-obstructive plaques with spontaneous fibrinolysis, coronary vasospasm and coronary microvascular dysfunction (85, 86). Coronary vasospasm is severe vasoconstriction of either normal or atherosclerotic coronary arteries, caused by hyperreactive vascular smooth muscle cells or endothelial dysfunction. Microvascular dysfunction is a dysfunction of the small coronary arteries leading to impaired coronary flow reserve, despite no epicardial obstruction. These mechanisms may occur separately or in combination and may also be precipitated by other conditions like arrhythmias, severe hypertension, severe anaemia, respiratory failure, and hypotension (79, 86).

1.3 Clinical presentation and diagnosis

The clinical course of CHD involves stable symptomatic and asymptomatic phases referred to as chronic coronary syndrome, interrupted by episodes of ACS (79, 87, 88). ACS encompasses acute MI (80%) and unstable angina (20%) (34, 89, 90). The most common presentation of ACS is acute chest pain/discomfort, present in around 90% of patients (91, 92). Exertional chest discomfort relieved by rest or nitrates is the typical presentation of stable angina (79, 93, 94). Other clinical presentations of CHD include arrhythmia, heart failure or sudden cardiac death. Further, myocardial ischemia and significant obstructive CAD may be present without any symptoms, and one-third of MIs are unrecognised (7, 8, 95, 96).

A patient presenting with suspected ACS should quickly be assessed with an electrocardiogram and identified as either ST-segment elevation MI (STEMI) or non-ST segment elevation ACS (NSTE-ACS). NSTE-ACS includes NSTEMI and unstable angina. NSTEMI is diagnosed based on evidence of acute myocardial ischemia and acute myocardial injury detected by a rise and/or fall in cardiac troponins with at least one value over the 99th percentile. Unstable angina is diagnosed if no acute myocardial injury is detected (97-100). The current definition of MI using the 99th percentile of hs-cTn led to a 4% absolute and 20% relative increase in the detection of NSTEMI, with a reciprocal decrease in unstable angina (90, 101).

The diagnosis of unstable angina and stable angina is mainly based on symptoms believed to be caused by myocardial ischemia and thus less objective than the diagnosis of MI which includes the objective criteria of a rise and/or fall in troponin. Suspected anginal symptoms may be classified as typical angina, atypical angina and non-cardiac chest pain based on the presence of three, two or one of the following clinical characteristics: 1) Chest pain/discomfort of characteristic localisation and quality, 2) provoked by exertion or emotional stress, and 3) relieved by rest or nitrates within five minutes (79). Typical angina is most likely caused by myocardial ischemia and obstructive CAD but only occurs in 10-15% of patients (5, 93, 102, 103). Unstable angina may present as angina at rest, new-onset angina, or destabilisation of a previously stable angina (79, 98).

1.4 Coronary angiography

Coronary angiography is the cornerstone in the diagnosis and treatment of CHD. Invasive coronary angiography detects CAD using x-rays and contrast injection into the coronary

arteries through a catheter from the radial or femoral artery. It may also be supplemented with techniques such as fractional flow reserve (FFR) to measure if a stenosis causes significant obstruction in the blood flow. Invasive coronary angiography is the gold standard for diagnosing CAD, and it is possible to directly perform percutaneous coronary intervention (PCI) to revascularise an obstructed coronary artery (79, 88, 104). Invasive coronary angiography and PCI is performed acutely in most ACS patients (97, 98, 104). Possible complications from invasive coronary angiography and PCI includes local vascular complications, perforation, stroke, MI and death (105, 106). Invasive coronary angiography alone has a relatively low risk of severe complications at around 1%, but the risk of complications is higher for more complex CAD and PCI (107). It is also a relatively costly procedure performed by specialised invasive cardiologists at tertiary hospitals. Coronary CT angiography is more available and associated with fewer complications than invasive coronary angiography. It uses intravenous contrast and a CT scanner to visualise the coronary arteries. During the last decade, it has been increasingly applied in the diagnostic evaluation of stable chest pain patients and low-risk ACS. Several studies have demonstrated high negative predictive values (NPV) to rule out CAD but lower specificity (108-110).

1.5 Risk stratification

Several risk stratification models and tools have been developed to guide management and treatment in individuals with established CHD or high risk of CHD. NORRISK 2 is a Norwegian risk score that predicts the 10-year risk of cardiovascular death or non-fatal stroke and MI in individuals with no prior CHD based on age, sex, smoking status, cholesterol levels, hypertension, use of antihypertensive drugs, and a family history of premature MI (111). Other scores, including the CAD consortium score and the updated Diamond-Forrester score, predict obstructive CAD in patients with suspected stable angina based on cardiovascular risk factors and symptoms (94, 102, 112). For the acute chest pain population, the HEART score uses the clinicians' suspicion, electrocardiogram, troponin, age and cardiovascular risk factors to predict cardiovascular events (113). In patients with established ACS, the GRACE (Global Registry of Acute Coronary Events) risk score and TIMI (Thrombolysis In Myocardial Infarction) score predicts prognosis (46, 114).

1.6 Pain tolerance

The reason why some patients present with angina and non-obstructive CAD, some have unrecognised MIs, and some have an initial presentation of CHD as either MI and three-vessel disease, or even sudden cardiac death is not known. Differences in pain tolerance have been suggested as a potential explanation (115). A study from the Tromsø study demonstrated that patients with unrecognised MI had higher pain tolerance than individuals with recognised MI (7). Patients with high pain tolerance may fail to recognise their symptoms and seek medical care (7). A small study of stable chest pain patients demonstrated that the 12 patients with normal coronary arteries had lower pain tolerance than ten patients with obstructive CAD (116). Further, a small study performing a stress test on stable angina patients found that patients with low pain tolerance experience angina earlier than patients with high pain tolerance (117).

1.7 Aims

This thesis aimed to investigate 1) whether a better pre-test selection of unstable angina patients before coronary angiography is possible, 2) to compare the outcomes after coronary angiography for unstable compared to stable angina, MI and an asymptomatic general population, and 3) to investigate if pain tolerance may explain the differences in clinical presentation and outcomes of CHD.

2 Methods

2.1 Study settings

The University Hospital of North Norway (UNN) Tromsø is the local hospital for 120,000 inhabitants in the Tromsø area and the tertiary care hospital for the 480,000 inhabitants of Northern Norway. It was the sole provider of coronary angiography in Northern Norway until 2020. Tromsø is the largest city in Northern Norway, with around 75,000 inhabitants. Northern Norway is a vast geographical region with an area of 113,000 km^2. There are 12 other hospitals in the region, including Longyearbyen hospital. The air distance from UNN Tromsø to the other hospitals ranges from around 135 km to 550 km, and 890 km, including Svalbard. The population of Northern Norway is predominantly Caucasian.

2.2 Data source

The data for this thesis was obtained from coronary angiography registries, patient hospital records, the Tromsø Study, the Norwegian National Registry and the Norwegian Cause of Death Registry. The 11-digit national personal identification number allowed linkage on an individual level.

2.2.1 Coronary angiography registries

From 1 January 2005, UNN Tromsø has recorded data on all consecutive invasive coronary angiographies, first in a local quality registry and from 1 May 2013 in the national Norwegian Registry of Coronary Angiography (NORIC). Data from CCTA has been recorded since the implementation in clinical practice. First in a local quality registry from 1 January 2013 to 31 December 2015, and in NORIC from 1 January 2016. From 2005 to 2018, there were around 27,500 invasive coronary angiographies and 1,500 CCTA procedures in the local registries and NORIC.

The interventional cardiologist and cardiac radiologists record data for each consecutive coronary angiography at the time of the procedure. This includes prior CAD and revascularisation, cardiovascular risk factors, symptoms, presentation and indication, findings and treatment. NORIC has over 99% coverage for invasive coronary angiography (4). In addition, NORIC contains predefined constrictions to avoid misclassifications. Suspected

misclassifications in the local quality registries were manually examined and updated according to the patients' hospital records, including stable angina and acute coronary angiography, ACS and elective coronary angiography, non-obstructive CAD and revascularisation, thrombolysis and no STEMI.

2.2.2 Patient hospital records

For paper I, we retrospectively collected more comprehensive data on clinical presentations and examinations before coronary angiography from the patient records at UNN. The candidate performed the data collection under close supervision by the supervisor, an experienced cardiologist. The data was plotted in EpiData Entry version 2.0.5.17 (EpiData Association, Odense, Denmark) with defined reference values to minimise potential errors. Only records before the invasive coronary angiography report were opened to avoid bias. Further, we performed a trial data collection of twenty patients. Based on this, we compiled a written guide for the data collection (Appendix). The written guide was updated as new challenges arose.

For papers II and III, the patient hospital records were used to resolve misclassifications in the coronary angiography registries.

2.2.3 The Tromsø Study (paper II and III)

The Tromsø Study is a single-centre, prospective cohort study with repeated health surveys in the municipality of Tromsø, Norway (118). This thesis uses data from the sixth survey of the Tromsø Study (Tromsø6) conducted from 2007 to 2008 (119). It invited entire birth cohorts and samples of birth cohorts with a total of 12 984 participants (66% attendance rate). The participants were 30 to 87 years old (mean age of 58 years), with 53% women. Data collection was performed as self-administered questionnaires, blood samples, and clinical examinations, including a cold pressor pain test.

The Tromsø Study have an independent endpoint committee that has validated all MI according to modified international criteria based on patient records and death certificates until 2012 at the time of data extraction (120). Possible cases were found by screening the hospital discharge diagnosis registry and the Norwegian Cause of Death Registry for International Classification of Disease 9th revision (ICD-9) codes 410-414, 430-438, 798-799 for 1994-1998, and then IDC-10 codes I20-125, I60-I69, R96, R98, and R99.

2.2.4 The Norwegian National Population Registry and the Norwegian Cause of Death Registry

In papers II and III, we collected data on death causes from the Norwegian Cause of Death Registry until 2017 and information on deaths from the National Population Registry in 2018. The National Population Registry is continuously updated and contains information on all residents in Norway and registered Norwegians, including fatalities. Norwegian Cause of Death Registry is a mandatory national registry containing information on the cause of all deaths occurring in Norway and the deaths of registered Norwegians occurring in other countries. The registry has over 98% completeness of medical information and coverage compared to the National Population Registry (121). However, the low rate of post-mortem exams in Norway and the use of unspecified and not meaningful diagnoses as the underlying death affects the data quality (121).

2.3 Study population

Paper I was a retrospective cohort study of the 1,936 invasive coronary angiographies performed in patients with a presumed diagnosis of unstable angina from 2005 to 2012 from the primary catchment area of UNN Tromsø. We excluded patients with a peak troponin value of the 99th percentile (n=813), consecutive procedures within the same admission (n=35), misclassifications (n=76), and patients with PCI within the last 30 days (n=33) as 91% of these patients had obstructive CAD (Figure 1).

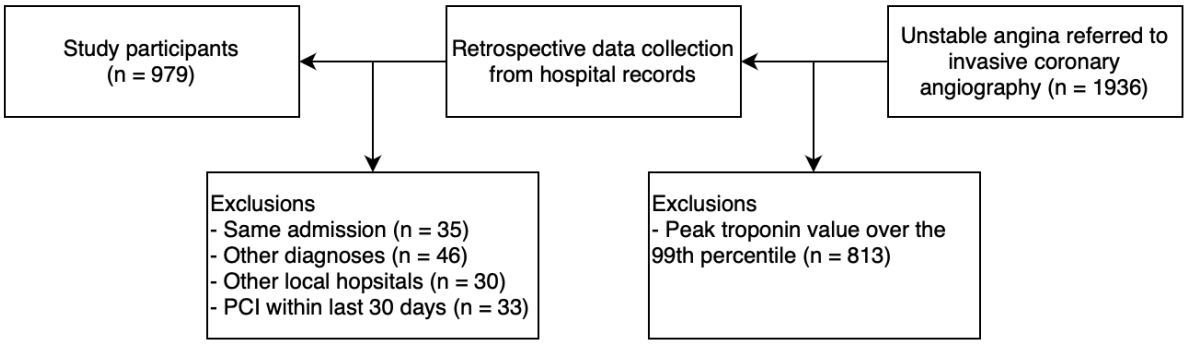

Figure 1. The study population for Paper I - Pre-test characteristics in unstable angina patients with obstructive coronary artery disease confirmed by coronary angiography.

Paper II was a prospective registry-based cohort of 13,214 individuals referred to coronary angiography for stable angina, unstable angina, NSTEMI or STEMI, and an asymptomatic

general population with 12,984 individuals recruited from Tromsø6. Individuals with prior CAD, misclassifications, other indications for coronary angiography, individuals aged<30 years and anamnestic angina were excluded (Figure 2).

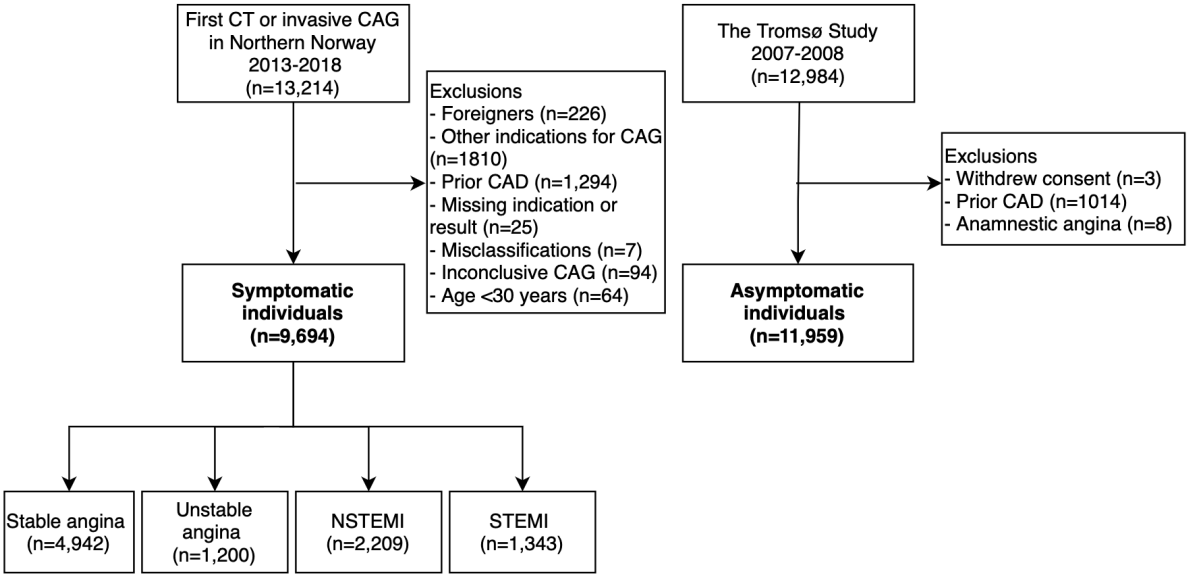

Figure 2. Selection of study participants for paper II – Outcomes after coronary angiography for unstable angina compared to stable angina, myocardial infarction and an asymptomatic general population

Paper III was a prospective cohort of 10,486 individuals that completed the cold pressor test in Tromsø6. We excluded all individuals with prior MI or coronary angiography (n=722), self-reported angina who underwent coronary angiography within 180 days (n=6), other indications for coronary angiography (n=175), missing indication or an inconclusive result of coronary angiography (n=7) (Figure 3).

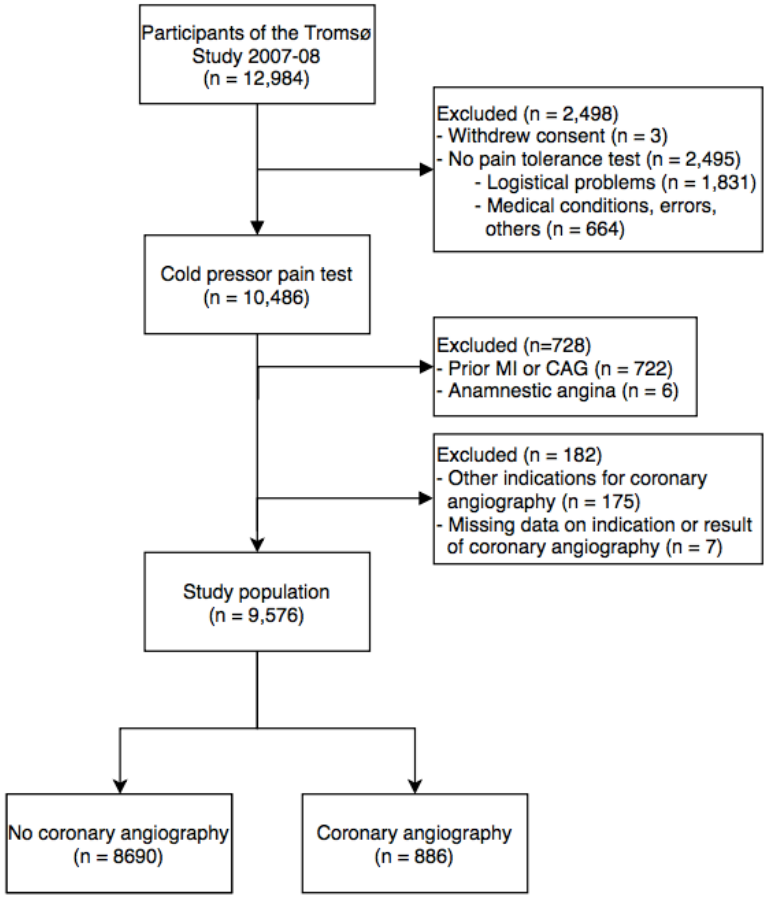

Figure 3. Selection of study participants for paper III – Low pain tolerance is associated with coronary angiography, coronary artery disease and mortality: The Tromsø Study

2.4 Exposures and covariates

2.4.1 Extent of coronary artery disease

The extent of CAD was assessed by the interventional cardiologist or the cardiac radiologist. Obstructive CAD was defined as ≥50% diameter stenosis or FFR below 0.8 in any epicardial coronary artery. FFR was generally measured when the coronary artery had visual diameter stenosis around 40-70%. Obstructive CAD was further described as a one-vessel disease, two-vessel disease, three-vessel disease or left main stem disease. Non-obstructive CAD was defined as 0-49% diameter stenosis. Procedures within seven days were included as one admission. We systematically reviewed the use of FFR, the extent of CAD, revascularisation and the order of procedures to establish the overall conclusion for each admission. CCTA procedures with obstructive CAD or inconclusive results, followed by an invasive coronary angiography in 180 days, were replaced with the results from the invasive coronary angiography.

In paper I, prognostically significant CAD was defined as obstructive CAD in the left main stem, proximal left anterior descending artery or three vessel-disease (65, 122).

2.4.2 High-sensitivity troponins and definition of unstable angina and myocardial infarction

High-sensitivity cardiac troponin assays were implemented in Norway during 2009, and the current definition of MI based on evidence of myocardial ischemia and a rise and/or fall of cardiac troponins with a least one value over the 99th percentile was implemented during 2012 and 2013 (99, 100, 123). A rise and/or fall of at least 20% is considered significant (99, 100). If one of the values are under the 99th percentile, a significant difference is ≥50% (99, 100). At UNN Tromsø, the hs-cTnT assay replaced the Roche fourth-generation troponin T in July 2009. The local coronary angiography registry includes the peak troponin value for around 90% of NSTE-ACS patients with UNN Tromsø as their primary hospital (34%). NORIC recorded the peak troponin value before and after invasive coronary angiography in 70% of unstable angina and 43% of NSTEMI patients. The definition of unstable angina, NSTEMI and STEMI is made by the interventional cardiologist at the time of the procedure based on the current guidelines. Generally, unstable angina would be diagnosed if chest pain at rest, new-onset angina or rapidly worsening angina, and no significant rise/and fall in troponin (88, 97).

In paper I, we excluded patients with chronically elevated troponins over the 99th percentile. These patients had a higher risk of CAD and should likely receive coronary angiography at a lower threshold. A fourth-generation troponin T value of 10 ng/L corresponds to around 30 ng/L with the hs-cTnT assay. Therefore, the troponin values measured by the fourth generation assay were multiplied by three to adjust for this (124, 125).

2.4.3 Clinical characteristics (Paper I)

We registered the angina threshold before admission by the Canadian Cardiovascular Society grading of angina pectoris (126). A variation in the angina threshold of two or more grades was defined as a variable threshold. A falling threshold of angina was not included as a variable threshold. Refractory angina was recorded if intravenous nitrates were administrated to the patient. We defined a history of typical angina as (1) retrosternal chest pain or discomfort, (2) provoked by physical exertion or emotional stress and (3) relieved by rest within minutes. Atypical angina was defined as two of these characteristics, and patients with

one of these characteristics were defined as having non-anginal chest pain. A positive stress test was defined as ≥1 mm of ST-segment depression or elevation in the electrocardiogram or stress-induced chest pain. The guideline criterion of acute heart failure was defined as Killip class II-IV. We calculated the GRACE risk score applying the Fox model for death between hospital admission and six months (127).

2.4.4 Pain tolerance and the cold pressor test (Paper III)

The cold pressor test is a well-established experimental pain test and a traditional test of vasospastic angina (128). The test uses cold, circulating water to activate the venous nociceptor and induce a deep aching pain (129, 130). In Tromsø6, the cold pressor test was performed on 10,486 participants (81% sampling rate). The main reason for not undergoing the test was insufficient testing capacity during peak hours (n=1,831). Participants under 60 years old were prioritised (100% sampling rate) as the attendance rate was lower. Other reasons for not having the test were technical and procedural errors, participant refusal or incomprehension, and medical conditions that could interfere with or lead to adverse reactions to the test (n=664). The cold pressor test was performed using a Julabo FP40HE (Julabo Labortechnik GmbH, Germany) connected to a 13-L external plexiglass container, with a calibrated water temperature of 3.0°C and a flow rate of 22 L/min. After a verbal explanation of the test, the participants were asked to place their dominant hand and wrist into the cold water and hold it there as long as they could endure, up to a maximum of 106 seconds. Pain tolerance was defined as endurance time. As most participants endured to the end of the test, we defined high pain tolerance as maximum endurance and low pain tolerance as hand withdrawal. Preliminary testing before implementation in the Tromsø Study demonstrated that most individuals that endured over 106 seconds would not withdraw their hands for a long time. The exact test time of 106 seconds was due to technical reasons.

2.5 Outcomes

In paper I, the outcome was obstructive CAD. In paper II, the primary endpoint was all-cause mortality, and the secondary endpoint was major adverse cardiovascular events (MACE), defined as either cardiovascular death or coronary angiography with obstructive CAD or MI. In paper III, the outcomes were referral to coronary angiography, clinical presentation, extent of CAD and all-cause mortality.

2.6 Statistical analysis

Statistical analyses were performed with Stata version 14.0-16.1 (Stata Corporation, College Station, TX, USA). All reported differences had two-sided p values<0.05. Baseline characteristics are reported as counts and percentages or means with standard deviations. In paper I, we applied logistic regression analysis to predict the odds ratio for obstructive CAD and build a multivariable model. We calculated the area under the curve to compare the discriminatory ability of our model compared to guidelines. Based on the multivariable model, we created a score to estimate the proportion of patients that could be safely discharged with a high NPV for prognostically significant CAD. In papers II and III, we calculated the crude incidence rates expressed as the number of events per 1000 person-years at risk. We applied the Cox proportional hazard regression models to estimate the hazard ratios (HR) for coronary angiography, CAD and death. The proportional hazard assumption was tested by Schoenfeld residuals. In paper III, age violated the proportional hazard assumption in most analyses, and we chose to adjust for age by using age as a time scale. Two-way interactions were tested by including cross-product terms between the exposure and the adjustment variables in the models. If the interaction product was significant, we either included the interaction product in the model (paper I) or presented the results stratified (paper II and III). We applied different methods to deal with missing information, including single imputation in paper I, list-wise and pair-wise deletion in papers I and III, and multiple imputation in paper II.

2.7 Ethics

This project was conducted in agreement with the Data Protection Official for Research at the University Hospital of North Norway (#0217). We performed a data protection impact assessment for papers II and III. All participants in the Tromsø Study gave informed written consent. The Regional Committee for Medical and Health Research Ethics approved papers II and III, while paper I was a clinical audit and not subject to evaluation.

3 Main results

3.1 Paper I – Pre-test characteristics of unstable angina patients with obstructive coronary artery disease confirmed by coronary angiography

In 979 patients with unstable angina, the overall rate of obstructive CAD was 45%, and the rate of prognostically significant CAD was 11%. There was an overall low GRACE risk score, with high-risk scores <1% and intermediate-risk scores in 11% of the patients. The risk criteria recommended in the American College of Cardiology/American Heart Association and European Society of Cardiology (ESC) guidelines and the GRACE risk score had an area under the curve of 0.58 and 0.59 for obstructive CAD, respectively. A history of typical angina symptoms, Canadian Cardiovascular Society angina grade 3 or 4, no variable threshold of exertional angina, no history of palpitations, prior PCI, positive stress testing, smoking, hypertension, age >65 years and male sex added significant information in a multivariable model, increasing the area under the curve for obstructive CAD to 0.77 (95% confidence interval [CI] 0.74-0.80, p<0.001). Applying the derived score, we found that 56% (n=546) of patients had a score of under 13, associated with an NPV of 95% for prognostically significant CAD. Stratified by sex, a cut-off level of <14 gave an NPV of 95% for 82% (n=330) of women, and a cut-off level of <12 and<13 gave NPVs of respectively 96% for 20% (n=177) and 93% for 43% (n=251) of men.

3.2 Paper II – Outcomes after coronary angiography for unstable angina compared to stable angina, myocardial infarction and an asymptomatic general population

We included 9,694 symptomatic individuals that underwent coronary angiography for stable angina (51%), unstable angina (12%), NSTEMI (23%) or STEMI (14%), and 11,959 asymptomatic individuals, with no prior history of CAD. The median follow-up time was 2.8 years for the symptomatic individuals and 10.4 years for the asymptomatic individuals. The incidence rate of death and MACE per 1000 person-years was 8.5 (95% CI 8.0-9.0) and 8.1 (95% CI 7.6-8.6) in asymptomatic individuals, 9.7 (95% CI 8.3-11.5) and 21.8 (95% CI 19.5-24.4) in stable angina patients, 14.9 (95% CI 11.4-19.6) and 23.5 (95% CI 18.9-29.2) in unstable angina patients, 29.7 (95% CI 25.6-34.3) and 44.0 (95% CI 38.9-49.8) in NSTEMI patients and 36.5 (95% CI 30.9-43.2) and 51.6 (95% CI 44.6-59.7) in STEMI patients, respectively.

In multivariable adjusted analyses, compared to unstable angina patients, stable angina patients had a 38% lower risk of death and a nonsignificantly lower risk of MACE (HR 0.62, 95% CI 0.44-0.89, HR 0.86, 95% CI 0.66-1.11). NSTEMI patients had a 2.5-fold higher risk of death (HR 2.47, 95% CI 1.30-4.71) and a 1.6-fold higher risk of MACE (HR 1.62, 95% CI 1.11-2.38) than unstable angina patients during the first year after coronary angiography, but a similar risk after that. There was no difference in the risk of death for unstable angina patients with non-obstructive CAD and obstructive CAD (HR 0.78, 95% CI 0.39-1.57).

