Identification of acute coronary syndrome in the era of high-sensitivity troponin assays

Ole-Thomas Steiro

Thesis for the degree of Philosophiae Doctor (PhD)
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Contents

Scientific Environment

This work is part of the study Aiming Towards Evidence-Based Interpretation of Cardiac Biomarkers in Patients Presenting with Chest Pain (WESTCOR) study led by Kristin Moberg Aakre at the University of Bergen and Haukeland University Hospital. The project is a cooperation between Haukeland University Hospital and Stavanger University Hospital. Members of the steering committee are Dr. Kjell Vikenes, Haukeland University Hospital, Dr. Øyvind Skadberg, Stavanger University Hospital, Dr. Vernon V. S. Bonarjee, Stavanger University Hospital, Professor Rune Bjørneklett, Haukeland University Hospital and Dr. Øistein Mjelva, Stavanger University Hospital.

Scientific advisors for the project are Professor Torbjørn Omland, Akershus University Hospital, and Professor Paul Collinson, St George's University Hospitals NHS Foundation Trust.

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Abbreviations and definitions

ACC	American College of Cardiology
ACCF	The American College of Cardiology Foundation
ACS	Acute coronary syndrome
ADP	Accelerated diagnostic protocol
AHA	The American Heart Association
AUC	Area under the curve
BMI	Body mass index
CAD	Coronary artery disease
CARE	Characteristics, Age, Risk factors, ECG
CCTA	Cardiac computed tomographic angiography
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase – myocardial band
CRP	C-reactive protein
cTn	Cardiac troponin
cTnC	Cardiac troponin C
cTnI	Cardiac troponin I
cTnT	Cardiac troponin T
CV	Cardiovascular
CV_A	Coefficient of variation
CVD	Cardiovascular disease
ECG	Electrocardiogram
ED	Emergency department
EDACS	Emergency Department Assessment of Chest Pain Score
EDTA	Ethylenediaminetetraacetic acid
ESC	European Society of Cardiology
GRACE	Global Registry of Acute Coronary Events
HEART	History, Electrocardiogram, Age, Risk factors, and Troponin
High-STEACS	High-Sensitivity Troponin in the Evaluation of patients with Acute Coronary Syndrome

hs-cTnI	High-sensitivity cardiac troponin I
hs-cTnT	High-sensitivity cardiac troponin T
IFCCC	The International Federation of Clinical Chemistry Committee
LOB	Limit of blank
LOD	Limit of detection
LOQ	Limit of quantitation
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
NA	Not available
NCDR	Norwegian Cause of Death Registry
NorPD	Norwegian Prescription Database
NPR	Norwegian Patient Register
NPV	Negative predictive value
NSTE-ACS	Non-ST-elevation acute coronary syndrome
NSTEMI	Non-ST-elevation myocardial infarction
OR	Odds ratio
PPV	Positive predictive value
PCI	Percutaneous coronary intervention
REK	Regional Ethic Committee
SMCs	Smooth muscle cells
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction
T-MACS	Troponin-only Manchester Acute Coronary Syndromes
UAP	Unstable angina pectoris
UDMI	Universal Definition of Myocardial Infarction
URL	Upper reference limit
WESTCOR-D	WESTCOR Derivation cohort
WESTCOR-CT	WESTCOR Validation Cohort from Stavanger University Hospital
WESTCOR-V	WESTCOR Internal Validation cohort
WHF	World Heart Federation
WHO	World Health Organization
WHF	World Heart Federation
WHO	World Health Organization

Abstract

Background: There is potential for future improvements in patient flow and diagnostic precision in patients presenting to hospital with suspected acute coronary syndrome (ACS). Long-term risk of cardiovascular (CV) events may be assessed by cardiac troponin (cTn) levels if certain concerns are addressed and resolved, like whether the established percentiles of normal range are biological equal between all commercially available assays. The thesis evaluates important diagnostic and prognostic tools in cardiac workup of patients with possible ACS: troponin (cTn) algorithms, clinical risk scores, and prognostic relevance of chronically elevated cTn. above the 99th percentile, termed chronic myocardial injury (CMI).

Methods: Patients admitted to Haukeland University Hospital with symptoms suggestive of ACS were included in the WESTCOR study (n=1506). Blood samples were collected at presentation and after 3 and 8-12 hours. Paper 1 (n=1506) calculate the diagnostic precision of chest pain characteristics and additional symptoms for the diagnosis of NSTEMI. Paper 2 (n=984) assess the short-term risk of adverse events when troponin-based 0/3-hour algorithms are combined with 11 different clinical risk scores. Paper 3 (n=1147) evaluate the prevalence of having cTn concentrations above the 99th percentile and long-term prognostic power of CMI compared to using lower cutoff values for risk stratification.

Results: The risk of having an NSTEMI based on specific symptoms were overall similar across sex and age groups. Low-risk patients identified by a risk score combined with low concentrations of cTn have very low short-term risk of adverse cardiac events. Patients with CMI have elevated risk for cardiovascular death and coronary events, but the prevalence of CMI is highly dependent on cTn assay.

Conclusions and implications: Patients classified as low risk based on the presentation of symptoms, clinical risk scores and hs-cTn assays had a very low short-term risk of CV events and could be considered for early discharge from hospital. Physicians should be aware of the increased long-term risk of CV events associated with CMI, but also the low concordance between the 99th percentile URLs of different cTn assays.