3.3 Paper III – Low pain tolerance is associated with coronary angiography, coronary artery disease and mortality

We included 9,576 individuals with no prior history of CAD, of whom 32% aborted the cold pressor test (low pain tolerance) after a median of 46 seconds, and 68% endured the test until the maximum time of 106 seconds (high pain tolerance). More women than men aborted the test (39% vs 23%). During a median follow-up time of 10.4 years, 886 individuals were referred to coronary angiography (9.3%), and 700 died (7.3%). Individuals with low pain tolerance had a 19% increased risk of coronary angiography (HR 1.19, 95% CI 1.03-1.38) and 22% increased risk of obstructive CAD (HR 1.22, 95% CI 1.01-1.47), adjusted for sex and age as time-scale. Adjusting for additional cardiovascular risk factors attenuated both results (HR 1.16, 95% CI 1.00-1.34 and HR 1.15, 95% CI 0.95-1.39, respectively). Among women who underwent coronary angiography, low pain tolerance was associated with a 54% increased risk of obstructive CAD (HR 1.54, 95% CI 1.09-2.18) compared to women with high pain tolerance adjusted for cardiovascular risk factors. There was no association between pain tolerance and non-obstructive CAD or clinical presentation to coronary angiography (i.e. stable angina, unstable angina, MI). Further, individuals with low pain tolerance had an increased risk of mortality after adjustment for CAD and cardiovascular risk factors (HR 1.41, 95% CI 1.20-1.65).

4 Discussion: Methodological considerations

4.1 Study design

All papers in this thesis use variations of the cohort study design. Paper I is a retrospective cohort, paper II is a prospective registry-based cohort, and paper III is a prospective population-based cohort. A cohort study is an observational study design that follows a group of individuals over time to assess whether they develop the outcomes of interest (131-133). The study participants are arranged by one or more exposures into different subgroups. Relative or absolute risk estimates are obtained by comparing the outcome rate in these subgroups (132). A prospective cohort study is initiated before any outcomes have occurred, while a retrospective cohort is initiated after both the exposure and the outcome have occurred (133, 134). In paper I, we retrospectively examined the risk of obstructive CAD in unstable angina patients with different clinical characteristics. In paper II, we followed patients with unstable angina, stable angina, NSTEMI and STEMI and compared the risk of death and MACE. Paper III compared the risk of coronary angiography, CAD, and death in individuals with low and high pain tolerance.

The level of evidence is generally considered to be highest in randomised controlled trials (RCT) followed by prospective and retrospective cohorts, and then case-control studies and cross-sectional studies. However, the level of evidence also depends on the research question and the study quality. A well-conducted prospective cohort study is a robust design with comparable results to RCTs (135-137). The strengths of cohort studies include higher external validity ensuring that the evidence applies to the heterogeneous patient population met in clinical practice, and cohort studies are often an essential complement to RCTs (138). Further underlining this, RCTs reporting outcomes after MI has been criticised for low external validity, including a high proportion of middle-aged, white men with few other comorbidities (139). Therefore, the prospective cohort study design is well-suited for investigating the risk of death and MACE in paper II. A further advantage of the cohort study design is that it may be applied to research questions that are impossible or unethical to explore with RCTs, including the research question of paper III that would be difficult to address using an RCT. Compared to other observational designs, a cohort study may investigate multiple outcomes in the same study, like in papers II and III. Further, it may lower the risk of selection bias and allow for the assessment of causality with a clear temporal sequence of events (131, 134). In

paper III, we were interested in testing pain tolerance before the individuals developed CAD to ensure that it is not CAD that affects the pain tolerance.

The disadvantages of cohort studies include the higher risk of confounding and bias compared to RCTs. Retrospective cohorts have further disadvantages with the inability to influence the data collection, often more missing data, and a higher risk of recall bias and information bias (131, 134, 140). For the research question in paper I, a prospective cohort with a validation cohort would ensure better data on symptoms characteristics and reduce the risk of bias. An RCT could test the usefulness and safety of the risk score compared to current clinical practice. The disadvantages of RCTs and prospective cohort studies are that they are resource-demanding to conduct, and it may be difficult to ensure adequate power. This is demonstrated in paper III, where we have relatively few events, especially for subgroups, despite a large cohort with long follow-up. Applying registry-based and retrospective cohort study designs and other observational study designs are often less resource-demanding. A registry-based cohort design utilises the data already collected in large patient registries, as in paper II. It also may reduce the potential selection bias usually associated with population-based cohort studies as most clinical registries cover whole populations. In contrast, population studies, including the Tromsø Study, may be biased by those choosing to attend (141). Further, several registries contain high-quality data with a low proportion of missing data, including NORIC (4).

4.2 External validity

The external validity describes how study results are generalisable to other populations (132). The papers in this thesis are based on real-world data, including individuals with old age and comorbidities, increasing the external validity of our results. For example, the coronary angiography registries include all individuals referred to coronary angiographies in Northern Norway. Further, the registries also include individuals referred to CCTA. This is important as many patients with suspected CAD are deferred from CCTA in clinical practice. Failure to include these patients could overestimate adverse outcome rates for patients referred to coronary angiography with stable angina and unstable angina in paper II. At UNN, CCTA is the primary non-invasive imaging test, and stress echo and other tests were not used as a first-line investigation, ensuring that we do not miss patients referred for suspected CAD.

Our data is collected from a single centre. This increases the risk of systematic differences in clinical practice affecting the generalisability to other populations. However, all patients in the coronary angiography registry were managed by interventional cardiologists, likely ensuring high compliance to the current guidelines for diagnosis, management and treatment. The Norwegian National Society of Cardiology endorses the ESC guidelines, except for the recommendation of invasive coronary angiography within 24 hours in patients with NSTE-ACS. Instead, it recommends invasive coronary angiography within 72 hours for stable NSTE-ACS patients (142). This is well-argued and not believed to cause poorer outcomes (142). Over half of the invasive coronary angiographies in these patients are also performed within 24 hours (4).

The external validity may further be affected by exclusion criteria. In paper II, we excluded individuals presenting to coronary angiography with other indications, including heart failure, arrhythmia and preoperative assessment, despite some of these patients also having CAD. We also excluded patients with prior CAD. Sensitivity analysis demonstrated distinctly higher mortality in these patients, and our results are likely not generalisable to them. Further, in paper II, we censored individuals in the general population at presentation to coronary angiography with other indications, which may underestimate the risk of adverse outcomes and mortality in this population. In paper I, we excluded patients with chronically elevated troponins and patients with PCI within the last 30 days. Chronically elevated troponins are associated with higher age, more CAD, chronic kidney failure, heart failure, and a higher risk of death (101, 143). Patients with PCI within the last 30 days had a very high rate of obstructive CAD, advocating a low threshold for coronary angiography. Consequently, our results are not generalisable to these high-risk populations.

Acute chest pain and suspected ACS are among the most common presentations in the emergency department, but only 5-20% end up with a final diagnosis of ACS (33-36). Individuals referred to coronary angiography are a highly selected population with a high suspicion of myocardial ischemia causing their clinical presentation. Therefore, the risk score developed in paper I may not be generalisable to unselected chest pain populations in the emergency department or emergency primary care clinics. In addition, not all patients with stable angina, unstable angina and MI are referred to coronary angiography, and the results may not represent these individuals. However, as coronary angiography is offered to most ACS patients, including the elderly, we believe our results apply to most CHD patients. Our results have higher generalisability than studies only including patients that undergo PCI.

In the Tromsø study, like most other population studies, the volunteering participants are likely younger, higher educated, more interested in health, and have a healthier lifestyle (144). Therefore, our results may underestimate the risk of outcomes for the general population. Further, Norway has a low incidence and mortality of CHD compared to many other countries, which may affect the generalisability of our results to populations with higher incidence and mortality (1).

A challenge for external validity is the continuous evolution in diagnostics and treatment of CHD and the falling incidence of CHD. In paper I, we applied the current definition of acute myocardial injury and adjusted for the lower sensitivity of prior troponin (99, 100). In paper II we only included patients after the implementation of hs-cTn and the current definition of MI. The development in diagnostic and treatment warrants new studies on outcomes like paper II.

Overall, the results of the papers in this thesis are likely generalisable to other predominantly Caucasian populations in high-income regions with high access to coronary angiography.

4.3 Internal validity

Internal validity describes whether the effect of the exposure on the outcome is attributable to the exposure and not chance or bias. Bias is a term for systematic errors and describes the tendency to produce results that systematically differs from the true results. This will produce an incorrect estimation of the association and, in the outermost consequence, produce a statistically significant result where the truth is no difference among groups (type I errors) or fail to detect a true difference among groups (type II errors) (132). Bias may be divided into three general categories: information bias, selection bias, and confounding, and will be discussed in the following sections.

4.3.1 Information bias and misclassification

Information bias occurs when there is a systematic error in the recall, measuring, recording or classification of data on exposure, outcome or covariates (132, 145). Misclassification occurs when these errors misplace an individual in the wrong exposure or outcome group. A non-differential misclassification occurs when the misclassification of exposure/outcome is equal between the different outcome/exposure groups. A differential misclassification occurs when the misclassification is not equally distributed. Differential misclassification may lead

to overestimating and underestimating the result, while non-differential misclassification generally leads to underestimating and diluting the result (145). The main potential sources of information bias in this thesis will be discussed.

Data from patient hospital records

The data collected from the patient hospital records in paper I have a high risk of information bias, especially the data on symptom characteristics. The hospital records contain unstructured physicians' notes with varying content and detail. We created a manual for the data collection, and the candidate performed the data collection under close supervision by the main supervisor, an experienced cardiologist. The risk of information bias could have been reduced if two experienced cardiologists had collected the data with cases of disagreement resolved by a third cardiologist. Intra- and inter-reproducibility could also have been examined. However, this was not feasibly within the resources and time frame available for this paper and was deemed not necessary with the exploratory aim of the study.

Observer bias is an information bias that occurs when the outcome status is known beforehand. To avoid observer bias, we collected the data on exposures and covariates without opening the coronary angiography report. However, the title of other following notes in the hospital records could indicate the finding on coronary angiography. For example, a gastroscopy report would strongly indicate further diagnostic work-up and no obstructive CAD, while a cardiovascular surgery report would indicate extensive obstructive CAD referred to coronary artery bypass graft surgery. This could have affected the interpretation of symptom characteristics.

Definition of unstable angina and myocardial infarction

High-sensitivity troponins and a new definition of MI were implemented during the work of thesis (81, 100). The implementation of hs-cTn increases the incidence of NSTEMI from 18% to 22% with a reciprocal decrease in the incidence of unstable angina from 13% to 11% (90, 97). Patients reclassified from unstable angina to NSTEMI have a poorer prognosis than the remaining unstable angina patients (90, 101). These changes in diagnosis could have introduced bias to our studies. In paper I, we retrospectively applied the 99th percentile definition of myocardial injury to the whole population to partly accommodate for this. However, the different sensitivity of the fourth-generation troponin and hs-cTn would still likely cause us to include some true NSTEMI patients as unstable angina patients from 2005 until 2009. These individuals have a higher risk of obstructive CAD and may have introduced

differential misclassification. However, this likely applies only to a few patients and we do not believe this has greatly affected our results. In paper II, we avoided this problem by including patients only after the implementation of hs-cTn and the new MI definition. The interventional cardiologist may have misclassified patients with small NSTEMI or unstable angina with chronically elevated troponin, but this is likely rare and would be non-differential misclassification and, therefore, unlikely to have affected our results. In paper III, we could not adjust for the change in the definition of unstable angina and NSTEMI during the study period. This may have affected the analyses comparing the clinical presentation of unstable angina and NSTEMI but not the main analyses in the study.

Coronary angiography registries

The coronary angiography registers contain one recording per consecutive procedure. One-third of the patients have more than one procedure. The classification of procedures close in time is challenging. Individuals may both be diagnosed with non-obstructive CAD or obstructive CAD at the initial coronary angiography, but due to uncertainty of the diagnosis, scheduled for a repeat procedure within a short time, where the conclusion could be changed. Individuals may also have a complication or a new event within a short time of the initial coronary angiography. Individuals with complicated CAD could also be scheduled for complete revascularisation at a later point in time. We processed this data following several rules. Our data had generally good agreement with patient hospital records and the discharge date recorded for most patients in NORIC. Individually checking the patient hospital record for each individual with close procedures would have limited this potential source of bias. However, most patients in the coronary angiography registries only have one procedure or procedures several months apart, limiting this problem.

Pain tolerance and the cold-pressor pain test

The cold pressor pain test was performed using standardised instructions to participants, technical procedures and documentation to minimise the risk of error. The test-retest-stability was tested in 263 participants, with one to three months between the first and second test. Half of these participants also underwent two repeated tests on the second visit. Both the same-day and the 1-3 months' test-retest stability was found to be high with an alpha >0.8 (146).

Most participants completed the cold pressor test without withdrawing their hand (68%). This led to a strong right-censoring of the exposure variable. Therefore, we chose to

dichotomise the variable into high pain tolerance (did not withdraw their hand) and low pain tolerance (withdrew their hand). This also improves the interpretability of the results. Dichotomisation of a continuous variable may increase the risk of bias and lead to loss of power (147). However, sensitivity analyses with time to withdrawal as a continuous and categorised variable demonstrated similar results as the dichotomised variable.

The long-time stability of cold pressor pain tolerance is unknown, although other studies have also demonstrated high short-term stability and evidence of heritability suggesting long-term stability (129, 146, 148, 149). Further, the concurrence between cold pressor pain tolerance and myocardial ischemia pain tolerance is not known. However, as cold pressor pain was a historical test of angina and provokes pain by activating venous nociceptors, it is theoretically more associated with myocardial ischemia than other experimental pain tests (130). There is no established method to test myocardial ischemic pain sensitivity, invasive or peripheral. The use of cold pressor pain tolerance and not a direct measure of myocardial ischemic pain tolerance, and the unsure long-term stability are important limitations in the interpretation of our findings.

4.3.2 Selection bias

Selection bias is a systematic error in the selection and follow-up of study participants causing the study population to no longer represent the source population. In cohort studies, individuals are generally selected for participation before the outcomes occur, excluding this as a potential source of selection bias. The study populations of this thesis were selected before the outcome status was known to the researchers, including the retrospective cohort in paper I.

Non-response or non-participation bias is a form of selection bias that may occur if the non-participating individuals differ from the participants in exposure status and risk of outcome (132, 145). The Tromsø Study and the other population studies report that the lowest participation rates are in the youngest and the oldest age groups (118, 150). Previous studies demonstrate that non-participants have more cardiovascular diseases, lower socioeconomic status and higher mortality than participants (144, 150). The Tromsø Study has higher attendance rates than other cohort studies, and Tromsø6 had an attendance rate of 66% (119). This reduces the risk of non-response bias affecting our results. Further, most studies have not observed substantial bias due to non-responders (144). In paper II, calculating the incidence of MACE and death, the estimates are likely lower in the population recruited from Tromsø6,

than the total population of Tromsø. However, we do not believe that the effect of pain tolerance on the outcomes would be substantially different among non-participants.

Loss to follow-up bias is a common type of selection bias in cohort studies. There was no loss to follow-up in paper I with the retrospective design and a very short follow-up time. In papers II and III, loss to follow-up is limited by using nationwide registries for the outcome. However, an individual could be lost to follow-up for death if both emigrated from Norway and no longer registered as a Norwegian citizen. Lost to follow-up for coronary angiography would occur if the coronary angiography was performed abroad or in another region of Norway before NORIC had full national coverage. We believe this applies to very few individuals, especially for death, and is not related to the exposure status, i.e. low or high pain tolerance or the different indications of coronary angiography. Therefore, it is unlikely to have affected our results.

Competing risk by death is another form of bias in the follow-up of individuals, which occurs when death precludes the event of interest. In paper II, death by other causes precludes the follow-up for MACE, and in paper III, death precludes the follow-up for coronary angiography and obstructive CAD. The events of interest in papers II and III were relatively common, lowering the impact of competing risk by death.

4.3.3 Confounding

Confounding is a mixing of effects. It may occur when a characteristic is related to both the exposure and the outcome and is unevenly distributed among the exposure groups (132). The confounder's effect may then wrongly be confused as an effect of the exposure on the outcome. Confounding may strengthen or weaken a true association and lead to type I and type II errors. The criteria define a true confounder: 1) it is causally associated with the outcome, 2) casually or non-causally associated with the exposure, and 3) it is not an intermediate variable in the causal pathway between exposure and outcome (132, 151). Confounding may be addressed in the study design with randomisation, restriction or matching, or statistical analysis of the data with stratification or multivariable regression (151). The ability to randomise individuals into evenly distributed groups, thereby avoiding confounding, is the main strength of RCTs and one of the main weaknesses of the observational study designs (134). In an RCT, unknown and unmeasured confounders are also likely equally distributed.

Assessing whether a variable is a confounder is based on the knowledge of pathophysiological mechanisms and potential pathways for different factors. Overadjustment and unnecessary adjustment occur when we adjust or stratify for a variable that is not a confounder. Overadjustment is adjusting for an intermediate variable on the causal pathway from exposure to outcome. This may underestimate the true association between the exposure and the outcome (152). Unnecessary adjustment is adjusting for a variable that does not affect the association between the exposure and outcome but increases variance and random error, demanding a higher statistical power to detect a true difference (152).

There is extensive knowledge regarding risk factors and confounders within the field of CHD and cardiovascular disease. In this thesis, we have used stratification and multivariable regression to deal with confounding. Papers II and III present both unadjusted analyses, analyses adjusted for age and sex, and analyses adjusted for additional cardiovascular risk factors including hypertension, hyperlipidaemia, diabetes, smoking status, BMI and kidney function. Paper III adjusted for age-as-time scale as age violated the proportional hazard assumption. This may also be a more precise way of adjusting for age. However, studies have shown similar estimates with age-as-time-scale and including age as a covariate in regression analyses (153, 154).

There is less knowledge on potential confounders in paper III and, therefore, a higher risk of residual confounding through both unknown and unmeasured confounders. A potential unmeasured confounder is inflammation, as later discussed in the discussion of main results. We did not have available data in our datasets for this. Another potential confounder is an anxious personality type, as a more anxious personality type could be associated with lower pain tolerance and more help-seeking and request of investigations including coronary angiography.

4.4 Missing data

Missing data is a challenge for most epidemiological studies. In our project, we have applied different methods according to the mechanism and pattern of the missing data to minimise bias and loss of power. There are three main mechanisms for missing data: missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) (155). MCAR is rare and includes accidental omissions. MAR is when other observed variables can explain the missingness of a variable. MNAR occurs when the

missingness of a variable is related to the value of the missing variable itself (156). It is impossible to determine the true mechanism of the missing data without knowing the missing values. MAR and MNAR may introduce bias to study results.

We have no or minimal missing data on outcomes in all papers, and these individuals were excluded. This data is interpreted as MCAR and is not believed to bias our results. Paper I had large amounts of missing data in several predictor variables (e.g. symptoms prior to presentation, angina threshold). This was expected as we used patient hospital records as the data source. We believe the missing data on symptom variables is MNAR as the missingness could be explained with the physicians not recording negative findings or reporting fewer symptom characteristics when the patient history indicates no CAD. The lower risk of obstructive CAD in patients with missing variables supports this. We did a regression imputation on the missing data, including it either as a separate categorical variable or combined with the reference group as appropriate. This method was chosen to avoid losing power. Further, we were interested in how missing data was associated with the outcome. This may have biased our results.

Papers II and III had under 0.1% missing data on the indication, finding, and treatment. These participants were excluded. As the missing data is perceived as MCAR or MAR and the rate of missing is very low, we do not believe this has affected our results. Further, we had 0-10% missing data on cardiovascular risk factors in paper II and 0-5% in paper III. Again, we believe this data is MCAR or MAR. For example, the recording of this data may not always be prioritised in clinical practice, perhaps especially in patients with no CAD or in the most acute presentations of CAD. For paper II, we applied multiple imputation to minimise bias and not lose power in the subgroup analyses. This is often the preferred method to deal with MAR (156). For paper III, we had a lower percentage of missing, a high percentage of complete data, and chose to exclude the participant from all analyses (list-wise deletion), or only include the individual in the age- and sex-adjusted analyses, and exclude participants in multivariable analyses (pair-wise deletion). These methods have a higher risk of introducing bias, but we still believe the risk is low as there was little missing data in paper III.

5 Discussion: Main results

5.1 Clinical characteristics of unstable angina patients with obstructive coronary artery disease and selection for coronary angiography

In paper I, we found that patients referred to acute invasive coronary angiography as unstable angina with normal troponins had low rates of obstructive CAD. Structuring symptom characteristics and cardiovascular risk factors could rule out or delay coronary angiography in more than half of the patients. We found that a history of symptoms prior to the acute admission predicted obstructive CAD, including typical or atypical angina, Canadian Cardiovascular Society angina grade III or IV, and a consistent or worsening threshold for symptoms. The symptoms on admission were not associated with obstructive CAD, except palpitations, which decreased the risk of obstructive CAD.

Other studies have demonstrated that cardiovascular risk factors increase the risk of obstructive CAD in NSTE-ACS patients (98, 157). In patients with suspected stable angina, typical and atypical symptoms improve the prediction of obstructive CAD beyond cardiovascular risk factors (2, 94). In acute chest pain patients presenting to the emergency department, typical symptoms may increase the likelihood of MI (91, 98, 158). To our knowledge, there are no other studies using symptoms to predict obstructive CAD in unstable angina patients. However, studies on predicting obstructive CAD on CCTA in acute chest pain population have found that the HEART score has an area under the curve of 0.53-0.75, while the CAD consortium clinical score, including typical or atypical angina, had an area under the curve of 0.79 (159, 160).

The unstable angina patients referred to coronary angiography in our study had undergone selection by physicians in primary care, the emergency department and the interventional cardiologists. Nevertheless, the rate of obstructive CAD was as low as 29% at the end of our study period, indicating poor patient selection. The diagnosis of unstable angina is challenging as there are rarely objective clinical criteria, and physicians are likely afraid to miss a diagnosis of CAD (161). Guidelines define unstable angina as the clinical presentation of either angina at rest, new-onset angina with Canadian Cardiovascular Society angina grade II or III, or destabilisation of previously stable angina with angina grade III, and the absence of acute myocardial injury defined by hs-cTn (81, 97, 98, 100, 162). Especially chest pain at

rest or with no activity relation is difficult to assess as multiple other diagnoses may present similarly, including musculoskeletal, gastrointestinal and psychological conditions (33-36, 98). Patients may also have symptoms originating, for example, from the musculoskeletal system and asymptomatic obstructive CAD.

Despite the low rates of obstructive CAD in our study, 79% of the patients fulfilled the criteria for acute coronary angiography within 24-72 hours according to the 2016 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Our new clinical risk score ruled out over half of the patients with an NPV of 95% for prognostic obstructive CAD (i.e. proximal LAD, left main stem or three-vessel disease). The 2016 ESC Guidelines could only rule out prognostic obstructive CAD in 21% of patients with an NPV of 95%. Our risk score had an area under the curve of 0.77 (95% CI 0.74-0.80), significantly higher than the ESC Guidelines and GRACE risk score with the area under the curves of 0.58 and 0.59, respectively. The poor performance of ESC guidelines risk criteria and GRACE risk score was likely due to a good short-term prognosis and low GRACE scores in unstable angina patients with negative hs-cTn, regardless of the presence of obstructive CAD.

Routine invasive coronary angiography for NSTE-ACS may lower the risk of non-fatal MI in high-risk individuals. However, it increases the risk of procedural complications, and it has no effect on all-cause death for the overall NSTE-ACS population (98, 163-167). The hs-cTn negative unstable angina population is low-risk and have likely even lower potential benefit than the NSTEMI population. The results of the ISCHEMIA trial (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) further support this, demonstrating no effect of revascularisation on death or MI in stable angina patients with moderate or severe ischemia (168). The unsure prognostic benefit of invasive coronary angiography combined with the low rate of obstructive CAD questions the resource utilisation of acute invasive coronary angiography in most unstable angina patients. The most recent 2020 ESC guidelines implement this, recommending a routine invasive strategy for NSTEMI and high-risk unstable angina patients and a selective invasive strategy for the remaining unstable angina patients. This is in clear contrast to the 2016 ESC guidelines recommending a routine invasive strategy for most patients. The 2020 ESC guidelines also focus on using CCTA or other non-invasive imaging testing to exclude CAD and ACS and as the initial investigation in low-risk unstable angina patients before deciding on invasive coronary angiography. Studies on CCTA for patients with suspected NSTE-ACS have high NPV for

CAD and excellent prognosis for these patients (108, 109, 169, 170). Less than 10% of the study population of paper I would classify as high-risk patients according to the new 2020 ESC guidelines with GRACE risk score ≥140 or ongoing ischemia on electrocardiogram, thereby qualifying for a routine invasive strategy. Consequently, the remaining 90% of our study population would today have been recommended to undergo a selective invasive strategy.

In addition to increased use of CCTA and a more selective invasive strategy for unstable angina, the current 2020 ESC guidelines also recommend implementing hs-cTn rapid rule-in and rule-out 0 h/1 h algorithms on patients presenting with symptoms suggestive of ACS (88). This algorithm rules out a higher number of patients with a very low risk of adverse events than the previous 0 h/3 h algorithm (88, 171-176). This algorithm also identifies a subset of unstable angina patients with small changes in troponin that are at a higher risk than patients with low, stable troponin levels. The patients assigned by the algorithm to the low-risk group are candidates for early discharge and outpatient management (88).

The ESC 0 h/1 h algorithm and CCTA may change how our hospital manages unstable angina patients and reduce the need for invasive coronary angiography. Especially in Northern Norway, with long distances to invasive centres, delaying or avoiding invasive coronary angiography can reduce cost and release capacity in the emergency health care systems. CCTA may be performed at more hospitals than invasive coronary angiography. Remote interpretation from cardiac radiologists is also possible. However, selecting patients from the low-risk chest pain population to CCTA will likely remain challenging. Risk scores including symptom characteristics may help select a strategy for these patients.

5.2 Outcomes of unstable angina compared to stable angina, myocardial infarction and an asymptomatic general population

In Paper II, we found that unstable angina patients had a higher risk of death but a similar risk of MACE as stable angina patients, and half the risk of death and MACE compared to NSTEMI patients during the first year after coronary angiography. This is consistent with the increasing evidence that unstable angina in the hs-cTn era is associated with a better prognosis than NSTEMI and a more similar prognosis as stable angina (48, 88, 171-180).

However, the other studies applying hs-cTn to detect acute myocardial injury and NSTEMI either only include patients that underwent PCI (179), patients with high-risk criteria (177),

relatively small populations (178), or unselected chest pain population presenting to emergency departments (171-175, 180). In a study using data from High-STEACS and APACE, 21% and 65% of the unstable angina patients were referred to coronary angiography, respectively, but 95% had obstructive CAD, higher than the NSTEMI patients (177). Further, 75% of the patients had prior CAD, and High-STEACS excluded all patients with chronically elevated troponin (177). This makes the results challenging to interpret. The RAPID-CPU had a relatively small population of 280 unstable angina patients and did not report adjusted survival analyses compared to NSTEMI (178). In addition, our study had a longer follow-up time than most of these studies, tested and reported sex interactions, and reported findings for unstable angina patients with non-obstructive CAD. Therefore, our study adds to the existing knowledge.

The High-STEACS, APACE and RAPID-CPU studies reported a 1-year incidence of death and MI in unstable angina was 3-4% and 3-11% (177, 178). This is higher than our results. The studies on the ESC hs-cTn 0 h/1 h and 0 h/2 h algorithms for rule-out, observe, and rule-in for MI in chest pain populations in the emergency department found a 1-year cumulative incidence of death of 0.0-2.2%, 4.0-7.6% and 9.8-16.1%, respectively (88, 171-175). Unstable angina patients may be present in all groups, yet our results were closest to the rule-out group. Our findings support the present 2020 ESC Guidelines on Acute Coronary Syndrome without Persistent ST-segment Elevations focusing on detecting the individuals with NSTEMI that have a significantly worse prognosis and a more individual workup for patients with suspected unstable angina (88). However, our unstable angina population had a higher risk of death than stable angina patients and a similar risk of death as NSTEMI after the first year. Other studies have also found that especially unstable angina with chronically elevated troponin has an increased risk (101, 178). We also found that unstable angina patients with non-obstructive CAD had a similar risk of death as unstable angina patients with obstructive CAD but a very low risk of MACE. This underlines that a thorough workup, including assessment for other differential diagnoses and microvascular disease, is indicated in a subset of these patients (79, 88). The low prevalence of obstructive CAD in unstable angina supports the increasing use of CCTA as initial investigation before invasive coronary angiography (98). CCTA may also have a higher potential to detect other differential diagnoses than invasive coronary angiography.

Unstable angina remained a substantial part of ACS in our study, receiving 25% of acute coronary angiographies and 13% of acute revascularisations, comparable or higher than

previous studies (48, 88, 177, 178). We found that 65% of stable angina, 60% of unstable angina, and 18% of NSTEMI patients have no obstructive CAD on coronary angiography, similar to or higher than reported in other studies (2, 6, 11, 64, 181). The definition of unstable angina is challenging in clinical practice and research as discussed. Nevertheless, our results are likely generalisable to a population perceived as having a high risk of unstable angina by physicians and cardiologists, demonstrated by referral to CCTA or ICA.

5.3 Pain tolerance, coronary angiography, coronary artery disease and mortality

Paper III is the first large population-based study investigating the association between pain tolerance and coronary angiography, presentation and extent of CAD and mortality. We found that low pain tolerance was associated with a higher risk of coronary angiography as hypothesised. However, we also found a higher risk of obstructive CAD and death. This was contrary to our hypothesis that individuals with low pain tolerance would present earlier with less obstructive CAD and be less likely to die without presenting to coronary angiography than individuals with high pain tolerance.

The increased risk of coronary angiography in individuals with low pain tolerance could be because they experience more cardiac symptoms and seek medical help earlier than individuals with high pain tolerance. This is consistent with the previous results from the Tromsø Study, demonstrating that high pain tolerance was associated with unrecognised MI (7), and other studies demonstrating decreased pain sensitivity and more efficient endogenous pain inhibition among individuals with painless MI (182, 183). However, the increased risk of coronary angiography might also be justified as the individuals with low pain tolerance had a higher risk of obstructive CAD and death than individuals with high pain tolerance. Further, we found it interesting that several well-established risk factors for CAD did not predict referral to coronary angiography, while pain tolerance did, indicating that other factors than the risk of CAD influence the referral to coronary angiography.

The increased risk of obstructive CAD was present in the overall population adjusted for age and sex, and in women referred to coronary angiography adjusted for age and cardiovascular risk factors. Our findings contradict that patients present with non-obstructive CAD or microvascular angina due to lower pain tolerance and increased symptom awareness. Previous studies compare pain tolerance in angina with and without obstructive CAD and had

6 Conclusions

Structuring symptom characteristics and clinical variables allowed for better identification of unstable angina patients with obstructive CAD. This could postpone or cancel over half of the acute coronary angiography in unstable angina.

Unstable angina patients have a higher risk of death, but a similar risk of MACE as stable angina patients presenting to coronary angiography with no prior CAD. Further, unstable angina patients have a lower 1-year risk of death and MACE than NSTEMI patients, but not thereafter. The risk of death was similar in unstable angina patients with obstructive CAD and non-obstructive CAD.

Low cold pressor pain tolerance was associated with a higher risk of coronary angiography, CAD and death. It did not explain the differences in the clinical presentation of CAD, or why more than half of patients presenting to elective coronary angiography do not have obstructive CAD.

7 Final remarks and future perspectives

The findings of this thesis demonstrate several of the challenges in the management of CAD. We need to identify high-risk individuals to initiate appropriate treatment and improve prognosis while avoiding unnecessary procedures and treatment in individuals who are unlikely to have or develop CAD. Implementing hs-cTn 0 h/1 h algorithms and CCTA will likely improve our management of unstable angina patients and reduce the need for invasive coronary angiography. However, managing the patients recommended for a selective invasive strategy, including which patients to refer to a CCTA, is uncertain. Adapting new clinical risk scores, including symptom characteristics, may be helpful. The SCOT-HEART trial indicated that identifying non-obstructive CAD in stable angina patients improves prognosis through better medical therapy. Perhaps should CCTA be performed on a relatively low threshold in patients with suspected stable angina or unstable angina with no prior CAD (5). The ongoing SCOT-HEART 2 trial (NTC03920176) may help answer this. Further, the benefits and timing of revascularisation in unstable angina patients are unclear, and RCTs exploring this is warranted.

The first clinical presentation of CAD varies from stable angina, unstable angina and MI, and the extent of CAD varies from non-obstructive CAD to three-vessel disease. This demonstrates that the identification and management of CAD are difficult in clinical practice. Differences in cold pressor pain tolerance could not explain the discrepancies, and contrary to our hypothesis, we found that low pain tolerance was associated with an increased risk of CAD and mortality. We propose that increased inflammation in low pain tolerance individuals may explain the increased risk of CAD and death, but further research is needed. Studies on the test-retest reliability over longer periods and comparing cold pressor pain tolerance with cardiac ischemic pain tolerance may further help interpret our findings. A better understanding of the natural history and outcomes of CAD will likely come from the follow-up of the 25,000 asymptomatic individuals investigated in the Swedish CArdioPulmonary bioImage Study (SCAPIS) (196). This will likely help guide future identification, risk assessment and treatment of symptomatic and asymptomatic CAD.

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Appendix

Veileder for uthenting av data til UA-databasen

	Variabelnavn	Verdier	Tolkning
Generelt	newpid	0-30 000	
	foedselsdato	01.01.1890 – 01.01.1990	
	prosedyredato	01.01.2005 – 31.12.2012	
	kjonn	1 – Mann, 2 – Kvinne	
	alder	20-99	Prosedyredato-foedselsdato
Blodprøver	hgb	7,0-22,0	Første verdi under innl
	kreat	20-400	Første verdi under innl
	glukose	1,0-70,0	Ved innkomst
	kolesterol	2,00-25,00	Første verdi under innl
	ldl	1,00-22,00	Første verdi under innl
	hba1c	2,0-15,0 %	Første verdi under innl. Evt. opptil et par uker før/etter.
	tropls_innl		LS troponin T. Første verdi. <0,01 settes til 0,007.
	tropls_3t		LS troponin T. Andre måling, minst 3 timer etter den første.
	trophs_innl	1-14	HS troponin T. Første verdi. <10 registreres som 7.
	trophs_3t	1-15	HS troponin T. Andre måling, minst 3 timer etter den første.
	ckmb_innl	1-25	Første verdi etter innl
	ckmb_maks	1-25 (>=ckmb_innl)	Høyeste CK-MB før angio/PCI.
	nstemi	Y/N	Konklusjon
Sykehistorie	royk	0 – Nei, 1 – Ja 9 – Ukjent	Ja – Nåværende røyker/<1mnd siden røykeslutt
	tidl_royk	Se over	Ja – >1 mnd siden røykeslutt.
	opphopning_ hjertesykdom	0 – Ingen 1 – Familieopphopning, uspesifisert 2 – Prematur hos én førstegradsslektning 3 – Prematur hos ≥2 førstegradsslektninger	0 – Når det er bekreftet negativ familiehistorie. 1 – Registrert opphopning i innkomst, men ikke beskrevet slektsforhold og alder. Prematur er K<65 år, M<55 år
	lungesykdom	0 – Nei 1 – KOLS/astma 2 – Kanskje	1 – Tidligere sykehistorie/journal 2 – Under utredning eller henvist ved utskrivelse
	hjertesvikt	Y/N	Tidligere sykehistorie/journal
	hypertensjon	Y/N	Tidligere sykehistorie/journal
	nyresvikt	Y/N	Tidligere sykehistorie/journal
	diabetes	Y/N	Tidligere sykehistorie/journal
	pvd	Y/N	Tidligere sykehistorie/journal
	vekt	30,0-250,0	Oppgitt eller målt +-3 mnd fra prosedyre. Kurve, andre notater, angioregister.
	hoyde	100,0-220,0 Høyde>vekt.	Oppgitt eller målt. Kurve, andre notater, angioregister.
	kommentar_ sykehistorie	Tekst	Evt. ekstraopplysninger om sykehistorie
Faste legemidler	acehemmer, at2blokker, kalsiumblokker, spirolakton, tiazid, betablokker_fast, loopdiuretika_fast, alfablokker	Y/N per legemiddel	Faste legemidler. Henvisning, innkomstjournal og medisinkurve.
	statin	0 – Ingen, 1 – Fluva, 2- Lova, 3 – Prava, 4 – Simva, 5 – Atorva, 6 – Rosuva, 7 – Ezetimib, 8 – Andre, 9 – Ja, men ukjent statin	Kolesterolsenkende legemidler. Henvisning, innkomstjournal og medisinkurve.
	antirefluksmiddel	1 – Antacida, 2 – H2, 3 – PPI, 4 – Alginat, 0 - Ingen	Fast bruk av antirefluksmidler. Henvisning, innkomstjournal og medisinkurve.
Nye legemi	betablokker_ny nitroinfusjon loopdiuretika_ny	Y/N Y/N Y/N	Oppstart under innleggelsen. Doseøkning markeres ved ja både på ny og fast. I 2005 og starten av 2006 er ikke medikamentkurvene scannet inn og informasjonen kan mangle
Klinisk undersøkelse ved innkomst	puls regelmessigpuls_obj	20-300 1 – Ja, 0 – Nei, 9 - Ikke rapportert	Innkomstjournal, akuttjournal
	s_bt	50-230	Innkomstjournal, akuttjournal
	d_bt	20-160	Innkomstjournal, akuttjournal
	knatrelyder	Y/N	Innkomstjournal. Knatrelyder på under halve lungefeltet. Rapporterer både ensidige og bilaterale funn.
	jvp_okt	Y/N	Innkomstjournal. "Antydning til halsvenestase" uten andre tegn til hjertesvikt i journal tolkes som nei.
	s3gallop	Y/N	Innkomstjournal.
	lungeodem	Y/N	Innkomstjournal.
	kardiogentsjokk	Y/N	Innkomstjournal.
Sykdomspresentasjon ved innleggelse	innl_smerter	Y/N	Har pasienten smerter i akuttmottaket? Spl-notat i mottak og innkomstjournal
	innl_hvilesmerter	Y/N/.	Er smertene tilstede i hvile? Eller bare ved anstrengelser som forflyttning? Spl-notat i mottak og innkomstjournal
	innl_anfall_siste24t	1 – Kun det aktuelle 2 – 2 anfall 3 – 3-5 anfall 4 - >5 anfall 9 – Ukjent	Antall anfall siste døgn. Smerter som har kontinuerlig kommet og gått i et døgn markeres som kun det aktuelle og i kommentarfeltet som kommer og går.

	for_andreplager_ hjertebank		Har pasienten hjertebank i tiden før innleggelse. Ved hjertebank som noen gang samfaller med anginaanfallene og andre ganger ikke, krysses det av både her og for for_anfall_hjertebank.
	forinnl_kommentar	Tekst	
EKG	ekg_st_deviasjon	0 – Ingen ST-deviasjon, 1 – ST-depresjon, 2 – ST-elevasjon, 3 – ST-dynamikk	EKG tatt ved innleggelse. ST-dynamikk er ikkesignifikante deviasjoner i ST-segmentet.
	ekg_maks_stampl	x,x	Amplituden på ST-deviasjonen i mm.
	ekg_maks_avl	1 – aVL, I, V5, V6, 2 – V1, V2, 3 – V3-V4, 4 – II, III, aVF, 9 – Ukjent	I hvilken avledning var amplituden for ST-deviasjonen størst.
	ekg_tinversjon	Y/N	T-inversjoner i to sideliggende avledninger. T-bølgen går motsatt vei av QRS-komplekset. Nedadvent T-bølge er normalt i V1 og aVR.
	ekg_qbolger	Y/N	Tolkning av EKG i innkomst.
	ekg_grenblokk	0 – Ingen grenblokk, 1 – Høyre, 2 – Venstre	Tolkning av EKG i innkomst.
Dynamisk EKG	dynekg_prehosp_ iskemi	1 – Ja 2 – Kanskje 0 – Nei	Er det rapportert iskemi fra henvisende lege eller har amb med ekg der det er iskemitegn? Stoler på sykehusets vurdering ved uenighet om samme ekg.
	dynekg_prehosp_ tinversjon dynekg_prehosp_ stdeviasjon	Y/N 1 – ST-deviasjon, 2 – ST-elevasjon, 3 – ST-dynamikk og 0 - Ingen	
	dynekg_avd_iskemi		Beskrevet EKG-forandringer etter innleggelse?
	dynekg_avd_ tinversjon dynekg_avd_ stdeviasjon	Se over.	
Ekko	ekko	0 – Nei, 1 - Ja	Er ekko nylig blitt tatt? Enten rett før innl eller i løpet av innl, også evt. etter angio.
	ekko_dato		Dato for ekkoundersøkelsen.
	ekko_ej_frak	10-90	Venstre ventrikkel EF
	ekko_hypokinesi	Ja/nei	Regional hypo- eller akinesi
	ekko_kommentar	Tekst	
AEKG etter innleggelse	aekg_innl	0 – Nei, 1 - Ja	Ble det tatt aekg før angio.
	aekg_innl_arsak_ ikketatt	Tekst	Rett til angio heller? Tatt elektivt rett før innleggelsen? Allerede henvist angio? Hopper til AEKG før innleggelse.
	aekg_innl_varighet	xx,x	Minutter varighet av belastning
	aekg_innl_protokoll	Tekst	Som oppgitt i notatet, f.eks. 50W+25W/2min
	aekg_innl_ arsakavsluttet_1	1 – Sliten, 2 – Utmattelse, 3 – Tungpust, 4 – Brystsmerter, 5 – Slitne ben, 6 – Arytmi, 7 – ST-deviasjon, 8 – Annet, 9 - Ukjent	Claudicatio eller "gått ut testen" registreres på annet og i tekstfeltet under. Kan registrere flere.
	aekg_innl_ andrearsaker	Tekst	Om markert annet på årsak 1-3
	aekg_innl_ stdeviasjon	0 - Ingen 1 – ST-depresjon 2 – ST-elevasjon 3 - ST-dynamikk	ST-deviasjoner under eller kort tid etter syklingen.
	aekg_innl_maks_ stdeviasjon	x,x	Hvor høy var den største deviasjonen.
	aekg_innl_maks_ avl		Hvilken avl hadde den høyeste st-deviasjonen. Ved laterale avl menes her V5 og V6 og da rapporteres V5.
	aekg_innl_arytmi	0 – Ingen arytmi, 1 – SVT, 2 – VES, 3 – VT, 4 – Grenblokk, 5 – Annet , 9 – Ukjent	
	aekg_innl_sbt_for	70-200	
	aekg_innl_dbt_for	30-120	
	aekg_innl_sbt_ maks	90-260	
	aekg_innl_dbt_ maks	30-140	
	aekg_innl_sbt_3m	50-200	
	aekg_innl_dbt_3m	30-120	
	aekg_innl_puls_for	30-120	
	aekg_innl_puls_ maks	50-260	
	aekg_innl_puls_3m	30-200	
	aekg_innl_ konklusjon	0 – Negativt, 1 – Positivt, 2 – Mulig positivt, 3 – Inkonklusivt, 4 – Annet, 9 – Ukjent	
	aekg_innl_sep_ betablokker	0 – Nei, 1 – Ja, 2 – NA, 9 – Ukjent	2 – Pasienten står ikke på betablokker. 9 - Pasienten står på betablokker, men det står ikke noe om den er seponert eller ikke
	aekg_innl_ kommentar	Tekst	Andre kommentarer til AEKGet. Blodtrykksfall under syklingen må kommenteres her.
	tidl_AEKG	0 – Nei 1 – Ja	AEKG tatt opptil 1 år i forkant. Dersom ja fylles det ut samme spørsmål som for aekg_innl_x, men med aekg_tidl_x.
	gastroskopi_3m	Y/N	Henvist til gastroskopi innen 3 mnd etter innl
	kommentar	Tekst	Andre opplysninger. Feks om operatøren tviler på klinisk effekt av stentingen. Nylig PCI på andre sykehus

	innl_anfall_varighet	1 – 0-14 min, 2 – 15-29 min, 3 – 30-59 min, 4 – 1-2 timer, 5 – 2-6 timer, 6 – 6-12 timer 7 – 12-24 timer, 8 – Over 24 timer 9 – Ukjent	Bruk varigheten på det alvorligste anfallet. Ved lik styrke, ta gjennomsnittet. Ambulansejournal, innkomst, henvisning og andre journalnotater. Ved smerter som kontinuerlig kommer og går markeres den totale varigheten.
	innl_sentrale_ brystsmerter	Y/N/.	Sentrale, retrosternale
	innl_utstraling	Y/N/.	Arm/erskuldre, hals, rygg, epigastriet.
	innl_tungpust	Y/N/.	Tungpust.
	innl_ anstrengelsesutlost	Y/N/.	Oppstod smertene av fysisk/psykisk angstrengelse. 2005: Ved konstante smerter, er Y her ytterligere forverring av brystsmertene
	innl_anstrengelse	1 – Oppstod ved anstrengelse 2 – Forverres av anstrengelse 0 – Ingen relasjon	2006+
	innl_gir_seg_hvile	Y/N/.	Hvile gir umiddelbart eller i løpet av få minutter symptomlindring.
	innl_gir_seg_nitro	Y/N/.	2005: Gir smertene seg ved nitro. "God effekt av nitro".
	innl_nitro	1 – Ja, 2 – Ja<5 min, 3 – Ja<10 min, 4 –Ja<15 min, 5 – «Ja»>15 min, 0 – Nei	Fra 2006. Effekt av sublingual nitro.
	innl_respavhengig	Y/N/.	Respirasjonsavhengig?
	innl_ stillingsavhengig	Y/N/.	Stillingsavhengig?
	innl_variabel_ terskel	0 – Nei 1 – Åpenbar inkonsitens 2 – CCS-nivåforskjell	1 - f.eks. om pas først har smerter i hvile og kan etterpå gå i gangen uten forverring. Våknet på natten med smerter, men gikk en lang tur på morgenen uten smerter før han gikk til lege.
	innl_hjertebank	1 – Ja 0 - Nei	Har pasienten kjent hjertebank?
	innl_regelmessig	1 – Ja 0 – Nei 9 - Ukjent	Utdypende spm. Opplevd av pasienten eller kjent av helsepersonell.
	innl_frekvens	0-300 9 - Ukjent	Utdypende spm.
	innl_taktskifte	Y/N/.	Utdypende spm. Slo hjertet brått om fra normal rytme til en veldig rask rytme ?
Utvikling før innleggelse	anginaplager_for_ innleggelse	0 – Nei (Hopper over resten av seksjonen) 1 – Ja	Har pasienten hatt anginarelaterte plager i forkant av det aktuelle som medførte innl
	forverring_for_ innleggelse	Y/N	Har plagene eskalert fram mot innleggelsen?
	elektivt_henvist	Y/N	Er pasienten allerede elektivt henvist for anginaplager?
	henvist_til	1 – AEKG 2 – Angio	Hva er pasienten henvist til?
	forverring_etter_ henvisning	Y/N	Har symptomene forverret seg etter henvisningen og den aktuelle hendelsen?
	hyppighet_plager_ forinnl	1 – 1 gang siste uken 2 – Flere ganger siste uken 3 – Flere ganger per dag 4 – Tidligere angina, symptomfri periode	1 – 1 gang siste uken 2 – Flere ganger siste uken 3 – Flere ganger per dag 4 – Tidligere angina, symptomfri periode
	ccs	1 – Ingen begrensninger ved normal fysisk aktivitet. 2 – Lette begrensinger 3 – Uttalte begrensninger 4 – Kan ikke utføre fysisk aktivitet uten smerter, evt. også hvilesmerter 9 – Ukjent	1 – Klasse I: Angina ved tung eller langvarig anstrengelse 2 – Klasse II: Kan gå 100-200 m og én etasje i normalt tempo og under normale forhold 3 – Klasse III: Klarer ikke gå 100-200 m eller én etasje. 4 – Klasse IV: Symptomer ved enhver fysisk anstrengelse. 9 – Utilstrekkelig informasjon
	for_anfall_varighet	1 – 0-14 min, 2 – 15-29 min, 3 – 30-59 min, 4 – 1-2 timer, 5 – 2-6 timer, 6 – 6-12 timer, 7 – 12-24 timer, 8 – Over 24 timer, 9 – Ukjent	Hvor lenge varer normalt de typiske anfallene pasienten har hatt i forkant?
	for_sentrale_ brystsmerter		Se over
	for_ustraling		Se over
	for_tungpust		Se over
	for_ anstrengelsesutlost		Se over
	for_gir_seg_hvile		Se over
	for_gir_seg_nitro		Se over
	for_nitro		Se over
	for_variabel_terskel	0 – Nei 1 – Åpenbar inkonsitens 2 – CCS-nivåforskjell	1 – Variasjon i terskelen som utløser angina fra CCS-klasse 0/1-4, 0-3. 2 – Varisjon ellers mellom CCS-klassene, 1-2, 1-3, 2-3 Åpenbar inkonsistens - F.eks. smerter ved å gå til postkassa eller våkner med symptomer på natta, men kan gå på fjellturer uten symptomer neste dag. Det er ikke variabel terskel at pasienten blir verre fram mot innleggelsen.
	for_hjertebank	Y/N	Kjenner pasienten hjertebank under symptomene.
	for_anfall_dyspesi	Y/N	Har pasienten sure oppstøt samtidig som anginaanfallene.
	for_anfall_hjertebank	Y/N	Har pasienten hjertebank samtidig som anginaanfallene.
	for_andreplager_ dyspesi	Y/N	Har pasienten generelt sure oppstøt i tiden før innleggelse. Ved sureoppstøt som noen gang samfaller med anginaanfallene og andre ganger ikke, krysses det av både her og for for_anfall_dyspepsi.

Paper I

openheart

Pre-test characteristics of unstable angina patients with obstructive coronary artery disease confirmed by coronary angiography

Kristina Fladseth,[1,2] Andreas Kristensen,[2] Jan Mannsverk,[2] Thor Trovik,[2] Henrik Schirmer[3,4]

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[1]Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway
[2]Division of Cardiothoracic and Respiratory Medicine, University Hospital of North Norway, Tromsø, Norway
[3]Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[4]Department of Cardiology, Akershus University Hospital, Lørenskog, Norway

Correspondence to
Dr Kristina Fladseth; kristina.fladseth@unn.no

ABSTRACT

Objective Patients referred for acute coronary angiography (CAG) with unstable angina (UA) have low mortality and low rate of obstructive coronary artery disease (CAD). Better pre-test selection criteria are warranted. We aimed to assess the current guidelines against other clinical variables as predictors of obstructive CAD in patients with UA referred for acute CAG.

Methods From 2005 to 2012, all CAGs performed at the University Hospital of North Norway, the sole provider of CAG in the region, were recorded in a registry. We included 979 admissions of UA and retrospectively collected data regarding presenting clinical parameters from patient hospital records. Obstructive CAD was defined as ≥50% stenosis and considered prognostically significant if found in the left main stem, proximal LAD or all three main coronary arteries. Characteristics were analysed by logistic regression analysis. A score was developed using ORs from significant factors in a multivariable model.

Results The overall rate of obstructive CAD was 45%, and the rate of prognostically significant CAD was 11%. The risk criteria recommended in American College of Cardiology/American Heart Association and European Society of Cardiology guidelines had an area under the curve (AUC) of 0.58. Adding clinical information increased the AUC to 0.77 (95% CI 0.74 to 0.80). Applying the derived score, we found that 56% (n=546) of patients had a score of <13, which was associated with a negative predictive value of 95% for prognostic significant CAD.

Conclusions The current results suggest that CAG may be postponed or cancelled in more than half of patients with UA by improving pre-test selection criteria with the addition of clinical parameters to current guidelines.

Key questions

What is already known about this subject?

- Patients with unstable angina have a low mortality and a low rate of obstructive coronary artery disease.
- Applying symptom characteristics to traditional risk factors improves risk prediction models in patients with stable angina.

What does this study add?

- This study demonstrates that by structuring symptom characteristics and clinical variables it is possible to improve pre-test selection beyond guidelines risk criteria.

How might this impact on clinical practice?

- Better pre-test selection criteria for acute coronary angiography in patients with unstable angina would reduce cost for healthcare systems and avoid exposing patients to unnecessary risk of complications.
- Prospective studies are needed to validate our findings.

INTRODUCTION

Acute chest pain is one of the most common presenting symptoms in emergency departments.[1] It poses a challenge to healthcare systems as critical conditions require prompt diagnosis and treatment, whereas benign disorders need to be identified early to prevent unnecessary and potentially harmful procedures. Suspected acute coronary syndrome refers to patients with chest pain presumably caused by acute myocardial ischaemia and encompasses myocardial infarction (MI) and unstable angina (UA). Patients with UA have no evidence of myocardial injury.[2 3] New, high-sensitive cardiac troponin (hs-cTn) assays detect myocardial injury in a group of patients previously diagnosed as UA, thus changing the diagnosis to MI.[4–6] Consequently, the present UA population have lower mortality and are less likely to have obstructive coronary artery disease (CAD).[5 7 8]

Despite this, the fear of missing an impending MI results in a liberal referral practice of patients with presumed UA to acute coronary angiography (CAG). European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of acute coronary syndrome in

patients without ST elevation recommend performing CAG within 72 hours if there is either an intermediate Global Registry of Acute Coronary Events (GRACE) risk score (109–140), relevant comorbidity, recurrence of symptoms or a positive ECG or stress test.[3 9] GRACE risk score predicts the risk of MI and death and is included in the guidelines as a tool to risk stratify these patients.[10]

A better pre-test selection is warranted. We aimed to assess the GRACE risk score, guidelines risk criteria and other clinical factors capability of predicting obstructive CAD in patients referred for acute CAG on the indication of UA.

METHODS

Study population

Between 1 January 2005 and 31 December 2012, all coronary angiographies (CAG) performed at the University Hospital of North Norway were recorded in a clinical registry. The University Hospital is the sole provider of CAG in Northern Norway, serving a local population of 127 000 and a total regional population of 481 000. We included the 1936 CAGs performed in patients with presumed UA from the local catchment area to facilitate further retrospective data collection from patient hospital records. Patients with more than one procedure per admission were only included once (n=35), and patients with a peak troponin level above the 99th percentile (n=813) were excluded.[2] We also excluded patients mislabelled as UA (n=46) and patients with other primary local hospitals (n=30), incorrectly registered as local patients. Patients who had undergone percutaneous coronary intervention (PCI) within the last 30 days (n=33) were excluded because 91% of these patients had obstructive CAD, warranting acute CAG. Subsequently, the final cohort included 979 UA patient admissions.