Sammendrag på norsk

Bakgrunn: Det er mulig å bedre pasientflyt og diagnostisk presisjon ved utredning av pasienter med mistenkt akutt koronarsyndrom (AKS). Konsentrasjonen av kardialt troponin (cTnT eller cTnI) kan benyttes til å forutse langsiktig risiko for kardiovaskulære hendelser dersom visse utfordringer blir avklart, for eksempel om de etablert persentilene innen normalområdet er biologisk like for alle tilgjengelige analyseapparater. Avhandlingen vurderer viktige diagnostiske og prognostiske verktøy i utredningen av pasienter med mulig AKS: troponin-algoritmer, kliniske risikoskalkulatorer og prognostisk betydning av kronisk forhøyede troponin-verdier over 99-percentilen, definert som kronisk myokardskade (KMS).
Metode: Pasienter innlagt på Haukeland Universitetssykehus med symptomer på AKS ble inkludert i WESTCOR-studien (n=1506). Blodprøver ble tatt ved innkomst og etter 3 og 8-12 timer. Artikkel 1 (n=1506) beregner diagnostiske presisjonen for diagnosen NSTEMI basert på brystsmertenes karakter og plassering, og tilleggssymptomer. Artikkel 2 (n=984) vurderer diagnostisk presisjon av troponin-baserte 0/3-timersalgoritmer og 11 ulike risiko-kalkulatorer. Artikkel 3 (n=1147) vurderer prevalens av troponin-verdier over 99-persentilen og prognostisk verdi av KMS sammenlignet mot å bruke lavere troponin-grenser for risikovurdering.
Resultater: Det var små forskjeller mellom kjønn og aldersgrupper i risiko for akutt koronarsykdom basert på spesifikke symptomer. Pasienter med lav risiko for AKS basert på risikokalkulatorer kombinert med lave troponin-konsentrasjoner har svært lav korttidsrisiko for kardiale hendelser. Pasienter med KMS har økt langtidsrisiko for kardiovaskulær død eller uønskede koronare hendelser, men prevalensen av KMS varierer mellom analyseapparater som analyserer cTnT og cTnI.
Konklusjon og implikasjoner: Pasienter med lav risiko for AKS basert på symptomer, kliniske risikokalkulatorer og høy-sensitive troponin-analyser har svært lav kortsiktig risiko for kardiovaskulære hendelser og kan vurderes for tidlig utskrivelse fra sykehus. Klinikere bør være kjent med den forhøyede langtidsrisikoen for fremtidige kardiovaskulære hendelser forbundet med KMS, men også den svake korrelasjonen mellom 99-persentilene for ulike troponin-analyseapparater.

List of Publications

Steiro O-T, Aakre KM, Tjora HL, Bjørneklett R, Skadberg Ø, Bonarjee VVS, Mjelva ØR, Omland T, MD, Vikenes K, Langørgen J. Association between symptoms and risk of non-ST segment elevation myocardial infarction according to age and sex in patients admitted to the emergency department with suspected acute coronary syndrome: a single-centre retrospective cohort study. BMJ Open. 2022;12:1–12.

Steiro O-T, Tjora HL, Langørgen J, Bjørneklett R, Nygård O, Skadberg Ø, Bonarjee VVS, Lindahl B, Omland T, Vikenes K, Aakre KM. Clinical risk scores identify more patients at risk for cardiovascular events within 30 days as compared to standard ACS risk criteria: the WESTCOR study. European Heart Journal: Acute Cardiovascular Care. 2020 Oct 2;10(3):287–301.

Steiro O-T, Langørgen J, Tjora HL, Bjørneklett R, Skadberg Ø, Bonarjee VVS, Mjelva ØR, Steinsvik T, Lindahl B, Omland T, Aakre KM, Vikenes K. Chronic myocardial injury diagnosed by three high-sensitivity cardiac troponin assays; differences in prevalence and prognostic implications. *Submitted for review 2023.*

1. Introduction

High-sensitivity troponin assays, clinical risk scores and algorithms for early detection or exclusion of coronary artery disease (CAD) has attracted a lot of academic and clinical attention during the past ten years. This thesis evaluates key aspects of the diagnostic workup of patients with suspected CAD, and understanding the pathophysiology of atherosclerosis is essential.

Atherosclerosis is the accumulation of plaque and thickening of the arterial walls. When coronary arteries are affected, the process may cause reduced blood supply to the myocardial cells, ischemic heart failure and lethal arrythmias. Post-mortem observations of degenerated arteries had been observed for centuries (1) before the term atherosclerosis was first used by Felix Marchand in 1904 (2). Plaque buildup is promoted by lifestyle factors and is a continuous process with a higher prevalence in older patients. However, CT scans of 4000-year-old mummies show the presence of atherosclerosis, indicating that pathological processes of the arteries have always occurred even in preindustrial and preagricultural populations with low-cholesterol diets, a non-sedentary lifestyle, and a short life expectancy due to other causes of death (3).

In the western world, infectious diseases were the most important cause of morbidity and mortality until in the twentieth century when increased life expectancy were achieved through the inventions of vaccines and antibiotic treatments, as well as improvements in living conditions and sanitation (4). By the middle of the 20th century, cardiovascular disease had outpaced infectious diseases as the main cause of reduced life expectancy.