Data collection

The registry contains data from all consecutive CAGs, recorded by the operator at the time of the procedure. Linkage to troponin levels from the Department of Clinical Chemistry at the University Hospital of North Norway and to patient hospital records was done by the national 11-digit identification number. From patient hospital records, we retrospectively collected data on symptoms and clinical findings at presentation, preceding symptoms, stress tests, risk factors, comorbidities and medication. The extent of CAD was evaluated by the interventional cardiologist. In patients with prior coronary artery bypass grafting, only those with new obstructive CAD were labelled with obstructive CAD. From July 2009, hs-cTnT replaced standard troponin assay. A standard troponin value of 10 ng/L corresponds to 30 ng/L hs-cTnT. To adjust for this, the troponin values measured up to July 2009 were multiplied by a factor of three.[11 12] In addition, we performed sensitivity analyses on the subpopulation with measured hs-cTnT.

Patients were referred as UA if chest pain at rest, new-onset angina or rapidly worsening angina. We registered the threshold of angina prior to admission by the Canadian Cardiovascular Society grading of angina pectoris. A variation in the threshold of angina of two or more grades was defined as a variable threshold. A declining threshold of angina was not included as a variable threshold. Refractory angina was recorded if intravenous nitroglycerine was given. We defined a history of typical angina as (1) substernal chest pain or discomfort, (2) provoked by physical exertion or emotional stress and (3) relieved by rest within minutes. Atypical angina was defined as two of these characteristics, and patients with one of these characteristics were defined as having non-anginal chest pain.[13] A positive stress ECG was defined as ≥1 mm of ST-segment depression or elevation, or stress-induced chest pain. The guideline criterion of acute heart failure was defined as Killip class II–IV. We calculated the GRACE risk score according to the Fox model for death between hospital admission and 6 months (http://www.outcomes-umassmed.org/grace/files/GRACE_RiskModel_Coefficients.pdf). Family history of CAD was defined as first-degree relatives with premature CAD stated in the patient hospital record. Diabetes mellitus was defined if the diagnosis occurred in the patient hospital records or HbA1c≥6.5%. Hypercholesterolaemia was defined by the use of lipid-lowering drugs or serum cholesterol level of ≥6.5 mmol/L.

Endpoint

As the mortality is very low in patients with UA in the hs-cTn era, we chose obstructive CAD as the primary endpoint of our analyses. To ensure high sensitivity, obstructive CAD was defined as ≥50% angiographic diameter stenosis or fraction flow reserve <0.8 in any epicardial coronary artery.[14] We defined obstructive CAD in the main stem, proximal left anterior descending artery or in all three main coronary vessels (three-vessel disease) as prognostically significant CAD.[14 15] UA resembles stable angina, both having negative hs-cTn and low mortality compared with MI, and an unsure prognostic benefit of revascularisation. Therefore, we assumed no immediate yield of acute revascularisation in the hs-cTn-negative UA patients without prognostically significant CAD.

Statistical analysis

Patient characteristics were reported as counts, percentages or means±SD. Logistic regression analysis was used to investigate predictors of obstructive CAD. In the final multivariable model, we included the predictors with clinical significance and $p<0.05$. We included interaction terms significantly improving the model by receiver operating characteristics (ROC) and the Net Reclassification Improvement. The Hosmer-Lemeshow goodness-of-fit test was not significant for the final model. To investigate the main contributing variables of the GRACE risk score and guidelines risk criteria, we used a forward selection logistic regression analysis, with inclusion at $p<0.05$.

We found that an increasing number of variables with missing information was significantly associated with no obstructive CAD (odds ratio (OR) 0.77, 95% confidence interval (CI) 0.71 to 0.83). We tested this assumption for all variables included in the final model; it was found to be true for all variables except symptom characteristics. Therefore, missing information was combined in the reference group for the other variables, but classified as an independent predictive category for symptom characteristics.

We created a score based on the final multivariable model, weighting the variables with the OR rounded off to the nearest integer. Applying the score, we estimated the proportion of patients with a high negative predictive value (NPV) for prognostically significant CAD, assuming these patients could have been safely discharged without a CAG or referred for elective CAG. The discriminative performance of the GRACE risk score, the ESC and ACC/AHA guidelines risk criteria, and the derived model and its score were tested by ROC analysis. Statistical analyses were performed with Stata V.14.0. All reported differences had two-sided p values<0.05.

RESULTS

Patient characteristics

Of the 979 patients with UA, the overall rate of obstructive CAD was 45% (n=443), falling from 56% (n=70) in 2005 to 29% (n=33) in 2012 (p for trend<0.001). Obstructive CAD of prognostic significance was prevalent in 11% (n=103) of the patients. Patient characteristics are shown in table 1. Patients with obstructive CAD were older, more often male, smoked more, had more hypertension and hypercholesterolaemia, a higher GRACE risk score and a higher rate of established CAD.

Performance of GRACE risk score and risk criteria from guidelines

We found that both patients with and without obstructive CAD had low GRACE risk scores, 83 versus 76, respectively. In total, <1% (n=7) of the patients with UA had a high GRACE risk score (>140) and 11% (n=104) had an intermediate GRACE risk score (109–140). In patients with a high GRACE score, five out of seven patients had obstructive CAD versus half of the patients with an intermediate GRACE score. According to the ESC guidelines, 21% (n=202) of the patients in our study were candidates for a selective invasive strategy based on the results of a non-invasive stress test. However, 26% (n=52) of these patients had obstructive CAD and 5.5% (n=11) had prognostic significant CAD. ACC/AHA guidelines would allocate conservative treatment to 31% (n=299) of the patients, of which 32% (n=96) had obstructive CAD and 4.3% (n=13) prognostic significant CAD. High-risk criteria from ESC and ACC/AHA guidelines were present in 25% (n=242) and 22% (n=216) of the patients, respectively. These

Table 1 Patient characteristics

	Obstructive CAD (n=443)	No obstructive CAD (n=536)	P values
Age (years)	65±11	60±12	<0.001
Male gender (%, n)	67% (297)	52% (281)	<0.001
BMI (kg/m^2)	28±5	28±6	0.543
Heart rate (beats/min)	68±14	71±16	0.014
Systolic blood pressure (mm Hg)	145±22	140±21	<0.001
Diastolic blood pressure (mm Hg)	81±12	80±13	0.223
Use of antihypertensive drugs (%, n)	77% (339)	63% (339)	<0.001
Hypercholesterolaemia (%, n)	74% (326)	66% (352)	0.008
Diabetes mellitus (%, n)	18% (79)	15% (82)	0.287
Established coronary artery disease (%, n)	59% (263)	39% (209)	<0.001
Previous MI (%, n)	36% (158)	21% (113)	<0.001
Previous PCI (%, n)	46% (205)	33% (177)	<0.001
Previous CABG (%, n)	18% (80)	14% (74)	0.069
Family history of CAD (%, n)	50% (220)	53% (285)	0.274
Smoking status			0.008
Current smoker (%, n)	29% (130)	27% (143)	
Former smoker (%, n)	44% (195)	38% (201)	
GRACE risk score	83±22	76±24	<0.001

Values are % (n) or mean±SD.
BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; GRACE, Global Registry of Acute Coronary Events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

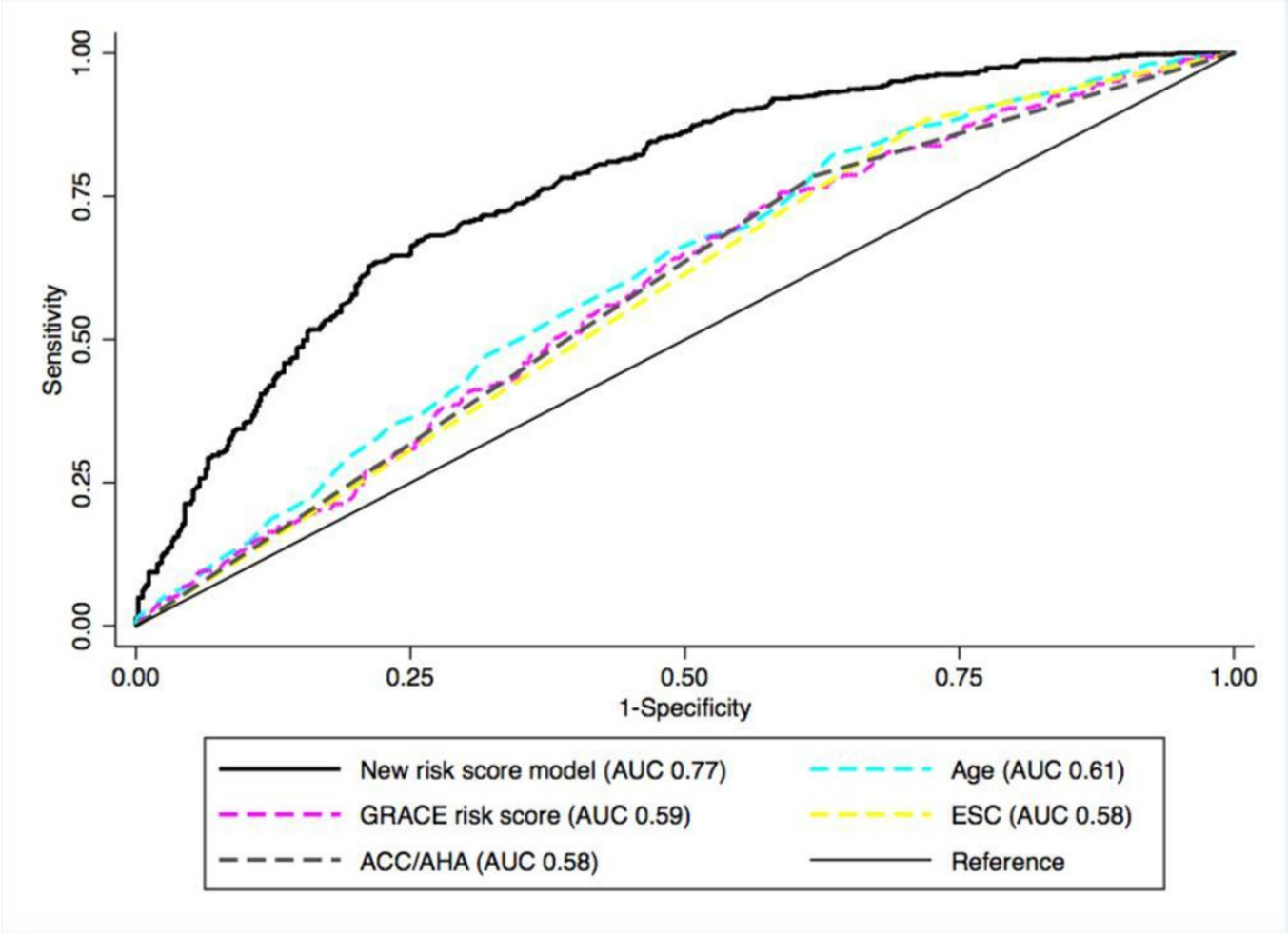

Figure 1 Prediction of obstructive coronary artery disease in unstable angina patients referred for coronary angiography. Receiver operating characteristics curves for age, Global Registry of Acute Coronary Events (GRACE) risk score, European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines risk criteria, and the new risk score model. AUC, area under the curve.

patients did not have more CAD than patients with intermediate-risk criteria.

GRACE risk score, ESC and ACC/AHA guidelines had similar area under the curve (AUC) for obstructive CAD, with AUC of 0.59 (95% CI 0.55 to 0.62), 0.58 (95% CI 0.56 to 0.61) and 0.58 (95% CI 0.55 to 0.61), respectively. Age alone had a significantly higher AUC of 0.61 (95% CI 0.58 to 0.65, p=0.037) (figure 1). The main contributing variables in the GRACE risk score and guidelines risk criteria were age, systolic blood pressure at admission, prior PCI, Killip class and a positive stress test. We did not find more ST-T abnormalities in the ECG of patients with obstructive CAD.

Prediction of obstructive coronary artery disease

A history of typical angina symptoms, Canadian Cardiovascular Society angina grade 3 or 4, no variable threshold of exertional angina, no history of palpitations, prior PCI, positive stress testing, smoking, hypertension, age >65 years and male gender all added independently significant information in a multivariable model, increasing the AUC for obstructive CAD to 0.77 (95% CI 0.74 to 0.80, p<0.001) (table 2, figure 1), significantly higher than the GRACE risk score and guidelines risk criteria. The significant interaction term between age and prior PCI was also included. From the model, we derived a score predicting obstructive CAD with an OR of 1.40 (95% CI 1.33 to 1.47, p<0.001) per score level increase. With a cut-off level of <13, the NPV was 95% for prognostic significant CAD in 56% (n=546) of patients with UA referred for acute CAG. For the 44% (n=295) of patients with a score <12 the NPV was 97%. Stratified by sex, a cut-off level of <14 gave a negative predictive value of 95% for 82% (n=330) of females, and a cut-off level of <12 and<13 gave NPVs of respectively 96% for 20% (n=177) and 93% for 43% (n=251) of males (table 3).

In univariable analysis, shorter pain duration predicted obstructive CAD (<2–6 hours, OR 1.82, 95% CI 1.34 to 2.48, p<0.001), whereas chest pain related to change in body posture (n=23) gave lower odds for obstructive CAD (OR 0.18, 95% CI 0.05 to 0.68). We found that pain relief by nitrates, dyspnoea, pain radiation and number of chest pain episodes during the last 24 hours were not

Table 2 Univariable and multivariable predictors of obstructive coronary artery disease in patients with unstable angina

Characteristics	n=979	Univariable model, OR (95% CI)	Multivariable model, OR (95% CI)	Score
Age >65 years	410	1.92 (1.49 to 2.49)	2.94 (1.97 to 4.41)	3
Male gender	578	1.85 (1.42 to 2.40)	2.03 (1.48 to 2.79)	2
Prior PCI	382	1.75 (1.35to 2.26)	1.85 (1.21 to 2.81)	2
Hypertension*				
1	303	2.79 (1.82 to 4.28)	2.26 (1.36 to 3.75)	2
2	151	2.27 (1.40 to 3.69)	2.08 (1.20 to 3.61)	2
3	372	3.05 (2.01 to 4.63)	2.36 (1.43 to 3.89)	2
Current smoker	273	1.48 (1.06 to 2.06)	2.53 (1.70 to 3.77)	3
Previous smoker	396	1.58 (1.17 to 2.14)	1.37 (0.97 to 1.95)	1
Positive stress test	278	1.60 (1.21 to 2.11)	1.85 (1.34 to 2.56)	2
Best CCS grade				
1	84	1.59 (1.01 to 2.51)	0.91 (0.54 to 1.56)	0
2	91	2.12 (1.36 to 3.30)	1.05 (0.62 to 1.78)	0
3–4	107	4.71 (2.97 to 7.48)	1.83 (1.03 to 3.26)	2
No variable threshold†	253	4.03 (2.96 to 5.48)	1.96 (1.28 to 2.99)	2
Symptoms before admission				
Non-anginal pain	243	2.50 (1.58 to 3.96)	1.89 (1.14 to 3.14)	2
Atypical angina	284	5.75 (3.67 to 9.01)	3.40 (2.01 to 5.75)	3
Typical angina	141	6.49 (3.90 to 10.8)	3.65 (1.99 to 6.69)	4
Missing	145	3.10 (1.87 to 5.12)	2.36 (1.36 to 4.08)	2
No palpitations	844	1.93 (1.26 to 2.94)	1.71 (1.07 to 2.74)	2
Interaction: prior PCI and age >65 years			0.50 (0.28 to 0.91)	–2
AUC			0.77 (0.74 to 0.80)	

*(1) Use of antihypertensive drugs and normal blood pressure on admission, (2) high blood pressure on admission, (3) 1+2.
†No random variation in the threshold of angina defined by two or more CCS grades.
AUC, area under the curve; CCS, Canadian Cardiovascular Society grading of angina pectoris; PCI, percutaneous intervention .

Table 3 Prevalence of obstructive coronary artery disease in unstable angina patients by score level

Score	n	Obstructive CAD, n (row %)	Prognostic significant CAD, n (row %)	Revascularised, n (row %)
≤5	25	–	–	–
6–7	54	4 (7.4%)	–	3 (5.6%)
8	74	15 (20%)	2 (2.7%)	15 (20%)
9	53	12 (23%)	2 (3.8%)	12 (23%)
10	114	26 (23%)	3 (2.6%)	23 (20%)
11	106	42 (40%)	7 (6.6%)	35 (33%)
12	120	49 (41%)	12 (10%)	36 (30%)
13	101	56 (55%)	17 (17%)	46 (46%)
14	90	63 (70%)	11 (12%)	51 (57%)
15	84	49 (58%)	10 (12%)	46 (55%)
16–17	97	78 (80%)	23 (24%)	69 (71%)
≥18	61	49 (80 %)	16 (26%)	46 (75%)
AUC		0.77 (0.74–0.79)	0.72 (0.68–0.77)	0.75 (0.71–0.78)

AUC, area under the curve; CAD, coronary obstructive artery disease.

associated with obstructive CAD. Neither were chest wall pain, pain related to breathing or self-reported similarity to prior CAD symptoms, but most patient records lacked this information. A GRACE risk score ≥109 was not significantly associated with obstructive CAD (OR 1.37, 95% CI 0.92 to 2.04).

In sensitivity analyses of the 340 patients included after the implementation of hs-cTnT, the AUC of the multivariabel model improved from 0.77 (95% CI 0.74 to 0.80) to 0.81 (95% CI 0.76 to 0.85, although with larger CIs) (online supplementary Table 1). The derived risk score performed similarly on the subpopulation with OR of 1.39 (95% CI 1.28 to 1.52). With a cut-off level of <13, we were able to exclude or delay 59% of the patients (n=201) to acute CAG with an NPV of 96% for prognostic CAD. Further, with a cut-off level of <9 the score demonstrated an NPV of 96% for any obstructive CAD in 21% of the patients (n=73) (online supplementary Table 2).

DISCUSSION

In our population-based cohort, we have demonstrated that patients with presumed UA referred for acute CAG have low rates of obstructive CAD and low GRACE risk score. By implementing symptom characteristics and clinical information in a new risk score, it was possible to rule out a higher number of patients with lower rates of obstructive CAD than by applying guidelines risk criteria.

There is to our knowledge no other studies using symptoms to predict obstructive CAD in patients with UA. The HEART score includes the clinicians' suspicion of critical disease to predict the risk of MI, PCI, CABG and death in an all-cause chest pain population.[16] In stable angina, typical angina symptoms added to risk scores is known to improve the prediction of obstructive CAD.[17 18] In our study, we found that a history of typical angina with a stable or consistently decreasing threshold in the time prior to the acute admission was strongly associated with obstructive CAD. The acute presentation leading to admission was of less importance. Traditional risk factors such as age and smoking were also strongly associated with obstructive CAD, followed by male gender, hypertension and prior PCI. Age however, was significantly reduced as risk factor for those with prior PCI. This led to a positive interaction term in the model and could indicate a protective effect of PCI, secondary prevention or most likely both.

The definition of unstable angina

Our population underwent clinical decision-making before referral. However, with rates of obstructive CAD as low as 29% in the end of the study period, patient selection was poor. It seems other aetiologies for chest pain dominated. We found that palpitations, a known symptom of panic disorder, was associated with lack of obstructive CAD on invasive angiography.[19] Gastrointestinal, musculoskeletal and panic disorders are all known to be highly prevalent in patients with acute or stable chest pain and no evidence of myocardial ischemia, and were likely prevalent in our population.[20–22]

Braunwald and Morrow suggested that increasingly sensitive troponins would make UA a redundant diagnosis.[23] However in clinical practice, UA remains a challenging diagnosis as objective criteria are rarely present. The fear of uncertainty among clinicians and patients may lead to overuse of presumed UA as indication for acute CAG, even in patients with low clinical suspicion of CAD. This is a likely cause for the low rates of obstructive CAD in our population. Despite the low prevalence of CAD in our population, 79% satisfied the guidelines criteria for acute CAG within 72 hours, which in our opinion warrants better pre-test selection criteria.

Relevance of guidelines risk criteria and GRACE risk score in the unstable angina population

The GRACE risk score predicts 3-year mortality in acute coronary syndrome with a superior AUC of 0.82.[10] The overall low GRACE score observed in both patients with and without obstructive CAD is reassuring and supports a low mortality in the present-day UA population. It may also explain why the GRACE risk score and guidelines encompassing non-ST elevation MI (NSTEMI) had poor discriminative ability for obstructive CAD in patients with UA.[3 10] The low mortality of hs-cTn-negative UA is also demonstrated in other studies, with a 90-day mortality and MI rate for hs-cTnT-negative UA patients of 0.6% and 1.7%, respectively.[8] Even high-risk UA have a 30-day combined death and MI rate of approximately 2%.[7 24]

Guidelines for NSTEMI/UA recommend an invasive approach in many patients with UA, but the implications of an invasive strategy are not known. Available trials do not report separate findings for patients with or have not implemented hs-cTn assays to discriminate between MI and UA. Meta-analyses of existing trials up to 2015 differ in opinion of the benefit of routine revascularisation for the combined UA and NSTEMI population.[25–28] It seems likely that hs-cTn-negative UA patients will have less benefit than NSTEMI patients.

The low rate of obstructive CAD, MI and death, as well as an unsure prognostic benefit of revascularisation in the hs-cTn-negative UA patients, questions the resource utilisation of acute CAG in most patients with UA. Our study indicates that it is possible to rule out or delay CAG in more than half of the patients with UA by implementing a new risk score with symptoms characteristics and clinical information in addition to risk criteria in guidelines.

Strengths and limitations

The major strengths of our study are the inclusion of all consecutive CAGs performed on the indication of UA within a confined geographical area for eight subsequent years, and that all variables included in our risk score are obtained in daily clinical practice. A potential limitation is the relatively small numbers of patients with prognostic significant CAD. We have exclusively investigated patients with UA referred for CAG, and thereby do not know how

the score performs in an extended chest pain/UA population. The accuracy and consistency of the retrospective information collected from hospital records as well as many missing variables are further limitations. To minimise observer bias, the data collection was blinded for the CAG result. However, if the CAG was soon after followed by coronary artery bypass grafting or gastroscopy, this was visible to the data collector, indicating positive or negative findings of the CAG result, respectively. Since we excluded patients with PCI within 30 days, we could not test the post-MI angina criterion, and the ACC/AHA criterion of PCI within 6 months was only applied for 1–6 months. Further, we did not have enough information on ESC guidelines' recurrence of symptoms to validate its potential role. We used the peak troponin value to define patients with MI. Therefore, we cannot exclude a significant bias due to the exclusion of UA patients with chronic hs-cTn elevation without a significant rise and/or fall (eg, due to chronic heart failure or severe renal dysfunction). However, as these patients have a higher risk of CAD, the authors believe that these patients usually should be offered CAG on a lower threshold and should be addressed in own focused prospective studies. As the adjustment for standard troponin to hs-cTnT was only applicable for patients with troponin values above the limit of detection, we may have included NSTEMI patients before the implementation of hs-cTnT in 2009.

CONCLUSIONS

Our results suggest that by structuring symptom characteristics and clinical variables it may be possible to postpone or cancel acute CAG in over half of the patients referred with presumed UA. This would reduce cost for healthcare systems, avoid exposing patients to unnecessary risk of complications and release capacity for more critical diagnoses. Prospective studies are needed to validate our findings.

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Supplementary files

Sensitivity analyses of the subgroup high sensitivity troponin population

In our study, 35% of the patients (*n* = 340) were included after the implementation of high sensitivity troponin (hs-cTn) assay in July 2009. In this subpopulation, the rate of obstructive coronary artery disease (CAD) was 35% (*n* = 119) and the rate of prognostic CAD was 9.4% (n = 32). Patients with obstructive CAD were younger in the hs-cTn subpopulation compared to the study population, but yet significantly higher than the patients with no CAD. However, there were no longer a significant difference in GRACE risk score between patients with and without obstructive CAD. The hs-cTn subpopulation had lower blood pressure, less established CAD, and more diabetes.

The multivariabel model have a numerically higher AUC of 0.81 (95% CI 0.76-0.85) in the subpopulation (Supplementary table 1). The derived risk score performed similarly on the subpopulation with OR of 1.39 (95% CI 1.28-1.52). With a cut-off level of <13, we were able to exclude or delay 59% of the patients (*n* = 201) to acute CAG with a negative predictive value (NPV) of 96% for prognostic CAD. Further, with a cut-off level of <9 the score demonstrated a NPV of 96% for any obstructive CAD in 21% of the patients (*n* = 73) (Supplementary table 2).

Supplementary table 1. Univariable and multivariable predictors of obstructive coronary artery disease in unstable angina patients. Sensitivity analyses in the high sensitivity troponin population.

Characteristics	*n* = 340	Univariable model, OR (95% CI)	Multivariable model, OR (95% CI)
Age > 65 years	126	1.24 (0.78-1.96)	1.45 (0.7-3)
Male gender	198	2.13 (1.33-3.41)	2.16 (0.1-1.3)
Prior PCI	109	1.88 (1.17-3.01)	1.75 (0.8-3.7)
Hypertension*			
1	108	2.65 (1.29-5.43)	2.25 (0.93-5.46)
2	54	1.54 (0.66-3.60)	1.25 (0.47-3.34)
3	113	2.95 (1.45-6.03)	2.88 (1.19-6.98)
Current smoker	88	1.73 (0.96-3.12)	2.80 (1.32-5.93)
Previous smoker	136	1.63 (0.95-2.77)	1.48 (0.78-2.81)
Positive stress test	107	1.75 (1.09-2.81)	2.72 (1.51-4.92)
Best CCS grade			
1	18	1.59 (0.59-4.25)	0.54 (0.16-1.81)
2	33	2.01 (0.99-4.34)	0.57 (0.20-1.62)
3-4	34	5.98 (2.73-13.1)	1.64 (0.54-4.97)
No variable threshold	91	4.42 (2.66-7.33)	2.64 (1.1-6.2)
Symptoms before			
Non-anginal pain	78	3.27 (1.35-7.93)	3.16 (1.21-8.24)
Atypical angina	92	9.27 (4.01-21.4)	5.92 (2.25-15.6)
Typical angina	58	8.87 (3.63-21.7)	4.69 (1.62-13.6)
Missing	33	6.54 (2.39-17.8)	7.07 (2.34-21.4)
No palpitations		2.30 (1.07-4.96)	2.32 (0.96-5.63)
AUC			0.81 (0.76-0.85)

AUC indicates area under the curve; CI, confidence interval; CCS, Canadian Cardiovascular Society grading of angina pectoris; GRACE, Global Registry of Acute Coronary Events; PCI,

percutaneous intervention and OR, odds ratio. *1: Use of antihypertensive drugs and normal blood pressure on admission, 2: high blood pressure on admission, 3: 1+2.

Supplementary table 2. Prevalence of obstructive coronary artery disease in unstable angina by score level. Sensitivity analyses in the high sensitivity troponin population.