Ischemic heart disease (IHD) accounts for 16% of total deaths worldwide, but with regional variations (5). In high-income countries, mortality and age-adjusted incidence have decreased in recent decades (6) mainly due to improvements in preventive treatment and risk factor reductions such as a decline in tobacco smokers (7). Increased access to early revascularization has reduced the mortality after STEMI. However, the incidence of non-fatal NSTEMI is slightly increasing, probably due to increased prevalence of metabolic conditions such as diabetes, hypertension, and

dyslipidemia (8). In addition to the individual risk of mortality and adverse cardiac events, the combined workload on the health care systems is a major concern. Longer life expectancy and worldwide adoption of unhealthy lifestyle habits that were previously more common in high-income countries, is the reason why cardiovascular diseases are described as an epidemic in industrialized nations and a potential pandemic for the world (9).

Symptoms suggestive of acute coronary syndrome (ACS) is a common cause of seeking emergency medical care. More than 5% of patients in emergency departments (ED) having chest pain as their main complaint (10). Shortness of breath, nausea, and diaphoresis contribute to the diversity of presenting symptoms that may require cardiac investigations. In the US alone, cardiovascular disease costs more than 320 billion dollars a year (11) and is expected to surpass 1 trillion dollars in 2035 (12). Due to the individual, financial and social burden, great efforts are put into primary prevention, effective treatment, and reducing the pressure on the health care system by patients less likely to have cardiovascular disease in need of treatment.

For coronary heart disease, the increasingly sensitive cardiac troponin (cTn) assay, point-of-care assays, early rule-in algorithms, and rule-out algorithms for patients unlikely to suffer from coronary artery disease, are some measurements that may help reduce the pressure on emergency departments (EDs). Studies indicate that early discharge of patients with low risk of coronary disease can reduce costs (13), which, in turn, can be directed to those more in need of costly diagnostics and treatments.

1.1 Atherosclerosis

Two opposing pathologists are considered the fathers of our understanding of atherosclerotic pathogenesis. The German pathologist Rudolph Virchow in 1844 described what we today call atherosclerosis as "excessive plaque formation on the interior of vessels" of the aorta, believing that lipid accumulation, cell proliferation, and the central role of inflammation were the causes of plaque formation (14). Austrian pathologist Karl von Rokitansky had an opposing view, believing that mural

thrombosis played the main role and inflammation was merely secondary and less important (15). The debate was fierce, but today both theories have been proven correct.

The understanding of atherosclerosis accelerated at the beginning of the twentieth century, as the German chemist Adolf Windaus found that atherosclerotic plaques consisted of connective tissue and cholesterol (16). Subsequent rodent experiments showed that high cholesterol intake initiated atherosclerosis (17). Later in the twentieth century, Virchow's theory of inflammation gained increased recognition by several scientists who introduced theories of inflammation and atherosclerosis. An important contribution to the understanding of atherosclerosis was the “response to injury hypothesis” of Ross et al. on endothelial dysfunction due to mechanical injury, toxins, or oxidative stress (18).

The transport of LDL, both native and oxidized, into the intima has been proposed as the initial step that attracts inflammatory cells and creates foam cells (19). Others have identified activated T cells, macrophages, and dendritic cells in coronary plaques (20). In summary, contemporary studies are based on a combination of theories in which thrombus combined with inflammatory healing of disrupted plaque form the foundation for atherogenesis.

1.2 Coronary artery disease

When the atherosclerotic process of plaque build-up in the intimal layer occur in coronary arteries, the end result is coronary artery disease (CAD) (21,22). Coronary plaques consist of a fibrous cap containing smooth muscle cells (SMC), extracellular matrix, and a necrotic core rich in lipids, see **Figure 1**. Eventually, lesions can become more complex, extensively calcified, and develop ulcerations on the luminal surface (23).

CAD can be subdivided based on pathophysiology with associated clinical presentation. It is a common cause of myocardial injury, which is subdivided based on cTn concentrations.

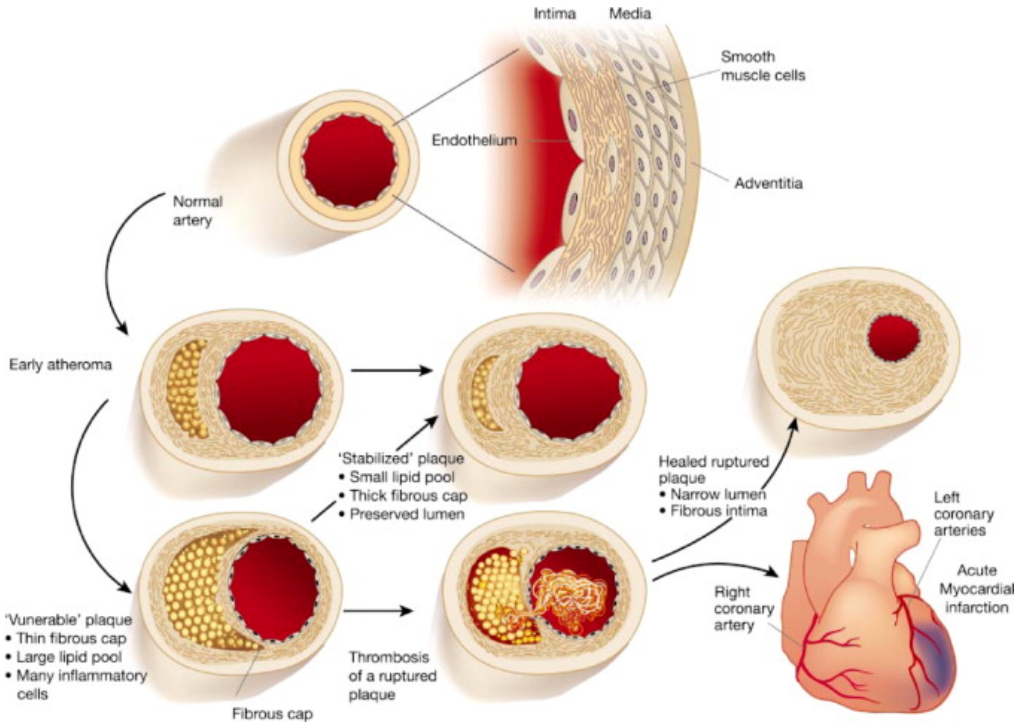

Figure 1. *Development of coronary artery disease. Figure by Libby P, Inflammation in atherosclerosis. Nature.* 2002;420(6917):868–74*, reprinted with permission from Springer Nature* (24).

1.2.1 Subdivision of CAD based on pathophysiology

The severity of CAD depends on the degree of atherosclerosis and stability of the coronary plaques. CAD with stable plaques is termed chronic coronary syndrome (CCS), and patients often present with stable angina pectoris. CAD with unstable plaques can develop into acute coronary syndrome (ACS), and the patient may present to clinic with either unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI), see **Figure 2**.

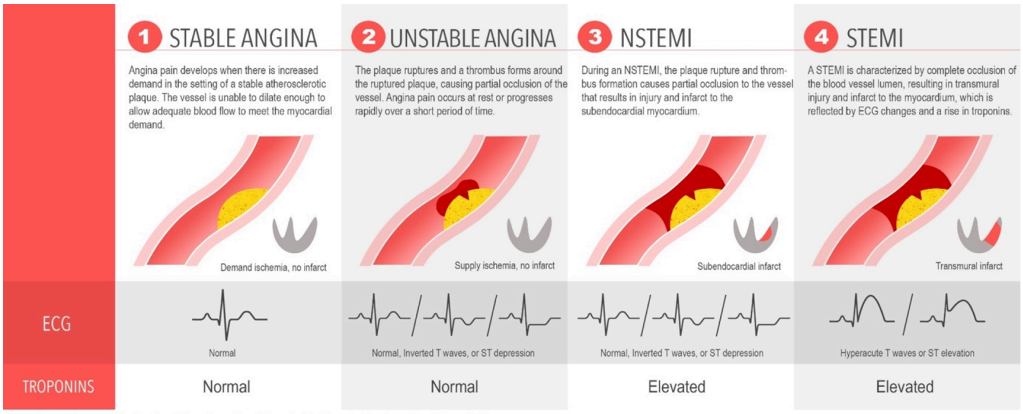

Figure 2. *Categorization of coronary artery disease based on pathophysiology and associated ECG findings and troponin concentration as either stable angina pectoris (1) or acute coronary syndrome (2, 3 and 4). Illustration by Paula Sneath and Leah Zhao for CanadiEM.org, slightly modified, published under Open Access and reprinted under the terms of the Creative Commons CC BY license.*

1.2.1.1 Chronic coronary syndrome

Continuous growth of advanced lesions can alter the blood flow through the stenosis and cause angina pectoris. Stable plaques often have thicker fibrous caps and macrocalcification (25, 26). Chronic CAD is rarely fatal if the myocardium is not scarred that causes arrhythmia and sudden death. However, even though the disease can be stable for a long period of time, the 2019 European Society of Cardiology (ESC) guidelines replaced the older term “stable coronary artery disease” with “chronic coronary syndrome” to reflect the continuum in which chronic CAD can become acute. If stable coronary plaques rupture or erode, an atherothrombotic event can occur (22).

CCS has the same pathophysiology and risk factors as ACS, with some minor differences. For example, smoking appears to increase the risk of AMI more than CCS (27).

1.2.1.2 Acute coronary syndrome

UAP, NSTEMI and STEMI (**Figure 2**, condition 2, 3 and 4) have similar pathophysiology, but different clinical presentation and prognosis. The conditions are caused by buildup of fatty deposits and atherosclerotic plaque formation with or without concomitant vasospasms and risk of thrombus formation when the plaque ruptures. In the case of rupture, the lesion will expose a highly thrombogenic necrotic core material that attracts circulating platelets to cause thrombosis and acute vessel occlusion as in a STEMI (25), see **Figure 2 and 3**.