Score	*n*	Obstructive CAD, *n* (row %)	Prognostic significant CAD, *n* (row %)
≤ 5	13	-	-
6-7	30	1 (3.0%)	-
8	30	2 (6.7%)	-
9	22	6 (27%)	1 (4.5%)
10	35	4 (11%)	1 (2.9%)
11	37	11 (30%)	1 (2.7%)
12	34	15 (44%)	6 (18%)
13	31	13 (42%)	4 (13%)
14	27	16 (59%)	4 (15%)
15	31	16 (52%)	4 (13%)
16-17	29	22 (76%)	7 (24%)
≥ 18	21	13 (62%)	4 (19%)
AUC		0.78 (0.73-0.83)	0.74 (0.67-0.82)

AUC indicates area under the curve and CAD, coronary obstructive artery disease.

Paper II

Outcomes after coronary angiography for unstable angina compared to stable angina, myocardial infarction and an asymptomatic general population

Kristina Fladseth, MD,[a,b] Tom Wilsgaard, PhD,[c] Haakon Lindekleiv, MD PhD,[b] Andreas Kristensen, MD,[b] Jan Mannsverk, MD PhD,[b] Maja-Lisa Løchen, MD PhD,[c] Inger Njølstad, MD PhD,[c] Ellisiv B Mathiesen, MD PhD,[a,d] Thor Trovik, MD PhD,[b] Svein Rotevatn, MD PhD,[e, f] Signe Forsdahl, MD PhD,[g] and Henrik Schirmer, MD PhD[a,h,i]

[a]Department of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway

[b]Department of Cardiology, University Hospital of North Norway, Tromsø, Norway

[c]Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway

[d]Department of Neurology, University Hospital of North Norway, Tromsø, Norway

[e]Department of Heart Disease, Haukeland University Hospital, Bergen, Norway

[f]Norwegian Registry of Invasive Cardiology, Bergen, Norway

[g]Department of Radiology, University Hospital North Norway, Tromsø, Norway

[h]Institute of Clinical Medicine, University of Oslo, Lørenskog, Norway

[i]Department of Cardiology, Akershus University Hospital, Lørenskog, Norway

Address for correspondence:

Kristina Fladseth

Cardiovascular Research Group, Department of Clinical Medicine, UiT The Arctic University of Norway, 9037 Tromsø, Norway

Telephone: +47 98412227

Fax: +47 77646838

E-mail: kristina.fladseth@unn.no

Twitter: @kristinaflad @UiTromso @UiThelsefak @UNN_HF

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Abstract

Background: The outcomes of real-world unstable angina (UA) patients in the high-sensitivity troponin era is unclear. We aimed to investigate the outcomes of UA patients referred to coronary angiography compared to stable angina (SA) and myocardial infarction (MI).

Methods: This is a registry-based cohort of patients with no prior coronary artery disease (CAD) referred to invasive or CT coronary angiography from 2013-2018 in Northern Norway (n=9694, 51% SA, 12% UA, 23%, non-ST segment elevation MI [NSTEMI] and 14% STEMI). We used Cox models to estimate the hazard ratios (HR) for all-cause mortality and major adverse cardiovascular events (MACE), defined as cardiovascular death, MI or obstructive CAD.

Results: Death and MACE occurred in 5.3% and 8.4% of patients during a median follow-up of 2.8 years, respectively. In multivariable adjusted analyses, compared with UA patients, SA patients had a 38% lower risk of death and a nonsignificantly lower risk of MACE (HR 0.62, 95% confidence interval [CI]) 0.44-0.89, HR 0.86, 95% CI 0.66-1.11). NSTEMI patients had a 2.4-fold higher risk of death (HR 2.39, 95% CI 1.38-4.14) and a 1.6-fold higher risk of MACE (HR 1.62, 95% CI 1.11-2.38) than UA patients during the first year after coronary angiography, but a similar risk thereafter. There was no difference in the risk of death for UA patients with non-obstructive CAD and obstructive CAD (HR 0.78, 95% CI 0.39-1.57).

Conclusion: UA patients had a higher risk of death but a similar risk of MACE compared to SA patients, and a lower 1-year risk of death and MACE compared to NSTEMI patients.

Keywords: High-sensitivity troponins, non-ST elevation acute coronary syndrome, non-obstructive coronary artery disease, prognosis

Abbreviations

CABG – Coronary artery bypass graft

CAD – Coronary artery disease

CCTA – Coronary computed tomography angiography

ESC – European Society of Cardiology

FFR – Fractional flow reserve

Hs-cTn – High-sensitivity troponins

ICA – Invasive coronary angiography

MACE – Major cardiovascular events

MI – Myocardial infarction

NORIC – Norwegian Registry of Invasive Cardiology

NSTE-ACS – Non-ST-segment elevation acute coronary syndrome

NSTEMI – Non-ST-segment elevation myocardial infarction

PCI - Percutaneous coronary intervention

SA – Stable angina

STEMI – ST-segment elevation myocardial infarction

UA – Unstable angina

Introduction

The diagnosis and management of unstable angina (UA) have changed over the last decade, with increasingly sensitive troponins and coronary CT angiography (CCTA) as an alternative to invasive coronary angiography (ICA) (1-3). The implementation of high-sensitivity troponins (hs-cTn) led to a 20% relative increase in detection of non-ST-segment elevation myocardial infarction (NSTEMI) and a reciprocal decrease in the diagnosis of UA (4). This is believed to have significantly improved the outcomes of UA. However, existing studies on the outcomes of UA either report results for an unselected chest pain population in the emergency department, combined results for UA and NSTEMI, apply older, less sensitive troponins and biomarkers to differentiate between UA and NSTEMI, or include individuals with high-risk features and percutaneous coronary intervention (PCI) (3-17). As non-obstructive CAD is highly prevalent and associated with a poorer prognosis than previously believed in both stable angina (SA) and myocardial infarction (MI) (18-23), the outcomes of all patients with suspected UA, including UA with non-obstructive CAD, are of high interest. Therefore, we aimed to study the outcomes of a real-world population with no prior CAD presenting to coronary angiography with clinically suspected UA compared to SA, MI and an asymptomatic general population.

Methods

Study population

This registry-based cohort study included patients referred to coronary angiography at the University Hospital of North Norway (UNN) from 1 January 2013 to 31 December 2018. UNN was the sole centre for coronary angiography for the 480,000 inhabitants of Northern Norway. We included patients referred to ICA or CCTA for SA, UA, NSTEMI or ST-

segment elevation MI (STEMI) (Figure 1). Patients without a valid personal identification number or not registered as inhabitants in Northern Norway at inclusion were excluded (n=226). Further, we excluded patients with prior CAD (n=1294) and patients with other indications for coronary angiography, including pre-operative assessment before heart valve surgery and arrhythmia evaluation (n=1810). Patients with missing data on the indication, findings or treatment (n=25) and misclassifications that could not be settled (n=7) were also excluded. We excluded 94 patients with obstructive CAD or inconclusive results on CCTA not followed by an ICA within 180 days. In addition, we excluded patients under the age of 30 years (n=64) to enable comparison with a general population above 30 years of age.

As an asymptomatic reference, we included individuals from the general population recruited from the sixth survey of the Tromsø Study (Tromsø6) conducted in 2007-2008. The Tromsø Study is a prospective, population-based cohort study in the largest city in Northern Norway (24). Tromsø6 included 12,984 men and women aged 30 to 87 years old, had 66% attendance and is described in further detail elsewhere (25). We excluded 1014 individuals with known CAD based on Tromsø Study data and the coronary angiography registry, including individuals registered with prior MI, PCI or/and coronary artery bypass grafting (CABG) at their first coronary angiography. We also excluded eight individuals with self-reported angina on the questionnaire followed by coronary angiography within 180 days. In addition, three participants withdrew their written consent and were also excluded.

In total, we included 9,694 symptomatic individuals and 11,959 asymptomatic individuals with no prior CAD (Figure 1). The participants were followed from the date of coronary angiography or the date of enrolment in Tromsø6 until 31 December 2018.

Data Collection

The interventional cardiologist or cardiac radiologist recorded data from each consecutive coronary angiography at the time of the procedure. This included prior medical history, risk factors, procedural data, and the indication for coronary angiography. Data from ICA has been recorded from 2005 to 31 April 2013 in a local registry and from 1 May 2013 in the national NORIC. Data from CCTA has been recorded since the implementation in routine practice in February 2013, first in a local registry, and from 1 January 2016 in NORIC. NORIC has over 99% coverage for ICA (26). We found no increase in missing data after transitioning from local registries to a national registry.

In the local registry, admissions with likely misclassifications, such as no obstructive CAD and revascularisation, were systematically examined and corrected based on the patient hospital records. NORIC contains predefined constrictions to avoid these misclassifications. Procedures within seven days were included as one admission. To conclude on the overall result of the admission, we systematically reviewed the use of fractional flow reserve (FFR), the extent of CAD, revascularisation and the order of the procedures. CCTA with obstructive CAD or inconclusive results followed by ICA within 180 days was replaced by the ICA results.

The Tromsø Study collects data about the study participants by physical examinations, blood samples and self-administered questionnaires. An endpoint committee has verified all incident MIs. Vital status, date of death and cause of death was collected from the National Population Registry and the National Cause of Death Registry, which contains data for all deaths occurring in Norway or abroad for Norwegian citizens. The national personal identification number allowed for linkage on an individual level.

Exposures and covariates

The extent of coronary artery disease

The extent of CAD was registered per segment by the interventional cardiologist and cardiac radiologist. Obstructive CAD was defined as ≥50% diameter stenosis of an epicardial coronary artery (27). Non-obstructive CAD was defined as 0-49% diameter stenosis. FFR was generally measured with visual diameter stenosis around 40-70%, and obstructive CAD was defined as FFR below 0.80. The extent of obstructive CAD was further divided into one-vessel (1VD), two-vessel (2VD) and three-vessel (3VD) and/or left main stem disease (LMS).

Indication for coronary angiography

The indication for coronary angiography (i.e., SA, UA, NSTEMI, or STEMI) was decided by the interventional cardiologist according to international guidelines and the universal MI definition (3, 28-30). Hs-cTn was implemented in 2009, and the Third Universal MI definition using a rise and/or fall with at least one value over the 99th percentile of hs-cTn to diagnose MI was implemented during 2012-2013 (31, 32). We included only patients from 2013 onwards to comply with the current MI definition (30).

NORIC contained information on troponin before and after ICA in 70% of UA patients and 43% of NSTEMI patients. The local registry had the maximum troponin value before ICA in over 90% of UA and NSTEMI patients with UNN as their local hospital (34% of the local registry). In NORIC, we redefined nine patients from UA to NSTEMI based on significantly falling or rising hs-cTn and no PCI. In patients with PCI, a rise in troponin is likely related to the procedure, and these patients remained categorised as UA.

Covariates

The coronary angiography registries contain information regarding age, sex, smoking status, diabetes, use of lipid-lowering and antihypertensive drugs, body mass index, and kidney function. Overall, there were low rates of missing data for cardiovascular risk factors (0-6%). Kidney function was reported as estimated glomerular filtration rate (eGFR) and was missing in 10% in the coronary angiography registries. The local CCTA registry from 2013 to 2015 did not record data on diabetes or drugs.

Outcomes

The primary endpoint was all-cause mortality, and the secondary endpoint was major adverse cardiovascular events (MACE). For the definition of MACE, the following endpoints were available: cardiovascular death, non-fatal MI referred to coronary angiography or new obstructive CAD confirmed by ICA.

Statistical analysis

Baseline characteristics are reported as counts, percentages or means ± standard deviation. Individuals were followed from the date of coronary angiography or date of enrolment in the Tromsø Study until the date of death or until the end of the study period, 31 December 2018. The cause of death was only available through 2017. Cumulative incidence was expressed as the number of events per 100 individuals at one and five years. Crude incidence rates (IR) were expressed as the number of events per 1000 person-years at risk. We used Cox proportional hazard regression models to estimate the survival functions and hazard ratios (HR) for all-cause mortality and MACE by indication of coronary angiography and extent of CAD. The reference group was UA. Individuals in the general population referred to coronary angiography during the study period contributed with person-time as the

asymptomatic general population until the date of the coronary angiography, after that as symptomatic.

Survival functions for all-cause mortality and MACE were presented adjusted for age and stratified by sex. The HR for all-cause mortality and MACE were estimated in two models; model 1 adjusted for age and sex, and model 2 adjusted for age, sex, smoking, antihypertensive drugs, lipid-lowering drugs, diabetes, BMI and kidney function. Statistical interactions between the exposure variables and sex were tested by including cross-product terms in the models and was significant for the general population and SA. The models are presented stratified by sex in the Supplementary Tables 1-3. The proportional hazard assumption was tested by Schoenfeld residuals. As expected, the assumption was violated as the relative risk of outcomes changed over time. Therefore, the main analysis was presented in two time periods, from 0-1 year and after the first year.

To handle missing data on cardiovascular risk factors, we first assessed if the patient had procedures close in time with available data and imputed this data. Then, the remaining missing data was replaced using multiple imputation. The patients with CCTA had fewer cardiovascular risk factors than patients with ICA, and the multiple imputation was performed separately for these groups.

We applied a two-sided significance level of 5%. The analysis was performed in Stata 16.1 (StataCorp, Texas, USA).

Ethics

The regional ethics committee and the local data protection official at UNN approved the study. We performed a Data Protection Impact Assessment in accordance with the European Union General Data Protection Regulation. The Tromsø Study is approved by the Norwegian

Data Protection Agency and the study participants in Tromsø6 gave informed written consent.

Results

We included 9,694 symptomatic individuals that underwent coronary angiography for SA (51%), UA (12%), NSTEMI (23%) or STEMI (14%), and 11,959 asymptomatic individuals from the general population, with no prior history of CAD. UA constituted 25% of the ACS patients, and this proportion remained stable during the study period (p for trend=0.40). Baseline characteristics are found in table 1. The UA patients had a mean age of 61 years, and 61% were men. The mean age was slightly lower than for SA, NSTEMI and STEMI patients, and the proportion of men was higher for UA patients than SA patients but lower than for NSTEMI and STEMI patients. UA patients had an intermediate level of cardiovascular risk factors compared to SA, NSTEMI and STEMI, and higher than the general population. The proportion of non-obstructive CAD was 65% for SA, 60% for UA, 18% for NSTEMI and 7% for STEMI patients (Table 1).

All-cause mortality

There were 511 (5.3%) deaths during a median follow-up time of 2.8 years (interquartile range 1.3-4.4) for patients referred to coronary angiography. Cardiovascular disease was the cause of death in 32% of the patients. Survival functions for all-cause death for SA, UA, NSTEMI, STEMI and the general asymptomatic population are shown in Figure 2 and Supplementary Figure 1. The mortality of UA and SA patients was similar to the general population during the first year, while NSTEMI and STEMI patients had higher mortality. After the first year, SA ad UA had higher mortality than the general population, and there

was less difference in mortality between the different presentations of CAD with more parallel curves.

IR and HR of all-cause mortality for UA compared to SA, NSTEMI, STEMI and the asymptomatic general population are shown in Table 2 and Table 3. The IR for death was 8.5 per 1000 person-years (95% confidence interval [CI] 8.0-9.0) in the general population, 9.7 (95% CI 8.3-11.5) in SA patients, 14.9 (95% CI 11.4-19.6) in UA patients, 29.7 (95% CI 25.6-34.3) in NSTEMI patients and 36.5 (95% CI 30.9-43.2) in STEMI patients. Cumulative 1-year and 5-year mortality rates are presented in Supplementary Table 4.

In multivariable adjusted analyses, the risk of death compared to UA patients was 46% lower in the general population (HR 0.54, 95% CI 0.39-0.76), 38% lower in SA patients (HR 0.62, 95% CI 0.44-0.89), nonsignificantly higher in NSTEMI (HR 1.26, 95% CI 0.90-1.78) and 62% higher in STEMI patients (HR 1.62, 95% CI 1.10-2.37) (Table 2). These findings were similar in analyses stratified by sex (Supplementary Table 2). The 1-year risk after coronary angiography compared to UA patients was lower in the general population (HR 0.48, 95% CI 0.24-0.95), nonsignificantly lower in SA patients (HR 0.53, 95% CI 0.26-1.06), 2.5-fold higher in NSTEMI patients (HR 2.47, 95% CI 1.30-4.71), and 4-fold higher in STEMI patients (HR 3.84, 95% CI 1.95-7.57) (Table 3).

Major adverse cardiovascular events

The secondary endpoint of MACE occurred in 811 (8.4%) patients referred to coronary angiography, of which cardiovascular death constituted 19% (n=152) and 23%, MI 26% (n=211), and obstructive CAD 55% (n=448). The IR and HR for MACE for UA compared to SA, NSTEMI, STEMI and the asymptomatic general population are shown in Table 4 and Table 5. Survival functions and cumulative 1-year and 5-year incidence of MACE are presented in Supplementary Figure 2 and Supplementary Table 2. The IR of MACE per 1000

person-years was 8.1 (95% CI 7.6-8.6) in the general population, 21.8 (95% CI 19.5-24.4) in SA patients, 23.5 (95% CI 18.9-29.2) in UA patients, 44.0 (9%% CI 38.9-49.8) in NSTEMI patients and 51.6 (95% CI 44.6-59.7) in STEMI patients. In multivariable adjusted analyses, the risk of MACE compared to UA patients was 50% lower in the general population (HR 0.50, 95% CI 0.39-0.64), similar in SA patients (HR 0.86, 95% CI 0.66-1.11), 38% higher in NSTEMI (HR 1.38, 95% CI 1.06-1.80) and 91% higher in STEMI patients (HR 1.91, 95% CI 1.42-2.57) (Table 4). These findings were similar in analyses stratified by sex (Supplementary Table 3). During the first year after coronary angiography, the risk of MACE compared to UA patients was still lower in the general population (HR 0.32, 95% CI 0.21-0.48), similar in SA patients (HR 0.77, 95% CI 0.53-1.13), 62% higher in NSTEMI patients (HR 1.62, 95% CI 1.11-2.38), and 3-fold higher in STEMI (HR 2.85, 95% CI 1.91-4.12) (Table 5).

The extent of coronary artery disease

Survival for all-cause death by indication and extent of CAD is shown in Figure 3. The mortality rate in UA patients with non-obstructive CAD and obstructive CAD was 14.1 (95% CI 9.9-20.2) and 16.2 (95% CI 10.8-24.4) per 1000 person-years, respectively. In multivariable adjusted analyses, there was no difference in risk of death among UA patients with non-obstructive CAD and obstructive CAD (HR 0.78, 95% CI 0.39-1.57). Among patients with obstructive CAD, the risk of death was not significantly different in SA (HR 0.78, 95% CI 0.47-1.29), non-significantly higher in NSTEMI (HR 1.50, 95% CI 0.93-2.41), and higher in STEMI (HR 1.90, 95% CI 1.15-3.14), compared to UA patients.

The IR of MACE in UA patients with non-obstructive CAD and obstructive CAD was 8.6 (95% CI 5.4-13.6) and 46.1 (95% CI 35.8-59.4) per 1000 person-years, respectively. In multivariable adjusted analyses, UA patients with obstructive CAD had a 5-fold higher risk

of MACE than UA patients with non-obstructive CAD (HR 4.73, 95% CI 2.45-9.16). Among patients with obstructive CAD, there was no difference in risk of MACE between the different clinical presentations, SA, UA, NSTEMI and STEMI (Supplementary Figure 3).

Discussion

In our real-world registry-based study, we found that UA patients had a higher risk of death but a similar risk of MACE as SA patients, and half the risk of death and MACE compared to NSTEMI patients during the first year after coronary angiography. This is in line with the increasing evidence that UA in the hs-cTn era is associated with a better prognosis than NSTEMI and a more similar prognosis to SA (3, 4, 10-17). However, the other studies in the hs-cTn era either only include patients that underwent PCI (10), patients with high-risk criteria (12), small populations (13), or unselected chest pain population presenting to emergency departments (3, 4, 11, 14-17). Therefore, our study adds to the existing knowledge.

The High-STEACS, APACE and RAPID-CPU studies reported a 1-year incidence of death and MI in UA was 3-4% and 3-11% (12, 13). This is higher than our results. These studies had a high rate of prior CAD likely contributing to this (12, 13). Further, in High-STEACS and APACE less than half of the UA patients was referred to coronary angiography, but 95% had obstructive CAD, which was higher than the NSTEMI patients in the study, making the results difficult to interpret (12). The RAPID-CPU had a relatively small population of 280 UA patients (13). The studies on the ESC hs-cTn 0 h/1 h and 0 h/2 h algorithms for rule-out, observe, and rule-in for MI in chest pain populations in the emergency department found a 1-year cumulative incidence of death of 0.0-2.2%, 4.0-7.6% and 9.8-16.1%, respectively (3, 11, 14-17). UA patients may be present in all groups, yet our results are comparable to the rule-

out group, indicating a very favourable short-term prognosis. Further underlining this is that our UA population was selected for coronary angiography by invasive cardiologists due to believed high risk of CAD but still had similar outcomes as a low-risk chest pain population.

Our findings support the 2020 ESC Acute Coronary Syndrome without Persistent ST-segment Elevations Guidelines focusing on detecting the individuals with NSTEMI that have a significantly worse prognosis and a more individual workup for patients with suspected UA (3). The guidelines further recommend using more CCTA to exclude CAD and UA. The high prevalence of non-obstructive CAD in our study supports this. Despite the overall favourable prognosis, we found that UA patients had a higher risk of death than SA patients and a similar risk of death as NSTEMI after the first year. Further, the risk of death was similar in UA patients with non-obstructive CAD as in UA patients with obstructive CAD. This may support that CCTA should be performed on a relatively low threshold. A subset of these patients should receive a thorough workup, including assessment for other differential diagnoses and microvascular disease (3, 29).

Strengths and limitations

The strengths of our study include our real-world data with up to a 5-year follow-up for 10,000 individuals referred to coronary angiography for the first time in the hs-cTn era. As patients with prior CAD have distinctly higher mortality, we chose to exclude these patients. Further, the use of data from both ICA and CCTA reflects the current clinical practice and allows for confirmation of all positive or inconclusive findings on CCTA by ICA. Other non-invasive imaging tests for CAD in patients with no prior CAD was generally not applied during the study period in our region. We had a relatively high rate of non-obstructive CAD for all indications of coronary angiography, but similar to other studies, and likely representative of clinical practice in high-resource health care systems (22, 33). Further, we

did not have data on the degree of non-obstructive CAD. The classification of SA, UA, NSTEMI and STEMI was based on the presumed diagnosis before the coronary angiography and not the final diagnosis. However, we believe this is representative of other coronary angiography populations and the population met in clinical practice.

National registries ensure near-complete follow-up data for the outcomes. However, an individual would be lost to follow-up if the coronary angiography was performed abroad or in another region of Norway before NORIC had full national coverage and lost to follow-up for death if both emigrated from Norway and no longer registered as a Norwegian citizen. We believe this is unlikely to have affected our results.

Further limitations include that our study population is recruited from a single centre. We did not have data on the individuals with CAD that did not undergo coronary angiography, including no data on MI as endpoint if not referred to coronary angiography. This is more likely to have been women and elderly patients, which may introduce selection bias in our results and lower the generalisability of our results to these groups. However, coronary angiography was performed in around 90% of STEMI patients and about 70% of NSTEMI patients under 85 years old, with only slightly lower rates in women reducing the risk of bias (34). Further, we have included a broader population than many other studies. We excluded patients with prior known CAD as these patients had a much higher risk of both death and MACE.

The cause of death was only available through 2017, so the MACE data is not complete for 2018. However, sensitivity analyses for MACE from 2013-2017 demonstrated similar risk estimates.

Conclusions

In a real-world population presenting to coronary angiography with no prior CAD, we found that UA patients had a higher risk of death but a similar risk of MACE as SA patients, and a lower 1-year risk of death and MACE than NSTEMI patients, but not after the first year. Unstable angina patients with non-obstructive CAD had a similar risk of death as UA patients with obstructive CAD.

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Conflict of interest

HS report lecture fees from MSD, AstraZeneca, Amgen and Sanofi, consulting fee and research collaboration contract from Novartis, and unpaid member of the Norwegian Heart Council. MLL report lecture fees from BMS.

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Figure legends

Figure 1

Selection of study participants.

Figure 2

SA indicates stable angina; UA, unstable angina; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction. For individuals aged 30-65 years old, the y-axis is 88-100% survival; for individuals aged over 65 years old, the y-axis is 65-100% survival.

Figure 3

CAD indicates coronary artery disease; non-obCAD, non-obstructive CAD; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; 1VD, one-vessel disease; 2VD, two-vessel disease; 3VD/LMS, three-vessel disease and/or left main stem disease. Age is adjusted to 65 years old.

Tables

Table 1. Baseline characteristics of patients referred to coronary angiography in Northern Norway from 2013 to 2018 and a general population from the Tromsø Study.

	SA (n = 4942)	**UA (n = 1200)**	**NSTEMI (n = 2209)**	**STEMI (n = 1343)**	**Gen. pop. (n = 11959)**
Age (yrs)	62±11	61±12	65±12	63±12	57±12
Male gender	53% (2641)	61% (733)	67% (1475)	74% (990)	45% (5372)
Current smoker	18% (858)	25% (280)	31% (661)	43% (514)	27% (3205)
Former smoker	47% (2227)	40% (450)	39% (818)	29% (344)	36% (4241)
Use of antihypertensive drugs	49% (2144)	41% (474)	45% (984)	31% (412)	20% (2318)
Use of lipid-lowering drugs	58% (2567)	41% (474)	36% (786)	15% (204)	9% (1070)
Diabetes mellitus	13% (591)	12% (135)	14% (320)	9% (121)	8% (893)
BMI (kg/m^2)	27±5	28±5	27±5	27±4	26±4
Estimated GFR (mL/min/1.73m^2)	82±18	85±18	82±20	85±19	93±15
Angiographic characteristics at admission					
Extent of CAD					
Non-obCAD[a]	65% (3232)	60% (717)	18% (403)	7% (90)	

1VD	18% (872)	21% (253)	42% (933)	56% (752)
2VD	8% (414)	10% (115)	21% (466)	23% (310)
3VD/LMS	9% (424)	10% (115)	18% (407)	14% (191)
Revascularization[b]	27% (1337)	38% (454)	78% (1717)	92% (1230)
PCI	20% (1010)	30% (366)	69% (1514)	89% (1191)
CABG	7% (366)	8% (97)	11% (252)	5% (61)
FFR	7% (345)	7% (83)	6% (130)	2% (23)
CCTA	41% (2016)	7% (86)		

Values are % (*n*) or mean±SD. BMI indicates body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; FFR, fractional flow reserve; GFR, glomerular filtration rate; non-obCAD, non-obstructive CAD; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SA, stable angina; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; 1VD, one-vessel disease; 2VD, two-vessel disease; 3VD/LMS, three-vessel disease and/or left main stem disease.

[a]Including the participants deferred after coronary CT angiography.

[b]There is a small overlap in patients receiving both PCI and CABG for revascularisation.

Table 2. Incidence rates (IR) and hazard ratios (HR) with 95% confidence intervals (CI) for all-cause mortality for patients referred to coronary angiography and a general population.