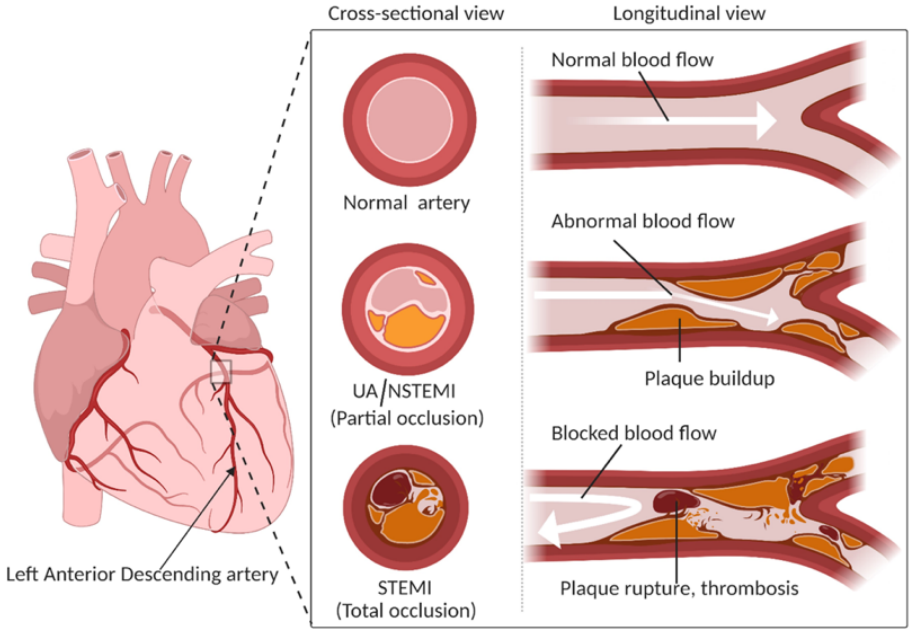

***Figure 3**. Classification of acute coronary syndromes based on pathophysiologic condition. Figure by Surendran A et al., Defining Acute Coronary Syndrome Through Metabolomics.* Metabolites*. 2021; 11(10):685, published under Open Access and reprinted under the Creative Commons CC BY license* (28).

Although most fatal myocardial infarctions occur through plaque rupture, around a fourth of cases are due to plaque erosion. Erosions may cause ruptured thrombi at locations of intimal thickening or fibroatheroma (25, 29).

A STEMI (**Figure 2**, condition 4) is most often caused by a thrombus that occludes the artery, and the patient has ST segment elevations on the electrocardiogram (ECG). Transmural necrosis occurs within one hour, and the risk of myocardial scarring and future heart failure is high unless coronary flow is restored urgently (30). Patients with STEMI patients can present with severe symptoms of intense and radiating pain, often accompanied by diaphoresis and nausea.

During UAP and NSTEMI (**Figure 2**, condition 2 and 3), the thrombus is incomplete and dynamic or may not be present at all. Patients can have ST segment depression or T wave inversions on the ECG and are distinguished from one another by the presence or absence of cTn leakage from cardiac myocytes (NSTEMI or UAP, respectively). NSTEMI inflicts ischemia on the myocardium to the extent that cardiomyocytes undergo reversible or non-reversible ischemia and release cTn into the circulation in a typical rise-and-fall pattern. Although patients with UAP often have similar ischemic symptoms, serial measurements of cTn reveal stable concentrations (21, 31). The symptoms of NSTEMI and UAP mimic those of STEMI, but the symptoms can be shorter in duration and less severe.

1.2.2 Subdivision of myocardial injury by cTn concentration

The term myocardial injury is used for conditions that involve cTn concentrations above the assay-specific 99th percentile regardless of clinical and imaging findings, as outlined in the Fourth Universal Definition of Myocardial Infarction (UDMI) from 2018 (31). Myocardial injury is subdivided based on cTn dynamics as shown in **Figure 4**.

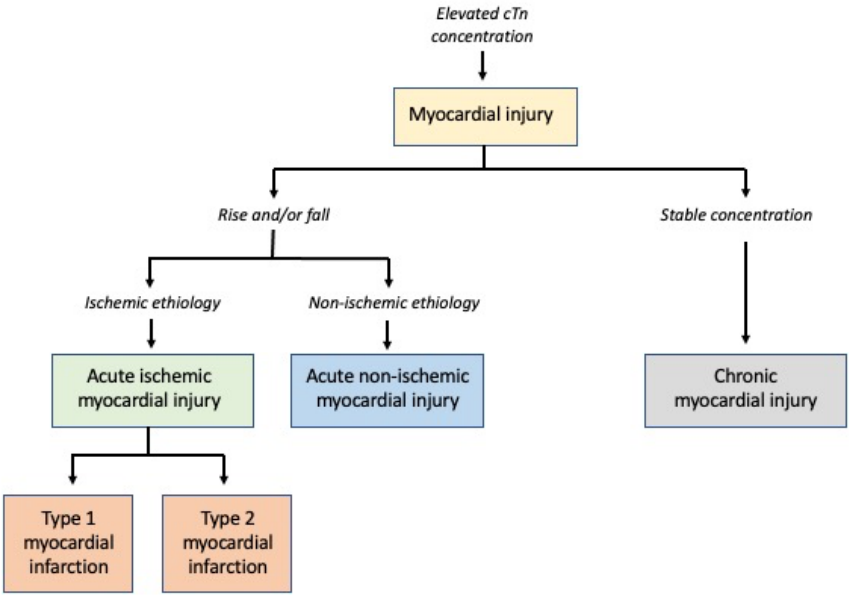

Figure 4. *Overview of the different types of myocardial injury.*

1.2.2.1 Acute myocardial injury

Acute myocardial injury involves an increase and/or decrease in cTn concentrations and is further divided according to ischemic or non-ischemic etiology, see **Figure 4**. Patients with typical ischemic symptoms may have an acute myocardial infarction. A rise and fall pattern without signs of acute cardiac ischemia is classified as acute nonischemic myocardial injury, typically caused by diseases such as acute heart failure, pulmonary embolism, or myocarditis. Physical activity can also induce myocardial injury, as seen in more than half of the participants in strenuous exercise (32).

1.2.2.2 Chronic myocardial injury

Chronic myocardial injury (CMI) is characterized by stable elevated cTn concentrations >99th percentile of the cTn assay and is associated with conditions like reversible myocardial ischemia, left ventricular hypertrophy, cardiac fibrosis, and

cardiac exposure to metabolic risk factors (33-36). Non-cardiac causes, such as pulmonary hypertension and renal failure, may also produce the same biochemical changes. Patients with chronic myocardial injury have higher mortality and risk of cardiovascular events, but possible modifiable risk factors are largely unknown apart from the treatment of risk factors for cardiac disease and the potential underlying condition (37, 38).

1.3 Biomarkers

The association between coronary thrombus and acute myocardial infarction was first described in postmortem observations in 1878 (39), but the diagnosis of AMI was subject to controversy and confusion for 80 years to follow (31). In 1957, an expert panel selected by the World Health Organization (WHO) established an ECG-focused definition of AMI (40). The definition was revised during the 1960s and 1970s, with diagnostics still based on clinical history, ECG findings, postmortem findings, and biomarkers with moderate specificity.

The journey to identify the perfect biomarker of cardiovascular disease started in the 1950s with aspartate aminotransferase (AST) through more sensitive and specific markers such as lactate dehydrogenase (1955), total enzyme activity of creatine kinase (CK) in 1960, isozyme activity of CK (CK-MB) in 1972 and mass of CK-MB in 1985. However, none of these biomarkers met the criteria of a perfect biomarker: Exclusive existence in the target organ, imminent release into serum at the time of injury, and sufficient stability in serum to enable quantification within a reasonable diagnostic window. Additionally, serum concentration should ideally reflect the degree of injury, and the test should be affordable and easy to perform (41).

Most of these criteria have been met with the discovery and development of cTn assays. cTn quantifications are based on the discovery by Setsuro Ebashi in 1963 that calcium induces the contractions of actin and myosin filaments and his later discovery of a new complex of proteins involved in the contractile process named troponins (42). 25 years later, research groups managed to develop assays for the two cardio specific Troponin I (1987) and Troponin T (1989).

During the following decades, increasingly sensitive assays have been developed which led to the redefinition of AMI in the year 2000. Representatives from the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) agreed on a biochemical and clinical definition of myocardial infarction in which AMI could be diagnosed in the presence of a typical rise and/or fall of CK-MB, cardiac troponin I (cTnI) or cardiac troponin T (cTnT) (43). Re-definitions followed where rise and/or fall of a biomarker became mandatory. cTn became the preferred biomarker in 2007 (44, 45) and mandatory in 2018 with revised UDMI (31).

The first cTnI assay had a limit of detection (LOD) of 10.000 ng / L, while some modern high-sensitivity cardiac TnI assays (hs-cTnI) have a LoD as low as 1 ng/L. The history of cTnT has been somewhat more troublesome due to cross-reaction to skeletal muscle and false positive tests in patients with, for example, rhabdomyolysis. However, with the introduction of human recombinant cTnT for calibration and fragment antigen binding (FAB), the specificity is high, and the sensitivity of the fifth-generation assay has increased to a LoD of 3-5 ng/L.

1.3.1 Cardiac troponin

Cardiac troponin is a complex of proteins consisting of three subunits, cTnT, cTnI, and troponin C (TnC). TnC is the calcium-binding component present in both cardiac, striated, and skeletal muscle, while cTnI and cTnT are present only in cardiac myocytes. The contractile unit consists of a thick filament (myosin) and a thin filament (actin), with cardiac troponin and tropomyosin attached to the latter. When calcium is released into the cardiomyocyte, cTn removes tropomyosin from actin exposing myosin-binding sites, and muscle contraction occurs. The role of cTnI is to inhibit the contractile interaction between myosin and actin while cTnT binds actin to tropomyosin (46), see **Figure 5**.