All-cause mortality	Events	Person-years	Crude IR (95% CI)[a]	Age- and sex-adjusted HR (95% CI)	Multivariable adjusted HR (95% CI)[b]
General population	980	115463	8.5 (8.0-9.0)	0.55 (0.41-0.74)	0.54 (0.39-0.76)
SA	140	14379	9.7 (8.3-11.5)	0.66 (0.48-0.90)	0.62 (0.44-0.89)
UA	53	3548	14.9 (11.4-19.6)	Ref.	Ref.
NSTEMI	182	6138	29.7 (25.6-34.3)	1.34 (0.98-1.82)	1.26 (0.90-1.78)
STEMI	136	3726	36.5 (30.9-43.2)	2.11 (1.53-2.89)	1.62 (1.10-2.37)

SA indicates stable angina; UA, unstable angina; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

[a]Per 1000 person-years.

[b]Adjusted for age, sex, smoking status, antihypertensive drugs, lipid-lowering drugs, diabetes, BMI and kidney function.

Table 3. Incidence rates (IR) and hazard ratios (HR) with 95% confidence intervals (CI) for all-cause mortality for patients referred to coronary angiography and a general population at 0-1 year and after 1 year.

	0-1 year			>1 year		
All-cause mortality	**Crude IR (95% CI)[a]**	**Age- and sex-adjusted HR (95% CI)**	**Multivariable adjusted HR (95% CI)[b]**	**Crude IR (95% CI)[a]**	**Age- and sex-adjusted HR (95% CI)**	**Multivariable adjusted HR (95% CI)[b]**
General population	3.6 (2.7-4.9)	0.37 (0.21-0.68)	0.48 (0.24-0.95)	9.0 (8.5-9.6)	0.56 (0.40-0.78)	0.52 (0.36-0.76)
SA	6.9 (4.8-9.8)	0.50 (0.27-0.93)	0.53 (0.26-1.06)	11.0 (9.2-13.3)	0.71 (0.49-1.03)	0.65 (0.43-0.97)
UA	13.6 (8.2-22.6)	Ref.	Ref.	15.5 (11.3-21.4)	Ref.	Ref.
NSTEMI	45.1 (36.6-55.5)	2.39 (1.38-4.14)	2.47 (1.30-4.71)	22.3 (18.2-27.4)	0.97 (0.66-1.41)	0.90 (0.60-1.36)
STEMI	68.0 (54.6-84.7)	4.44 (2.56-7.71)	3.84 (1.95-7.57)	22.0 (16.9-28.5)	1.22 (0.81-1.85)	0.97 (0.60-1.57)

SA indicates stable angina; UA, unstable angina; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

[a]Per 1000 person-years.

[b]Adjusted for age, smoking status, antihypertensive drugs, lipid-lowering drugs, diabetes, BMI and kidney function.

Table 4. Incidence rates (IR) and hazard ratios (HR) with 95% confidence intervals (CI) for major adverse cardiovascular events (MACE) for patients referred to coronary angiography and a general population.

MACE	Events	Person-years	Crude IR (95% CI)[a]	Age- and sex-adjusted HR (95% CI)	Multivariable adjusted HR (95% CI)[b]
General population	936	115384	8.1 (7.6-8.6)	0.49 (0.39-0.63)	0.50 (0.39-0.64)
SA	301	13801	21.8 (19.5-24.4)	0.93 (0.73-1.19)	0.86 (0.66-1.11)
UA	80	3406	23.5 (18.9-29.2)	Ref	Ref.
NSTEMI	251	5701	44.0 (38.9-49.8)	1.44 (1.12-1.85)	1.38 (1.06-1.80)
STEMI	179	3470	51.6 (44.6-59.7)	1.88 (1.44-2.45)	1.91 (1.42-2.57)

SA indicates stable angina; UA, unstable angina; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction. MACE is defined as cardiovascular death or MI or new obstructive CAD on coronary angiography.

[a]Per 1000 person-years.

[b]Adjusted for age, sex, smoking status, antihypertensive drugs, lipid-lowering drugs, diabetes, BMI and kidney function.

Table 5. Incidence rates (IR) and hazard ratios (HR) with 95% confidence intervals (CI) for major adverse cardiovascular events (MACE) for patients referred to coronary angiography and a general population at 0-1 year and after 1 year.

	0-1 year			>1 year		
MACE	**Crude IR (95% CI)[a]**	**Age- and sex-adjusted HR (95% CI)**	**Multivariable adjusted HR (95% CI)[b]**	**Crude IR (95% CI)[a]**	**Age- and sex-adjusted HR (95% CI)**	**Multivariable adjusted HR (95% CI)[b]**
General population	8.2 (6.8-10.0)	0.29 (0.20-0.43)	0.32 (0.21-0.48)	8.1 (7.6-8.7)	0.61 (0.44-0.84)	0.59 (0.42-0.82)
SA	28.1 (23.6-33.5)	0.79 (0.55-1.13)	0.77 (0.53-1.13)	18.8 (16.2-21.8)	1.05 (0.75-1.48)	0.92 (0.65-1.30)
UA	35.9 (26.2-49.1)	Ref.	Ref.	17.7 (13.0-24.0)	Ref.	Ref.
NSTEMI	70.3 (59.4-83.2)	1.63 (1.14-2.34)	1.62 (1.11-2.38)	30.7 (25.6-36.8)	1.29 (0.90-1.85)	1.22 (0.85-1.77)
STEMI	107 (89.6-128)	2.68 (18.7-3.85)	2.85 (1.91-4.27)	24.5 (18.9-31.7)	1.15 (0.77-1.73)	1.16 (0.74-1.80)

SA indicates stable angina; UA, unstable angina; NSTEMI, non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction. MACE is defined as cardiovascular death or MI or new obstructive CAD on coronary angiography.

[a]Per 1000 person-years.

[b]Adjusted for age, smoking status, antihypertensive drugs, lipid-lowering drugs, diabetes, BMI and kidney function.

Figures

Figure 1. Study population.

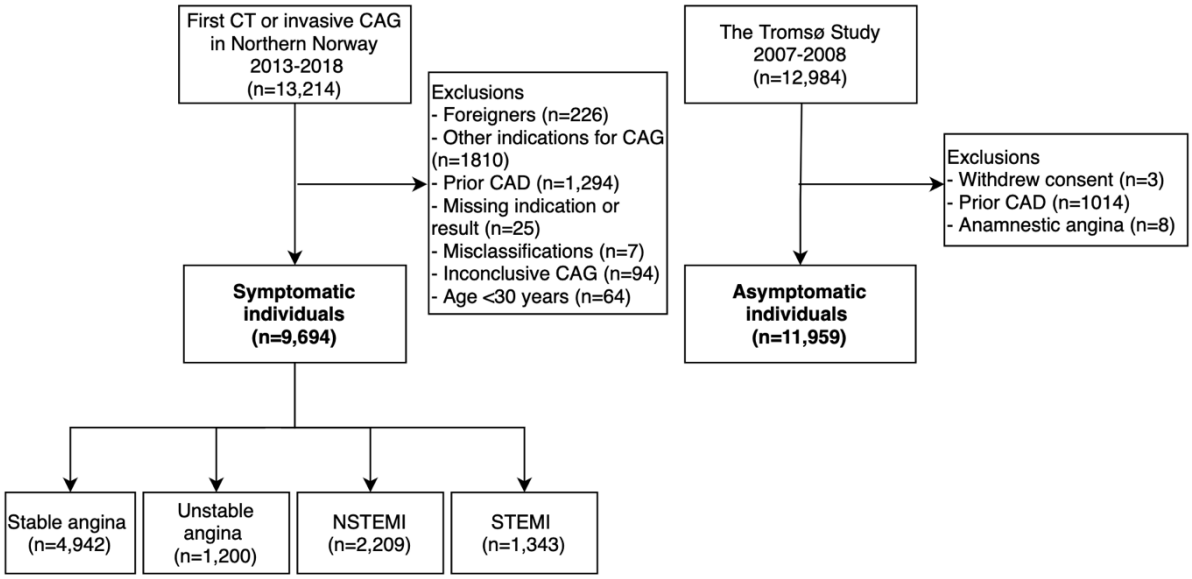


Figure 2. Survival function for all-cause mortality in patients referred to coronary angiography compared to a general population.

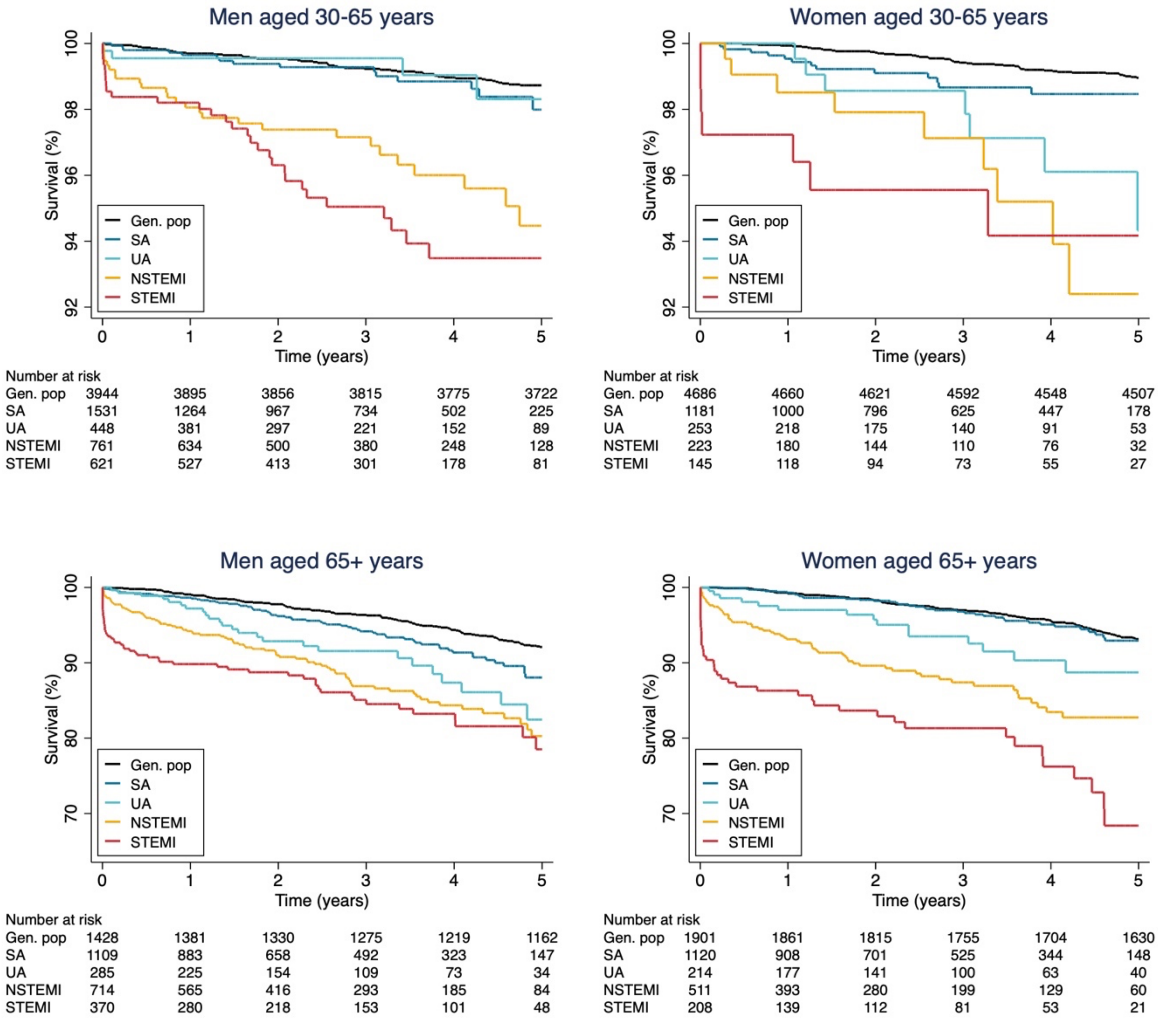
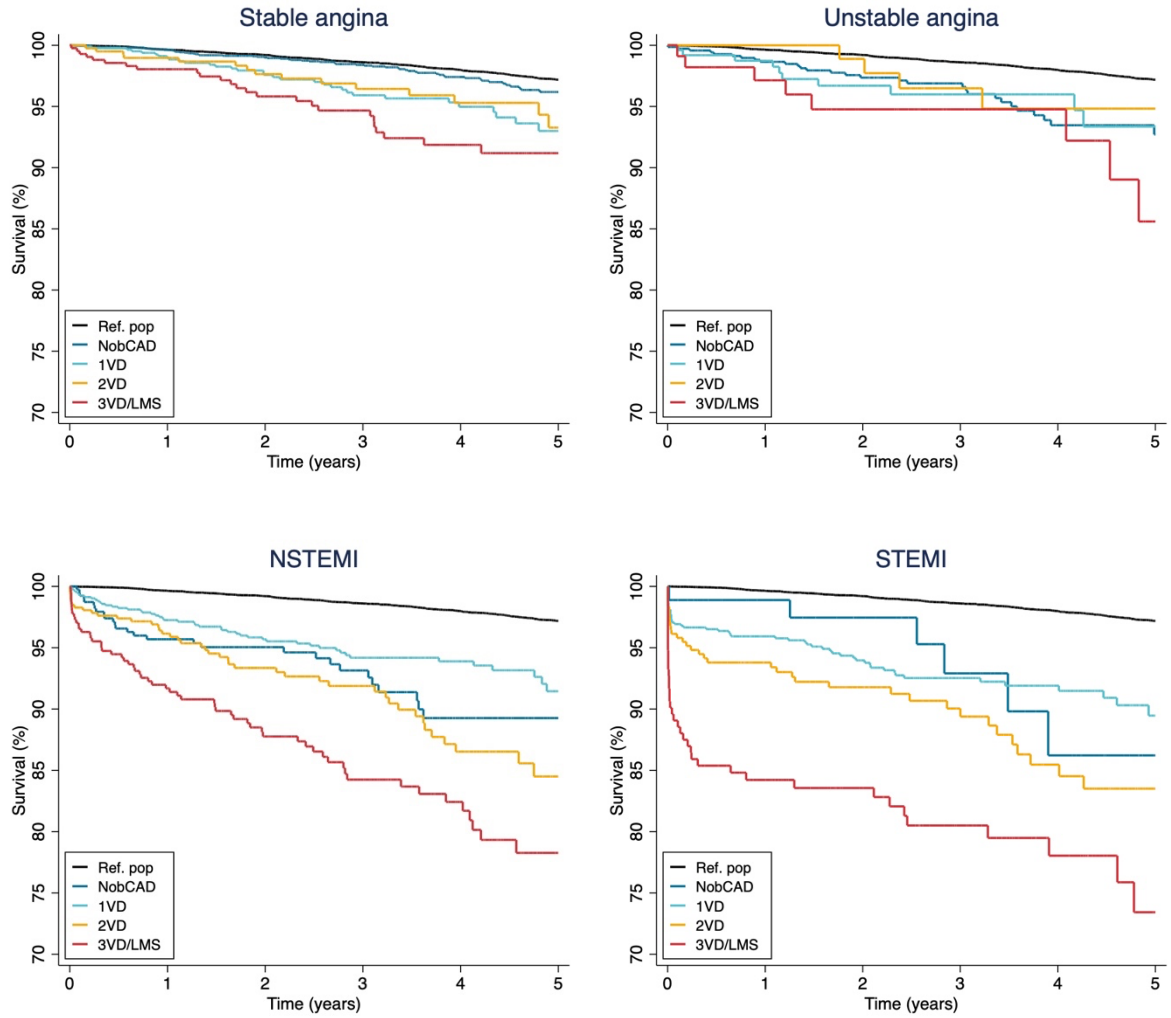


Figure 3. Survival functions for all-cause mortality for patients referred to coronary angiography by the extent of coronary artery disease



CAD indicates coronary artery disease; non-obCAD, non-obstructive CAD; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; 1VD, one-vessel disease; 2VD, two-vessel disease; 3VD/LMS, three-vessel disease and/or left main stem disease.

Supplementary Table 1. Baseline characteristics of men and women referred to coronary angiography in Northern Norway from 2013 to 2018 compared to a general population from the Tromsø Study.

	SA		**UA**		**NSTEMI**		**STEMI**		**Gen. pop.**	
	Men (n=2641)	Women (n=2301)	Men (n=733)	Women (n=467)	Men (n=1475)	Women (n=734)	Men (n=990)	Women (n=353)	Men (n=5372)	Women (n=6587)
Age (yr)	61±11	63±11	61±12	62±12	64±12	69±12	61±11	68±13	56±12	57±13
Current smoker	18% (464)	18% (394)	27% (185)	22% (95)	32% (463)	29% (198)	41% (362)	51% (152)	27% (1433)	27% (1772)
Former smoker	50% (1261)	44% (966)	43% (298)	35% (152)	40% (576)	35% (242)	32% (284)	20% (60)	39% (2060)	34% (2181)
Use of anti-hypertensive drugs	48% (1177)	49% (967)	40% (287)	42% (187)	43% (628)	49% (356)	28% (278)	39% (134)	18% (982)	21% (1336)
Use of lipid-lowering drugs	61% (1480)	55% (1087)	39% (280)	44% (194)	34% (500)	39% (286)	15% (144)	11% (37)	9% (462)	9% (608)
Diabetes mellitus	14% (347)	12% (244)	12% (89)	10% (46)	14% (200)	16% (120)	9% (84)	8% (29)	8% (400)	8% (493)
BMI (kg/m^2)	28±4	27±5	28±5	27±5	27±5	26±5	27±4	26±5	27±4	26±5
Estimated GFR ($mL/min/1.73m^2$)	83±18	82±18	86±17	85±18	85±19	77±20	87±18	79±21	94±14	93±15
Angiographic findings										
Non-obCAD[a]	54% (1421)	79% (1811)	49% (356)	77% (361)	12% (177)	31% (226)	6% (61)	8% (29)		

1VD	22% (581)	13% (291)	27% (197)	12% (56)	44% (656)	38% (277)	57% (562)	54% (190)
2VD	12% (304)	5% (110)	12% (90)	5% (25)	24% (356)	15% (110)	23% (232)	22% (78)
3VD/LMS	13% (335)	4% (89)	12% (90)	5% (25)	19% (286)	16% (121)	14% (135)	16% (56)
Revascularization[b]	37% (970)	16% (367)	49% (358)	21 (96)	84% (1245)	64% (472)	92% (915)	89% (315)
PCI	26% (696)	14% (314)	39% (286)	17% (80)	73% (1080)	59% (434)	89% (886)	86% (305)
CABG	12% (306)	3% (60)	11% (77)	4% (20)	13% (191)	7% (51)	5% (45)	5% (16)
FFR etc.	9% (306)	5% (118)	8% (60)	3% (23)	6% (94)	5% (36)	2% (19)	1% (4)
CCTA	37% (965)	46% (1051)	5% (40)	10% (46)				

Values are % (*n*) or mean±SD. BMI indicates body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; FFR, fraction flow reserve; GFR, glomerular filtration rate; non-obCAD, non-obstructive CAD; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; 1VD, one-vessel disease; 2VD, two-vessel disease; 3VD/LMS, three-vessel disease and/or left main stem disease.

[a]Including the participants deferred after coronary CT angiography.

[b]There is a small overlap in patients receiving both PCI and CABG for revascularisation.

Supplementary Table 2. Incidence rates (IR) and hazard ratios (HR) with 95% confidence intervals (CI) for all-cause mortality by sex and indication for coronary angiography

All-cause mortality	**Events**		**Person-years**		**Age-adjusted IR (95% CI)[a]**		**Multivariable adjusted HR (95% CI)[b]**	
	Men	Women	Men	Women	Men	Women	Men	Women
General population	4777	503	50914	64549	11.4 (10.7-12.1)	12.9 (12.1-13.8)	0.60 (0.39-0.94)	0.46 (0.28-0.75)
Stable angina	88	53	7537	6845	8.7 (7.3-10.1)	9.9 (8.2-11.5)	0.81 (0.51-1.28)	0.42 (0.24-0.74)
Unstable angina	31	22	2110	1438	13.4 (9.8-17.1)	15.2 (11.1-19.4)	Ref.	Ref.
NSTEMI	112	70	4180	1958	18.4 (15.7-21.1)	20.9 (17.8-23.9)	1.38 (0.88-2.15)	1.12 (0.66-1.92)
STEMI	85	51	2779	941	29.3 (24.4-34.2)	33.2 (27.7-38.8)	1.55 (0.95-2.55)	1.80 (0.98-3.31)

NSTEMI indicates non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

[a]Per 1000 person-years.

[b]Adjusted for age, smoking status, antihypertensive drugs, lipid-lowering drugs, diabetes, BMI and kidney function.

Supplementary Table 3. Incidence rates (IR) and hazard ratios (HR) with 95% confidence intervals (CI) for major adverse cardiovascular events (MACE) by sex and indication for coronary angiography

MACE	Events		Person-years		Age-adjusted IR (95% CI)[a]		Multivariable adjusted HR (95% CI)[b]	
	Men	Women	Men	Women	Men	Women	Men	Women
General population	587	349	50874	64510	11.4 (10.7-12.2)	13.0 (12.1-13.8)	0.50 (0.37-0.67)	0.50 (0.31-0.81)
Stable angina	212	89	7122	6682	9.1 (7.6-10.7)	10.4 (8.7-12.1)	0.91 (0.67-1.22)	0.77 (0.47-1.27)
Unstable angina	59	21	2009	1397	14.4 (10.5-18.2)	16.3 (11.9-20.7)	Ref.	Ref.
NSTEMI	178	73	3867	1835	19.6 (16.7-22.5)	22.2 (19.0-25.5)	1.33 (0.98-1.80)	1.53 (0.91-2.57)
STEMI	132	47	2574	890	30.8 (25.6-35.9)	34.9 (29.0-40.8)	1.73 (1.23-2.43)	2.59 (1.43-4.69)

NSTEMI indicates non-ST elevation myocardial infarction; STEMI, ST-elevation myocardial infarction. MACE is defined as repeat angiography with obstructive CAD and/or MI, or cardiovascular death.

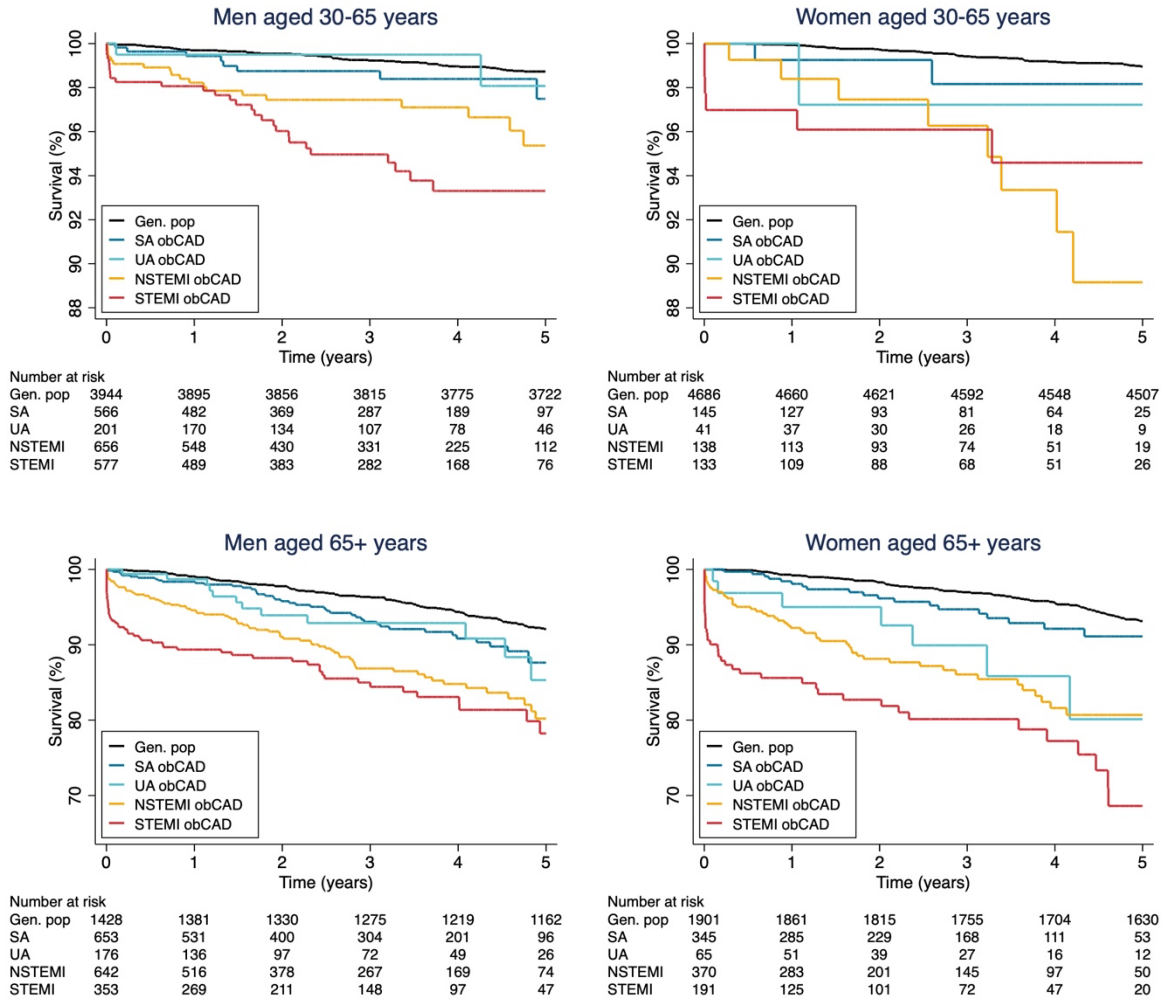
[a]Per 1000 person-years.

[b]Adjusted for age, smoking status, antihypertensive drugs, lipid-lowering drugs, diabetes, BMI and kidney function.