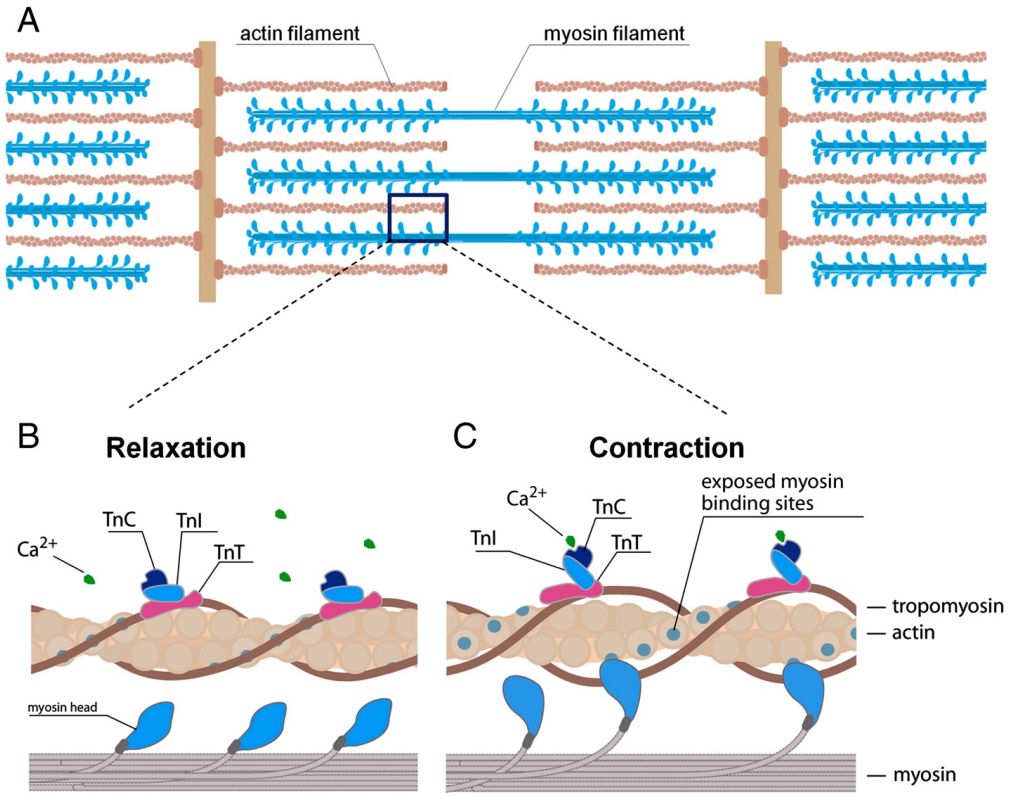

Figure 5. *The Troponin contractile unit during calcium exposure. Figure by Streng AS et al. Posttranslational modifications of cardiac troponin T: an overview. J Mol Cell Cardiol. 2013 Oct;63:47-56, reprinted with permission from Elsevier* (47).

1.3.2 Release of cTn into the circulation

cTn are mainly bound to the contractile apparatus, but small amounts exist in the cytosol, 6-8% for cTnT and 2.8-4.1% for cTnI (48). Circulating cTn can be measured in blood samples from healthy individuals and can vary in concentration between <1 ng/L and approximately 50 ng/L for cTnI and <5 ng/L to 14 ng/L for cTnT. Normal values are 1.2-2.4 times higher in men than in women and may increase with age, especially after 60 years of age (49, 50). cTnT and cTnI in cardiomyocytes undergo regular replacement with relatively similar half-lives of 3.5 and 3.2 days, respectively

(51, 52). It is not clear whether measurable cTn is caused by constant release by living cardiomyocytes or apoptosis and regeneration as part of normal heart renewal, or both (53, 54). The regeneration process is slow, with less than 50% of myocytes being renewed during a lifespan (55).

An AMI occurs when the supply of oxygen-rich blood to cardiomyocytes is reduced due to occlusion of a coronary artery, vasospasm, or other causes of supply-demand mismatch (31). Cardiac tissue with reduced access to oxygen will adapt and undergo molecular and cellular changes. As a first compensatory mechanism, ATP is produced through anaerobic rather than aerobic metabolism, and metabolites such as lactate are released into the circulation within minutes after the onset of reversible ischemia. Permanent damage occurs after approximately an hour of oxygen deprivation. Macromolecules cannot enter the circulation directly but will transfer to the lymphatic system and gradually pass into the circulation according to size. The smaller myoglobin molecules exit the damaged tissue first, followed by cTnI and cTnT, and lastly the larger CK and LDH molecules (56).

In cases of total occlusion, cTn concentrations will peak after 24 to 50 hours, while patients with restored flow will have peak concentrations after 10 to 20 hours (57, 58). Although cTn has a half-life of 2 hours (59), concentrations will remain elevated for 10-14 days after an AMI possible due to continued leakage of cTn from necrotic cells (60) in contrast to exercise-induced troponin leakage where cTn values return to baseline within 24 hours (61, 62).

Possible mechanisms for the release of cTn into the circulation include irreversible damage to cardiomyocytes and reversible causes.

1.3.3 Necrosis and apoptosis

Prolonged ischemia can cause necrosis and the release of cTn into the circulation due to the destruction of cell membranes and organelles. Cardiomyocytes are more prone to necrosis than other cells due to the calcium (Ca^{2+}) and oxygen paradox. When reperfusion occur after oxygen depletion, a massive influx of Ca^{2+} into the myocardial cells cause membrane disruption, myofibrillar hypercontractility and mitochondrial damage (63). Programmed cell death has been proposed to be a contributing factor

explaining some of the leakage of cTn in response to ischemia or other stressors, as enzymes believed to be mediators of apoptosis are present after AMI (64). The size of the infarction is reduced when apoptosis pathways are inhibited in animal models (65). Others argue that apoptosis cannot be the main factor in the leakage of cTn, since apoptotic bodies are enclosed by membranes and should not release cTn into the circulation (66, 67). Studies arguing that apoptosis is an important contributor to cTn release have methodological weaknesses (36), and to date, no treatment for heart failure targeting apoptosis has been developed.