Supplementary table 4. 1-year and 5-year cumulative incidence for death and major cardiovascular events (MACE) per 100 individuals with 95% confidence intervals (CI) by indication of coronary angiography

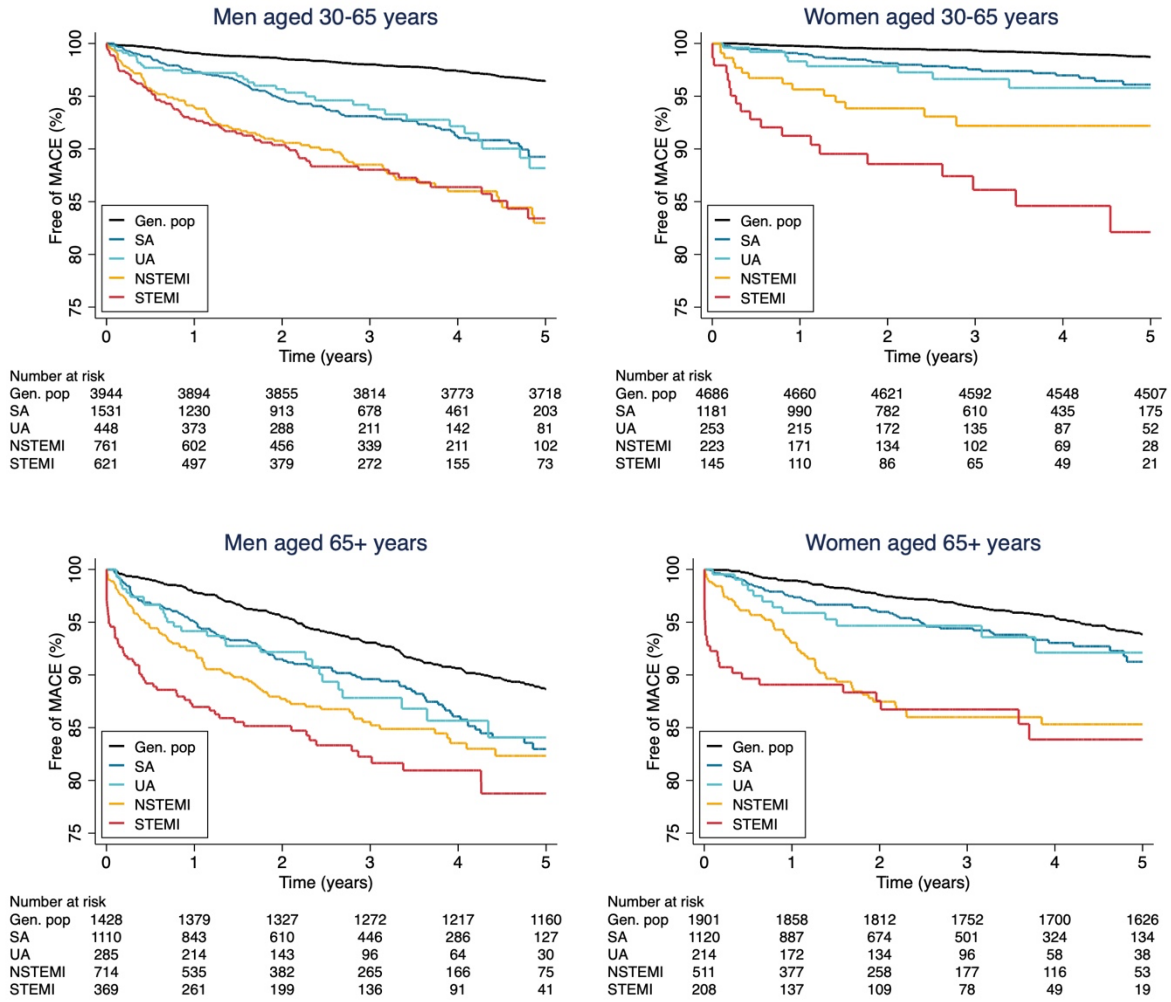
	1-year	5-year
All-cause mortality		
General population	0.4 (0.3-0.5)	2.8 (2.5-3.1)
SA	0.7 (0.5-1.0)	5.1 (4.2-6.2)
UA	1.4 (0.8-2.2)	7.7 (5.7-10.3)
NSTEMI	4.4 (3.6-5.4)	12.9 (11.0-15.1)
STEMI	6.4 (5.2-7.9)	14.8 (12.3-17.7)
MACE		
General population	0.4 (0.3-0.5)	2.9 (2.6-3.2)
SA	0.7 (0.5-1.0)	5.2 (4.3-6.3)
UA	1.4 (0.8-2.3)	8.2 (6.1-11.0)
NSTEMI	4.8 (3.9-5.8)	13.4 (11.5-15.7)
STEMI	6.9 (5.6-8.5)	15.1 (12.6-18.1)

Supplementary figure 1. Survival function for all-cause mortality in patients referred to coronary angiography with obstructive CAD compared to an asymptomatic reference population.



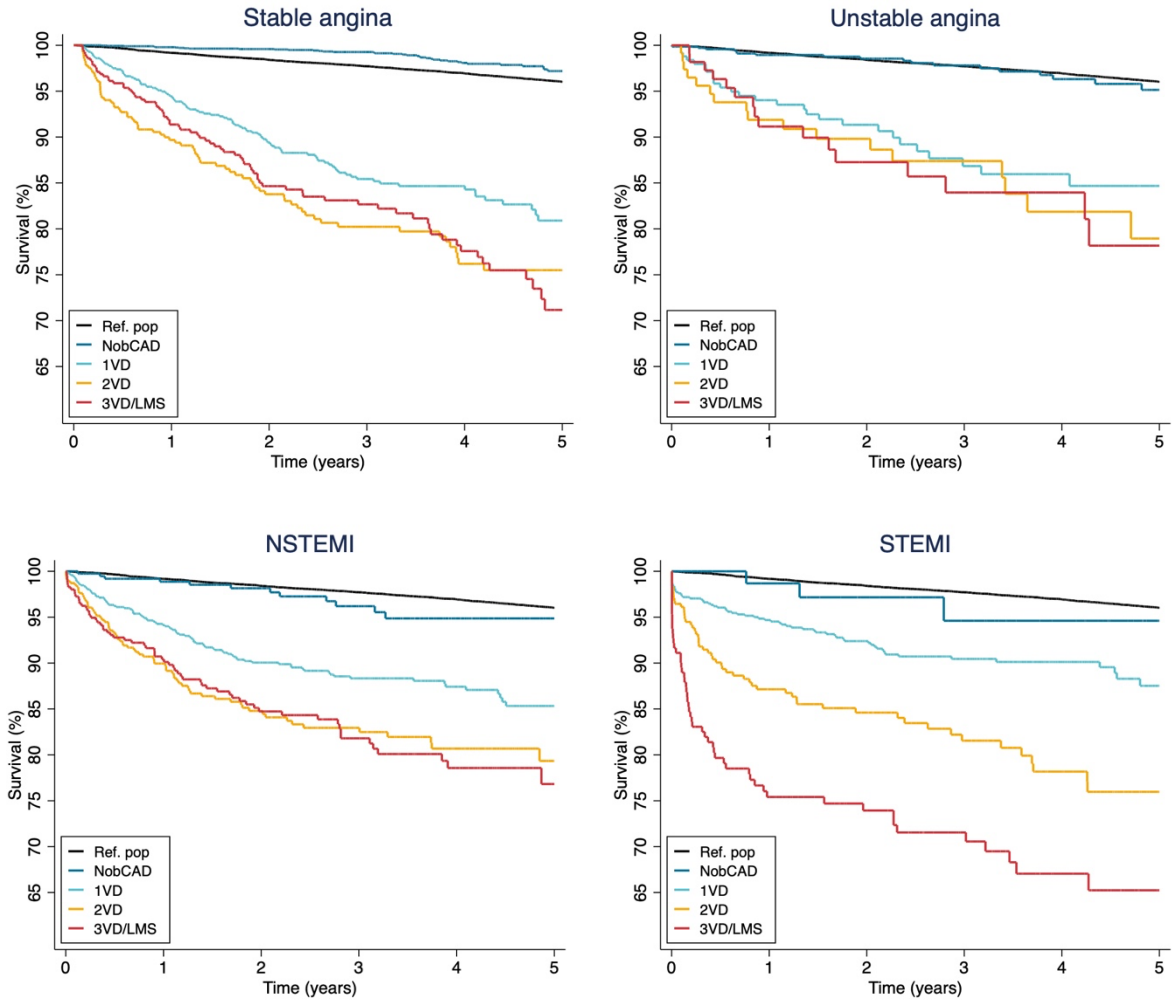
CAD indicates coronary artery disease; obCAD, obstructive CAD; NSTEMI, non-ST segment elevation myocardial infarction; SA, stable angina; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

Supplementary figure 2. Survival function for major adverse cardiovascular events in patients referred to coronary angiography compared to an asymptomatic reference population.



NSTEMI indicates non-ST segment elevation myocardial infarction; SA, stable angina; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

Supplementary figure 3. Survival function for major adverse cardiovascular events for patients referred to coronary angiography by extent of coronary artery disease



CAD indicates coronary artery disease; non-obCAD, non-obstructive CAD; NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; 1VD, one-vessel disease; 2VD, two-vessel disease; 3VD/LMS, three-vessel disease and/or left main stem disease.

Paper III

Journal of the American Heart Association

ORIGINAL RESEARCH

Low Pain Tolerance Is Associated With Coronary Angiography, Coronary Artery Disease, and Mortality: The Tromsø Study

Kristina Fladseth, MD; Haakon Lindekleiv, MD, PhD; Christopher Nielsen, PhD; Andrea Øhrn, MD, PhD; Andreas Kristensen, MD; Jan Mannsverk, MD, PhD; Maja-Lisa Løchen, MD, PhD; Inger Njølstad, MD, PhD; Tom Wilsgaard, PhD; Ellisiv B Mathiesen, MD, PhD; Audun Stubhaug, MD, PhD; Thor Trovik, MD, PhD; Svein Rotevatn, MD, PhD; Signe Forsdahl, MD, PhD; Henrik Schirmer, MD, PhD

BACKGROUND: The initial presentation to coronary angiography and extent of coronary artery disease (CAD) vary greatly among patients, from ischemia with no obstructive CAD to myocardial infarction with 3-vessel disease. Pain tolerance has been suggested as a potential mechanism for the variation in presentation of CAD. We aimed to investigate the association between pain tolerance, coronary angiography, CAD, and death.

METHODS AND RESULTS: We identified 9576 participants in the Tromsø Study (2007–2008) who completed the cold-pressor pain test, and had no prior history of CAD. The median follow-up time was 10.4 years. We applied Cox-regression models with age as time-scale to calculate hazard ratios (HR). More women than men aborted the cold pressor test (39% versus 23%). Participants with low pain tolerance had 19% increased risk of coronary angiography (HR, 1.19 [95% CI, 1.03–1.38]) and 22% increased risk of obstructive CAD (HR, 1.22 [95% CI, 1.01–1.47]) adjusted by age as time-scale and sex. Among women who underwent coronary angiography, low pain tolerance was associated with 54% increased risk of obstructive CAD (HR, 1.54 [95% CI, 1.09–2.18]) compared with high pain tolerance. There was no association between pain tolerance and nonobstructive CAD or clinical presentation to coronary angiography (ie, stable angina, unstable angina, and myocardial infarction). Participants with low pain tolerance had increased risk of mortality after adjustment for CAD and cardiovascular risk factors (HR, 1.40 [95% CI, 1.19–1.64]).

CONCLUSIONS: Low cold pressor pain tolerance is associated with a higher risk of coronary angiography and death.

Key Words: coronary angiography ■ coronary artery disease ■ heart disease risk factors ■ microvascular angina ■ pain measurement

Coronary artery disease (CAD) may initially present as stable angina, unstable angina, or myocardial infarction (MI). The typical presentation of stable angina is exertional chest pain relieved by rest, while acute chest pain is the most common symptom of unstable angina and MI. However, one third of MIs are unrecognized, and sudden coronary death may be the first clinical presentation of CAD.[1–4] On the other hand, half the patients presenting to elective invasive coronary angiography (ICA) and up to 80% of patients presenting to coronary computed tomographic angiography (CCTA) do not have obstructive CAD.[5–8] These discrepancies are challenging because we are likely missing high-risk individuals and exposing low-risk individuals to unnecessary risk of procedural complications at excessive costs to the health care systems.

Symptoms are usually the incentive for seeking medical attention, and determine further testing, diagnosis, and treatment. One hypothesis for the discordance in clinical presentation of CAD is that

Correspondence to: Kristina Fladseth, Cardiovascular Research Group, Department of Clinical Medicine, UiT The Arctic University of Norway, 9037 Tromsø, Norway. E-mail: kristina.fladseth@unn.no

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For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Low cold pressor pain tolerance was associated with a higher risk of coronary angiography and higher mortality.
- Low cold pressor pain tolerance was not associated with angina with nonobstructive coronary artery disease.

What Are the Clinical Implications?

- Low cold pressor pain tolerance does not explain the discrepancies in the presentation to coronary angiography, from angina with no obstructive coronary artery disease to myocardial infarction with 3-vessel disease.
- Further research is needed to investigate the proposed link between low cold pressor pain tolerance and inflammation.

Nonstandard Abbreviations and Acronyms

FFR	fractional flow reserve
ICA	invasive coronary angiography
IR	incidence rate

differences in pain tolerance affect symptom recognition and help seeking.[9] Smaller studies have demonstrated an association between low pain tolerance, lower anginal threshold, and normal coronary arteries.[10–12] Furthermore, a previous publication from the Tromsø Study found that individuals with unrecognized MI have higher pain tolerance and likely experience fewer symptoms than individuals with recognized MI.[13]

We aimed to investigate the association between pain tolerance and coronary angiography, CAD, and mortality in a general population. We hypothesized that low pain tolerance would be associated with earlier and more coronary angiographies with less obstructive CAD and more often angina than MI. Furthermore, we hypothesized that low pain tolerance would be associated with lower mortality because of earlier diagnosis and/or treatment of CAD.

METHODS

Qualified researchers may apply for access to the data supporting the findings of this study from the Tromsø Study. The syntaxes are available from the corresponding author.

Study Population

The Tromsø Study is a prospective, population-based study, with repeated health surveys of the inhabitants of Tromsø, the largest city in Northern Norway. The sixth survey (Tromsø6), conducted in 2007 to 2008, invited entire and random samples of birth cohorts with a total of 12 984 participants (attendance rate 66%). The participants completed questionnaires and underwent clinical examinations, including experimental pain testing. Further details on recruitment and testing procedures in Tromsø6 have been reported previously.[14] The University Hospital of North Norway is the primary hospital for all inhabitants of Tromsø and was the sole provider of coronary angiography in Northern Norway. From 2005, procedural data from all ICAs performed at the University Hospital of North Norway have been registered in a local quality registry and from May 1, 2013 in a national registry, the NORIC (Norwegian Registry of Invasive Cardiology). By January 1, 2014, the majority of Norwegian hospitals, and from January 1, 2016, all hospitals reported ICA data to NORIC with >99% coverage.[15] In 2013, CCTA was implemented at University Hospital of North Norway as the primary investigation for suspected angina without known CAD, and has been recorded in a registry since then. The national personal identification number allowed for linkage between Tromsø6 and coronary angiography registries on an individual level. Vital status, date of death, and cause of death were obtained from the National Population Register and the Norwegian Cause of Death Registry. The Norwegian Cause of Death Registry is based on the underlying cause of death listed on death certificates, with cardiovascular death defined by ICD (International Classification of Diseases and Related Health Problems), ICD-10: I00–I99, and coronary death defined by ICD-10: I20–I25. More than 80% of deaths in Norway occur in hospitals or other health institutions, thus enabling better determination of cause of death.

Three participants withdrew their consent. We included the 10 486 remaining participants (81%) in Tromsø6 who completed the cold-pressor test (Figure 1). The main reason for not completing the cold pressor test was insufficient test capacity during peak hours (n=1831). Other causes were technical and/or procedural errors, participant refusal or incomprehension, and medical conditions that could interfere with or lead to adverse reactions to the test (n=664). Additionally, we excluded the 722 participants with prior MI or coronary angiography, identified through the MI registry of the Tromsø Study and the coronary angiography registries. This included participants registered with a prior MI or revascularization at their first coronary angiography. Six

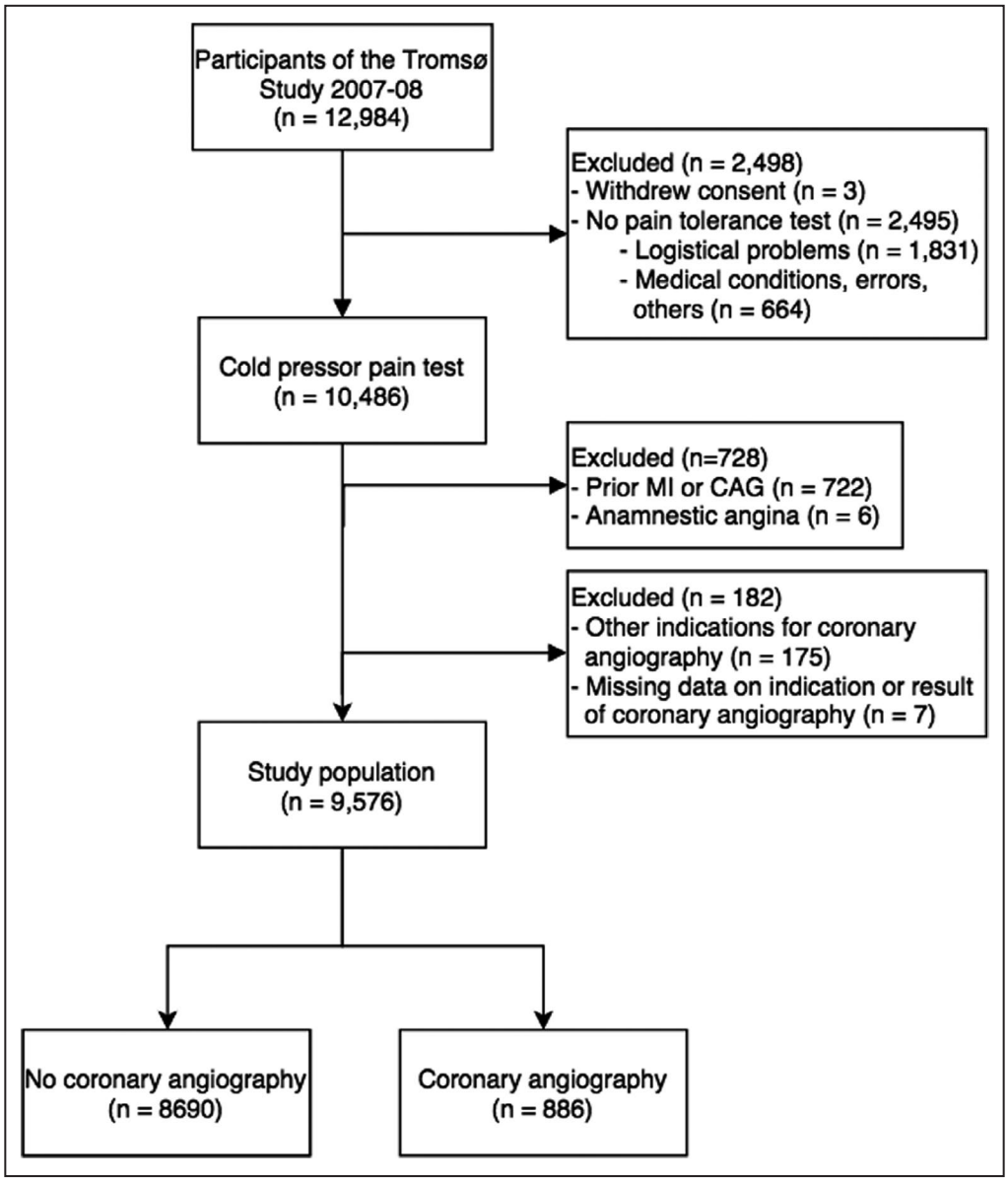

Figure 1. Selection of study participants for The Tromsø Study.
CAG indicates coronary angiography; and MI, myocardial infarction.

participants with self-reported angina and who underwent coronary angiography within 180 days after the baseline examination were excluded. We also excluded 7 participants with missing indication and/or inconclusive result of coronary angiography without a follow-up coronary angiography. Participants referred to coronary angiography as stable angina, unstable angina, and MI were included. Other indications for coronary angiography, such as preoperative assessment before valve surgery, were excluded (n=175). Accordingly, 9576 participants from Tromsø6 were included and followed until coronary angiography, death, or end of follow-up at December 31, 2018. Cause of death was available until December 31, 2017.

Exposures and Covariates

Pain Tolerance and the Cold Pressor Test

The cold pressor test is a well-established experimental pain test, as well as a traditional test of vasospastic angina. The test uses cold, circulating water to induce a deep aching pain by activation of venous nociceptors.[16,17] After a verbal explanation of the test, the participants were asked to place their dominant hand and wrist into a container with 3°C circulating water, and keep it there for as long as possible, up to a maximum of 106 s. The short administration time makes the test well suited for population surveys. Endurance of the cold stimulus until the maximum time was defined as high pain tolerance, whereas aborting the cold

stimulus before the maximum time was defined as low pain tolerance. Further details of the pain testing in Tromsø6 have been reported previously.[18]

Cardiovascular Risk Factors

Data regarding cardiovascular risk factors were collected through clinical examination, blood samples, and self-reported questionnaires. Diabetes was defined as self-reported diabetes, use of antidiabetic drugs and/or hemoglobin A1c ≥48.0 mmol/mol (6.5%); hypertension as self-reported hypertension, mean systolic blood pressure ≥140 mm Hg, mean diastolic blood pressure ≥90 mm Hg, and/or the use of antihypertensive drugs; hypercholesterolemia was defined as the use of lipid-lowering drugs, and low-density lipoprotein ≥5.0 mmol/L and/or total cholesterol ≥7.0 mmol/L. Family history of MI was defined as self-reported MI in parents or siblings before the age of 60 years. Body mass index was calculated as measured weight in kilograms divided by the square of measured height in meters. Estimated glomerular filtration rate was calculated according to the CKD-EPI-equation.[19]

Coronary Angiography

The interventional cardiologist or the cardiac radiologist assessed the extent of CAD at the time of the procedure; obstructive CAD was defined as ≥50% diameter stenosis in any epicardial coronary artery.[20] Nonobstructive CAD was defined as 0 to 49% diameter stenosis. When fractional flow reserve (FFR) was measured, obstructive CAD was defined as FFR <0.80. FFR was generally measured with visual diameter stenosis ≈40% to 70%. The extent of obstructive CAD was further described as 1-vessel disease, 2-vessel disease, or 3-vessel disease and/or left main stem disease. CCTA procedures with obstructive CAD or inconclusive results, followed by an ICA in 180 days, were replaced with the results from the ICA. An ICA with obstructive CAD assessed without FFR or revascularization, followed by an ICA with nonobstructive CAD assessed by FFR within 7 days, was replaced with the result of the second ICA. Stable angina, unstable angina, and MI were defined by the interventional cardiologist according to international guidelines at the time of the coronary angiography.

Outcomes

The outcomes were referral to coronary angiography, obstructive CAD (angina or MI with obstructive CAD or coronary death with no preceding coronary angiography), clinical presentation of CAD (stable angina, unstable angina, and MI), extent of CAD (nonobstructive CAD, 1-vessel disease, 2-vessel disease, 3-vessel disease, and/or left main stem disease), and all-cause mortality. Cardiovascular mortality was used as a secondary end point.

Statistical Analysis

Baseline characteristics are reported as counts and percentages or means with SDs. Crude incidence rates (IR) were expressed as number of events per 1000 person-years at risk. The differences in IR were tested using the log-rank test. We used Cox proportional hazard regression models to estimate the hazard ratios (HR) for the association between pain tolerance and coronary angiography, clinical presentation, CAD, and mortality. Because the majority of participants did not abort the cold pressor test, pain tolerance was dichotomized into low pain tolerance and high pain tolerance. Two-way interactions were tested by including cross product terms between the exposure and the adjustment variables in the models. The results were presented stratified if the interaction for sex was significant. There were no other significant interactions. The proportional hazard assumption was tested by Schoenfeld residuals. Because age violated the proportional hazard assumption in most of the analyses, we chose to adjust for age by using age as time-scale. We found the estimates of both methods to be similar. In the mortality analyses, we modeled coronary angiography as a time-varying covariate so that participants contribute with person-time to the no coronary angiography group until the date of the coronary angiography, and afterwards to the angina or MI group.

Covariates had low rates of missing values (0–3%). The rate of missing values for family history of MI is unknown because the variable only included yes or missing response. In the multivariable models, the 9222 participants (96%) with no missing variable for covariates are included.

Statistical analyses were performed in STATA version 16.1 (Stata Corporation, College Station, TX).

Ethics

All participants gave informed written consent, and the Regional Committee for Medical and Health Research Ethics approved the study. The project conducted a data protection impact assessment in agreement with the data protection officials at the University Hospital of North Norway.

RESULTS

We included 9576 participants with no prior history of CAD, of whom 32% aborted the cold pressor test (low pain tolerance) after a median of 46 s and 68% endured the test until the maximum time of 106 s (high pain tolerance). More women than men aborted the

test (39% versus 23%). Baseline characteristics are shown in Table 1. Daily smoking, diabetes, and hypercholesterolemia were more common in participants with low pain tolerance. The median follow-up time was 10.4 years.

Pain Tolerance and Coronary Angiography

Eight hundred eighty six participants were referred to coronary angiography (9.3%), as presumed stable angina (n=468), unstable angina (n=134), or MI (n=284). The IR of coronary angiography was 9.8 (95% CI, 8.7–11.0) and 9.2 (95% CI, 8.5–10.0) per 1000 person-years in participants with low pain tolerance and high pain tolerance, respectively (*P*=0.38). In survival analysis adjusted for sex and age as time-scale, participants with low pain tolerance had a 19% increased risk of coronary angiography (HR, 1.19 [95% CI, 1.03–1.38]) compared with participants with high pain tolerance (Figure 2). There was no interaction by sex for the association between pain tolerance and coronary angiography (*P*=0.80). In a multivariable model predicting coronary angiography, age, sex, hypertension, diabetes, overweight, and family history of premature MI were significant in addition to pain tolerance, which was mildly attenuated to HR 1.17 (95% CI, 1.01–1.34). Other traditional cardiovascular risk factors including smoking did not significantly predict referral to coronary angiography (Table S1).

Pain tolerance was not associated with the presentation of unstable angina versus stable angina (HR, 0.94 [95% CI, 0.52–1.38]), MI, and coronary death versus angina (HR, 1.06 [95% CI, 0.82–1.38]), or acute versus elective referrals (HR, 1.03 [95% CI, 0.80–1.31]).

Pain Tolerance and Degree of CAD

The initial clinical presentation of obstructive CAD was stable angina (n=199), unstable angina (n=66), MI (n=256), and coronary death (n=22). Overall, the IR of obstructive CAD was 5.7 (95% CI, 5.2–6.4) in participants with high pain tolerance and 5.5 (95% CI, 4.7–6.4) in participants with low pain tolerance per 1000 person-years (*P*=0.78) (Table 2). However, adjusting for sex and age as time-scale, participants with low pain tolerance had 22% increased risk of obstructive CAD compared with high pain tolerance (HR, 1.22 [95% CI, 1.01–1.47) (Table 2). The discrepancy in IR and HR is explained by women having less obstructive CAD and more often low pain tolerance. The IR for obstructive CAD per 1000 person-years was 2.7 (95% CI, 2.2–3.4) and 3.4 (95% CI, 2.7–4.3) in women and 8.6 (95% CI, 7.7–9.6) and 9.9 (95% CI, 8.1–12.1) in men with high and low pain tolerance, respectively. There was no interaction by sex for the association between pain tolerance and obstructive CAD in the overall population (*P*=0.64). The association between pain tolerance and obstructive CAD weakened after adjustment for cardiovascular risk factors (HR, 1.16 [95% CI, 0.95–1.40]) (Table 2). All traditional cardiovascular risk factors predicted obstructive CAD (Table S1).

Among participants referred to coronary angiography, women with low pain tolerance had a 54% increased risk of obstructive CAD (HR 1.54 [95% CI, 1.09–2.18]) compared with women with high pain tolerance, after adjustment for cardiovascular risk factors. There was no association in men (Table 2). The interaction term for sex was significant (*P*=0.05). Among women with obstructive CAD, low pain tolerance was associated with nonsignificant higher risk of 3-vessel and/or left main stem disease (HR, 1.99 [95% CI, 0.96–4.13]). Low pain tolerance was not associated with nonobstructive CAD (HR, 1.03 [95% CI, 0.83–1.28]).

Table 1. Baseline Characteristics: The Tromsø Study

Characteristics	High pain tolerance (n=6550)	Low pain tolerance (n=3026)
Age (y)	55±12	56±12
Male sex	53 (3440)	33 (999)
Daily smoker	19 (1259)	25 (760)
Former daily smoker	41 (2665)	40 (1196)
Hypertension	46 (2984)	44 (1322)
Systolic blood pressure (mm Hg)	135±22	132±23
Use of antihypertensive drugs	17 (1097)	20 (596)
Hypercholesterolemia	20 (1297)	23 (702)
Diabetes	6 (420)	9 (280)
Family history of MI	17 (1146)	20 (606)
Body mass index (kg/m^2)	27±4	27±4
Estimated glomerular filtration rate (mL/min per 1.73 m^2)	95±14	95±14

Numbers are mean±SD or percentage (n). Hypertension is defined as self-reported hypertension, use of antihypertensive drugs, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg; hypercholesterolemia if self-reported, use of lipid-lowering drugs, serum total cholesterol ≥7.0 or serum low-density lipoprotein ≥5.0 mmol/L; diabetes if self-reported, use of antidiabetic drugs, or hemoglobin A1c ≥48 mmol/mol. MI indicates myocardial infarction.

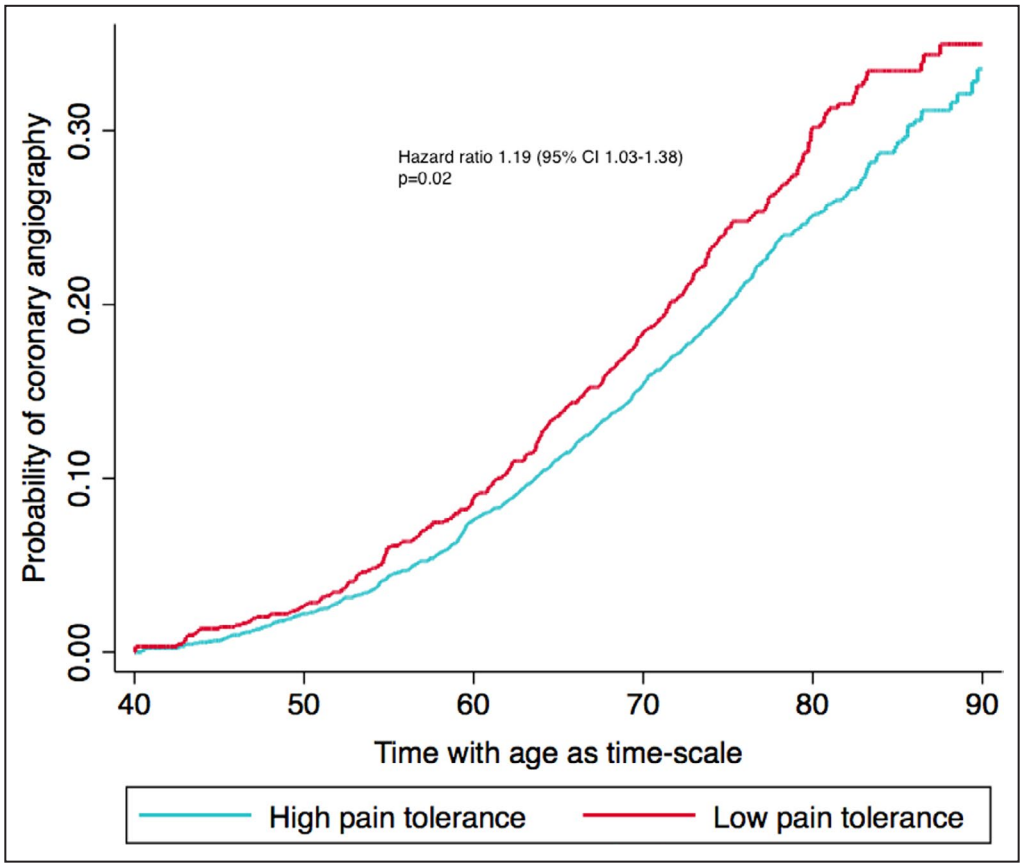

Figure 2. Cumulative incidence function of The Tromsø Study.
Cumulative incidence function for coronary angiography in participants with low pain tolerance and high pain tolerance, adjusted for sex and age as time-scale.

Pain Tolerance and Mortality

A total of 700 participants died (7.3%): 385 men (8.7%) and 315 women (6.1%). The cause of death was available until 2017 for 590 participants, of which 19% was because of cardiovascular disease (69 men and 44 women). Other main causes of death were cancer (51%), injury (8%), respiratory disease (6%), and neurological disease (6%). Overall, the IR of death was 6.4 (95% CI, 5.8–7.0) in participants with high pain tolerance and 8.7 (95% CI, 7.7–9.8) in participants with low pain tolerance (P<0.01). Adjusted for sex and age as time-scale, participants with low pain tolerance had 39% higher risk of death than participants with high pain tolerance (HR, 1.39 [95% CI, 1.19–1.63]) (Figure S1).

Figure 3 show a gradient increase in mortality rate from high pain tolerance to low pain tolerance, and no coronary angiography to MI (P for trend <0.001). In multivariable analyses adjusted for cardiovascular risk factors, participants with no coronary angiography and low pain tolerance had 37% higher risk of death (HR, 1.37 [95% CI, 1.16–1.63]) than participants with no coronary angiography and high pain tolerance. Participants with angina and low pain tolerance had a 2-fold higher risk of death (HR, 2.17 [95% CI, 1.06–4.44]) than participants with angina and high pain tolerance. In participants with MI, the mortality rate was substantially higher, and there we found no association between pain tolerance and mortality.

Table 3 demonstrates the risk of death in univariable and multivariable analyses for low pain tolerance, cardiovascular risk factors, and CAD. Participants with low pain tolerance had increased risk of death after adjustment for CAD and cardiovascular risk factors (HR, 1.40 [95% CI, 1.19–1.64]). The interaction term between pain tolerance and sex was not significant (P=0.73). In sensitivity analyses on cause of death, the results were similar for both cardiovascular death (HR, 1.41 [95% CI, 0.95–2.12]) and other causes of death (HR, 1.39 [95% CI, 1.17–1.66]).

DISCUSSION

We found that low pain tolerance was associated with a 19% higher risk of coronary angiography compared with high pain tolerance. Our results may indicate that individuals with low pain tolerance experience more cardiac symptoms and seek medical help earlier than

Table 2. Incidence Rates and HR for Obstructive Coronary Artery Disease According to Pain Tolerance: The Tromsø Study

Obstructive coronary artery disease*	Events	Person-years	Crude IR per 1000 (95% CI)	Model 1, HR (95% CI)	Model 2, HR (95% CI)
Total population					
High pain tolerance	379	65 936	5.7 (5.2–6.4)	Ref.	Ref.
Low pain tolerance	164	29 896	5.5 (4.7–6.4)	1.22 (1.01–1.47)	1.16 (0.95–1.40)
Men with coronary angiography					
High pain tolerance	282	2475	114 (101–128)	Ref.	Ref.
Low pain tolerance	88	828	106 (86–131)	0.94 (0.74–1.20)	0.89 (0.69–1.15)
Women with coronary angiography					
High pain tolerance	82	1950	42 (34–52)	Ref.	Ref.
Low pain tolerance	69	1298	53 (42–67)	1.46 (1.05–2.01)	1.54 (1.09–2.18)

Model 1 is adjusted for age as time-scale and/or sex; model 2 is adjusted for model 1 + smoking, diabetes, hypertension, hypercholesterolemia, and family history of MI. Hypertension is defined as self-reported hypertension, use of antihypertensive drugs, systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg; hypercholesterolemia if self-reported, use of lipid-lowering drugs, serum total cholesterol ≥7.0 or serum low-density lipoprotein ≥5.0 mmol/L; diabetes if self-reported, use of antidiabetic drugs or hemoglobin A1c ≥48 mmol/mol. HR indicates hazard ratios; IR incidence rate.

*Angina or myocardial infarction with obstructive coronary artery disease on coronary angiography. In the total population, participants with coronary death with no preceding coronary angiography are also included as obstructive coronary artery disease.

individuals with high pain tolerance. This is in line with previous results from the Tromsø Study demonstrating that high pain tolerance was associated with unrecognized MI,[13] as well as 2 studies demonstrating decreased pain sensitivity and more efficient endogenous pain inhibition among individuals with painless MI.[21,22]

Overall, we found that participants with low pain tolerance had a higher risk of obstructive CAD than participants with high pain tolerance adjusted for age as time-scale and sex, but not adjusted for cardiovascular risk factors. Among participants referred to coronary angiography, women with low pain tolerance had a higher risk than women with high pain tolerance for obstructive CAD. These were unexpected findings because we hypothesized that the opposite would be the case. Our findings contradict that patients present with nonobstructive CAD and/or microvascular angina because of lower pain tolerance and increased symptom awareness. Previous studies that compared pain tolerance in angina with and without obstructive CAD had small sample sizes and reported conflicting results with similar cold pressor pain tolerance, higher heat pain tolerance, and lower pain tolerance for ischemic and electrical, as well as cardiac stimuli in angina with no obstructive CAD compared with angina with obstructive CAD.[23–25]

Furthermore, we found that low pain tolerance was associated with increased all-cause mortality in all participants, regardless of referral to coronary angiography. Furthermore, the risk was similarly elevated for cardiovascular death and other death causes. This confutes our hypothesis that individuals with low pain tolerance had a lower risk of dying from CAD, while individuals with high pain tolerance had a higher risk of dying from CAD, even without ever presenting to coronary angiography. We are not aware of any previous study examining associations between pain sensitivity and mortality.

The mechanism by which low pain tolerance might increase the risk of obstructive CAD and all-cause mortality is unclear. We suggest 3 potential mechanisms. First, in our study we observed that individuals with low pain tolerance had a higher burden of traditional cardiovascular risk factors with more daily smoking, hypercholesterolemia, and diabetes. Although we adjusted for these factors in the analysis, and notably pain tolerance was a stronger predictor than many of the traditional risk factors, we still cannot exclude the possibility of residual confounding. Second, low pain tolerance is associated with chronic widespread pain,[18,26] which is further also associated with both increased cardiovascular- and all-cause mortality.[27] Third, another study from the Tromsø Study found higher serum levels of the C-reactive protein in individuals with low pain tolerance.[28] Increased C-reactive protein concentration and inflammation are known risk factors for cardiovascular disease and all-cause mortality, and anti-inflammatory treatment reduces the risk of cardiovascular events.[29–32] Furthermore, the Tromsø Study Fit Futures demonstrated that low cold pressor pain tolerance was associated with lower levels of the omega-3 fatty acids EPA and DHA, lower levels of urokinase plasminogen activator, and higher levels of several inflammatory biomarkers in healthy adolescents aged 15 to 19 years.[33] High levels of EPA are associated with lower risk of cardiovascular disease.[34] Urokinase plasminogen activator is an enzyme used as a thrombolytic agent, and higher levels of urokinase plasminogen activator receptor are associated with cardiovascular mortality.[31] Inflammation as the potential link between low cold pressor pain tolerance and

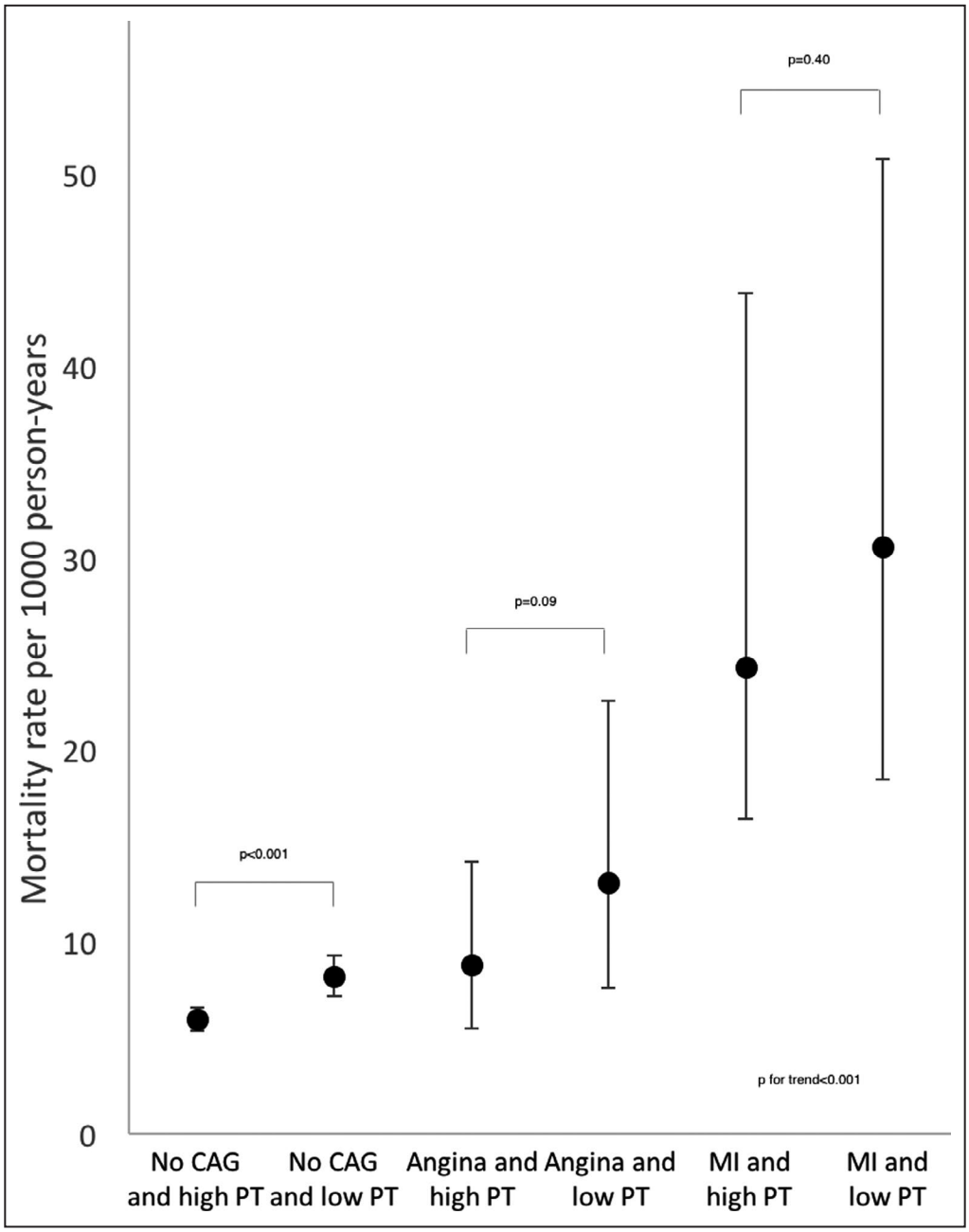

Figure 3. Mortality rate by pain tolerance and coronary artery disease in The Tromsø Study. Forest plot showing the unadjusted mortality rate in participants with high pain tolerance and low pain tolerance, by no coronary angiography, angina, and MI. CAG indicates coronary angiography; MI, myocardial infarction, and PT, pain tolerance. Error bars signify 95% CI.

increased risk of morbidity and mortality is an intriguing hypothesis for further research.

Strengths and Limitations

The strengths of this study include the population-based, prospective cohort design, with cold pressor pain tested in >10 000 individuals, and >10 years of follow-up. Furthermore, the combination of CCTA and ICA data allows for both identification of participants deferred by CCTA and confirmation of all positive findings on CCTA by ICA. We do not know how cold pain tolerance correlates with cardiac ischemic pain tolerance. One small study demonstrated that chest pain was associated with cardiac pain sensitivity, but not with heat pain sensitivity.[23] However, the cold pressor test elicits vascular pain from venous nociceptors, produces vasoconstriction in coronary arteries with endothelial dysfunction and atherosclerosis, and was traditionally used as a noninvasive test of vasospastic angina, and thereby is likely more suitable

Table 3. Univariable and Multivariable Analysis for HR for All-Cause Mortality: The Tromsø Study

	Univariable analysis, HR (95% CI)	Multivariable analysis 1, HR (95% CI)	Multivariable analysis 2, HR (95% CI)
No. of deaths/total no.	663/9222	663/9222	663/9222
Low pain tolerance	1.31 (1.12–1.54)	1.38 (1.18–1.62)	1.40 (1.19–1.64)
Male sex	1.66 (1.42–1.93)	1.74 (1.48–2.04)	1.74 (1.48–2.05)
Hypertension	1.04 (0.87–1.24)	1.05 (0.88–1.26)	1.04 (0.87–1.24)
Hypercholesterolemia	0.94 (0.80–1.12)	0.97 (0.81–1.15)	0.97 (0.81–1.15)
Diabetes	1.50 (1.20–1.87)	1.36 (1.08–1.71)	1.33 (1.06–1.67)
Smoking			
Daily smoker	2.60 (2.10–3.21)	2.46 (1.99–3.05)	2.45 (1.98–3.04)
Former daily smoker	1.50 (1.25–1.81)	1.33 (1.10–1.61)	1.33 (1.10–1.61)
Family history of MI	1.08 (0.88–1.31)	1.10 (0.90–1.34)	1.09 (0.89–1.33)
Body mass index >30 kg/m^2	1.09 (0.90–1.31)	1.12 (0.93–1.36)	1.13 (0.93–1.37)
Estimated glomerular filtration rate <60 mL/min per 1.73 m^2	1.14 (0.84–1.56)	1.08 (0.79–1.47)	1.06 (0.78–1.46)
Coronary angiography			
No coronary angiography	Ref.		Ref.
Angina with obstructive coronary artery disease	1.06 (0.73–1.54)		1.06 (0.73–1.54)
Myocardial infarction	1.69 (1.21–2.36)		1.36 (0.97–1.91)

Hypertension is defined as self-reported hypertension, use of antihypertensive drugs, systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg; hypercholesterolemia if self-reported, use of lipid-lowering drugs, serum total cholesterol ≥7.0 or serum low-density lipoprotein ≥5.0 mmol/L; diabetes if self-reported, use of antidiabetic drugs or hemoglobin A1c ≥48 mmol/mol. Coronary angiography is a time-varying variable. Univariable analysis is adjusted for age as time-scale. In multivariable analysis 1, low pain tolerance is adjusted for age as time-scale, sex, hypertension, hypercholesterolemia, diabetes, smoking, family history of MI, body mass index, and estimated glomerular filtration rate. In multivariable analysis 2, low pain tolerance is adjusted for the variables in multivariable analysis 1 + angina with obstructive coronary artery disease or myocardial infarction with no angiography and nonobstructive coronary artery disease as reference. HR indicates hazard ratios; and MI, myocardial infarction; Ref., reference.

than other peripheral experimental pain measures.[17,35] Furthermore, cold pressor pain tolerance is a hereditary trait and has demonstrated high test–retest reliability.[16,36] Future studies comparing cold pressor test tolerance to cardiac ischemic pain tolerance, and the test–retest reliability over longer periods of time could shed new light on these problems. The conduction of large-scale cardiac pain tolerance testing seems challenging.

Despite the large sample and long follow-up, there were few events of angina, MI, coronary death, and sudden cardiac death. Furthermore, we did not have cause of death for the 110 individuals who died in 2018. This reduces the statistical power of the study, and increases the risk of type II error, particularly in the difference between angina versus MI, and stable angina versus unstable angina, mortality risk ratios among individuals with MI, and cardiovascular mortality. Also, the number of sudden cardiac deaths was too low to conduct meaningful statistical analysis. Sensitivity analyses with pain tolerance run as a continuous or categorized variable demonstrated similar results. National registries ensure near complete follow-up data for the outcomes. However, an individual would be lost to follow-up if the coronary angiography was performed abroad or in another region of Norway before NORIC had full national coverage, and lost to follow-up for death if both emigrated from Norway and no longer registered as a Norwegian citizen. We believe this is unlikely to have affected our results.

CONCLUSIONS

This cohort study indicates that low cold pressor pain tolerance is associated with a higher risk of coronary angiography and all-cause death. Pain tolerance does not seem to explain the different manifestations of CAD, or why more than half of patients presenting to elective coronary angiography do not have obstructive CAD, but further research is needed.

ARTICLE INFORMATION

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Affiliations

Cardiovascular Research Group, Department of Clinical Medicine (K.F., H.S.), Department of Community Medicine (C.N., M.L., I.N., T.W.), Department of Psychology (A.O.) and Department of Clinical Medicine (E.B.M.), UiT The Arctic University of Norway, Tromsø, Norway; Department of Cardiology (K.F., H.L., A.K., J.M., T.T.) and Department of Neurology (E.B.M.), University Hospital of North Norway, Tromsø, Norway; Division of Ageing and Health, Norwegian Institute of Public Health, Oslo, Norway (C.N.); Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway (C.N., A.S.); Institute of Clinical Medicine, University of Oslo, Lørenskog, Norway (A.S., H.S.); Department of Cardiology, Haukeland University Hospital, Bergen, Norway (S.R.); Department of Radiology, University Hospital North

Norway, Tromsø, Norway (S.F.); and Department of Cardiology, Akershus University Hospital, Lørenskog, Norway (H.S.).

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Supplementary Material

Table S1
Figure S1

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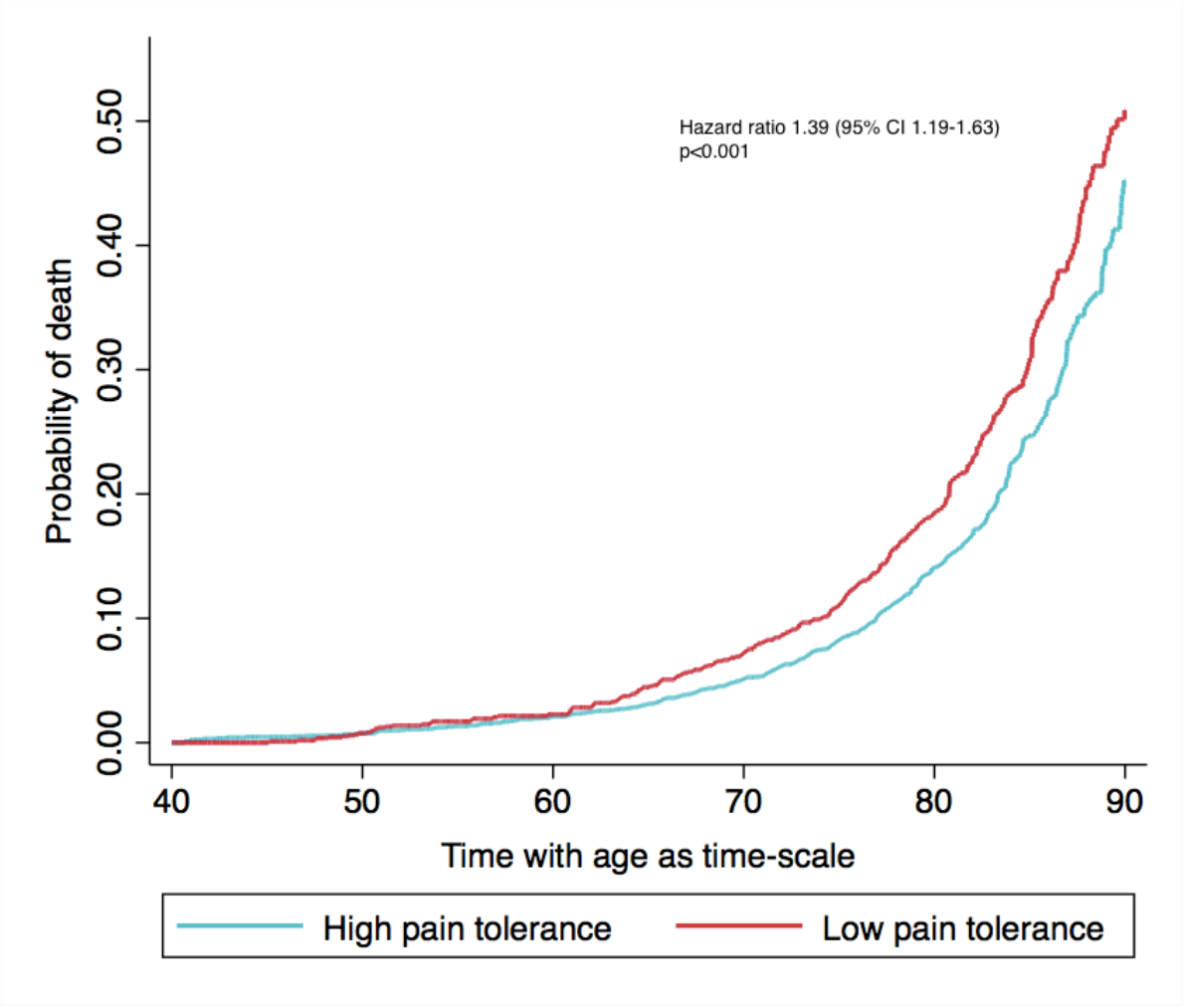
Supplementary Table 1. Risk of Coronary Angiography, Obstructive CAD and Mortality by Cardiovascular Risk Factors and Pain Tolerance, Adjusted for Age as Time-scale and Sex. The Tromsø Study.

	Coronary angiography, HR (95% CI)	**Obstructive CAD, HR (95% CI)**	**All-cause mortality, HR (95% CI)**
Daily smoker	1.12 (0.95-1.32)	1.51 (1.24-1.85)	2.12 (1.78-2.51)
Former daily smoker	1.02 (0.89-1.16)	0.91 (0.77-1.08)	0.93 (0.80-1.08)
Hypertension	1.44 (1.25-1.67)	2.00 (1.64-2.43)	1.05 (0.88-1.24)
Hypercholesterolemia	1.17 (1.00-1.36)	1.22 (1.00-1.47)	1.03 (0.87-1.21)
Diabetes	1.46 (1.19-1.80)	1.67 (1.31-2.14)	1.37 (1.11-1.70)
Family history of MI	2.00 (1.73-2.31)	2.15 (1.79-2.59)	1.13 (0.93-1.37)
Body mass index >30 kg/m^2	1.26 (1.08-1.48)	1.27 (1.04-1.55)	1.13 (0.95-1.36)
Estimated glomerular filtration rate < 60mL/min/1.73 m^2	0.73 (0.42-1.28)	1.07 (0.62-1.85)	1.26 (0.94-1.69)
Low pain tolerance	1.19 (1.03-1.38)	1.22 (1.01-1.47)	1.39 (1.19-1.63)

The Tromsø Study 2007-2008. HR indicates hazard ratio; CI, confidence interval. Diabetes is defined as self-reported diabetes, use of anti-diabetic drugs and/or HbA1c≥6.5%; hypertension as self-reported hypertension, use of anti-hypertensive drugs and/or systolic blood pressure≥140 mmHg or diastolic blood pressure ≥90 mmHg; hypercholesterolemia as self-reported, use of lipid-lowering drugs, total cholesterol level≥7 mmol/L and/or low-density lipoprotein ≥5 mmol/L.

Supplementary Figure 1. Cumulative Incidence Function. The Tromsø Study.



Cumulative incidence function for death in participants with low pain tolerance and high pain tolerance, adjusted for sex and age as time-scale.