1.3.4 Reversible ischemia

cTn molecules can be released from live cardiomyocytes without necrosis or apoptosis. Older studies on hepatocytes (68) and cardiomyocytes (69, 70) have shown that cells develop membranous blebs containing cell components in response to ischemia. When oxygenation is restored, the content can be released without the cell ever becoming necrotic (71). The half-life of cTn is shorter if significant irreversible ischemia is not confirmed by imaging, for example, as seen after exercise (32, 72). The longest half-life of cTn is seen in patients with a large transmural infarction. This late-occurring elevation of cTn was believed to occur because of slow degradation of the myofibrils after irreversible damage. Newer studies challenge this notion by demonstrating how cTn concentration after a transmural infarction can be delayed due to decreased washout from ischemic cells when blood supply is decreased after coronary occlusion (73-75). When coronary reperfusion is restored immediately, cTn increases quickly (75).

Although not extensively studied, the pathophysiological cause of cTn elevation may be disclosed by differences in the distribution of complete cTn molecules versus smaller fragments. A current hypothesis is that cTn molecules exist as intact molecules the first hours after an AMI before being degraded into cTn fragments (76, 77). Detected elevations of cTn after vigorous exercise without myocardial necrosis are most often due to the presence of small fragments of cTn (78). Similarly, patients with myocardial injury of noncardiac origin have a higher fraction of cTn fragments (79). Airaksinen et al. compared the concentration of intact or long forms of cTnT to

smaller fragments of cTnT typically present in patients with kidney failure, and found a higher ratio of long/intact vs total cTnT in patients with NSTEMI and STEMI compared to patients with kidney failure (80). Commercially available cTn assays do not differentiate between intact and fragmented cTn molecules. Future studies may determine whether the composition of fragments and complete molecules can be used to assess the cause of elevated cTn concentrations.

1.4 Cardiac troponin assays

cTnT and cTnI have unique N-terminal amino acid sequences that allow them to be identified by antibodies and quantified in an enzyme-linked immunosorbent assay (ELISA). cTn exist in serum bound in I-C complexes, T-I-C complexes, oxidized, reduced, and phosphorylated forms. cTnT, but not cTnI are also easily detected in free forms (81). Antibodies used in different assays detect different epitopes of the cTn molecule. Since the terminal regions of the cTn molecule are susceptible to proteolytic degradation, antibodies should target cTn epitopes located within the stable central region (82). Measurements are based on the sandwich principle in which a capture antibody attaches to the cTn molecule and allows a detecting antibody to bind and release signals detected by the analyzer that are proportionate to the concentration of cTn in the substrate (83, 84).

1.4.1 Analytical characteristics

Several factors are important when describing the smallest concentration of an analyte that can be measured by an assay (84). The limit of blank (LoB) is the highest value likely to be observed if blank samples are analyzed repeatedly. It is calculated as LoB = mean (zero calibrator) + 1.645 x SD (zero calibrator). LoD is the lowest concentration of an analyte that can be reliably distinguished from LoB and is calculated by analyzing replicates of a sample known to contain low concentrations and the formula LoD = LoB + 1.645 x SD (low concentration calibrator). The limit of quantification (LoQ) is the smallest concentration that can be reliably and repeatedly measured, usually at the level where the analytic variation is below 20% (coefficient

variation, CV_A, measured as 100 x SD/mean). LoQ is mainly used in contemporary assays where LoD or LoB cannot be reported due to CV_A >20%. After the introduction of high-sensitivity cTn assays, LoB and LoD are the clinically most important terms in most laboratories. However, in the USA, the FDA has approved the use of hs-cTn assays with LoQ used as the lower limit (85).

1.4.2 The 99th percentile URL

Since first recommended in the guidelines more than 20 years ago (43), the 99th percentile has defined the border between normal and abnormal cTn concentrations. The 99th percentile is calculated by the manufacturer after excluding the highest 1% values in a group of healthy volunteers. A cohort size of at least 400 male and 400 female volunteers is considered sufficient according to current guidelines (86), but the cohort sizes used by today's commercially available assays vary between 250 and 1000 participants of each sex. Manufacturers must adhere to criteria for correct analysis and ensure that the CV_A does not exceed 10% at the 99th percentile for high-sensitivity assays.

A vast number of cTn assays exist and all have their own 99th percentile calculated from a healthy reference group. The cutoff varies as the assays use different monoclonal antibodies that recognize different epitopes on the cTn molecule with different affinity (87). Questions have been raised concerning the biologic equality of the 99th percentiles calculated by each manufacturer. New recommendations from the International Federation of Clinical Chemistry Committee are intended to reduce the differences between different assays by applying rigorous screening of a sufficiently large group of healthy adults and high-precision sample treatment and statistical calculations (86).

Most other biomarkers use the 97.5th percentile to define abnormality. Lowering the cut-off value for cTn concentrations was discussed in 1999 (88), but was never implemented. An important reason is the magnitude of clinical studies conducted based on the 99th percentile. Patients with cTn >99th percentile benefit from antiplatelet therapy and revascularization, but this may not be true for patients with cTn between the 97.5 and 99th percentile. Harmonizing the AMI percentile with the

rest of the biomarker specter would increase the risk of unnecessary treatment and examinations.

Some argued that the 99th percentile is too low. After transfer from conventional cTn assays to hs-cTn assays, many patients were reclassified as having a myocardial infarction or myocardial injury. These patients have an increased risk of cardiovascular mortality (89, 90), but it is not fully known whether all reclassified patients benefit from aggressive treatment with dual antiplatelet inhibitors and coronary angiography, as the outcome after reclassification does not improve (91). The risk of CV events based on cTn concentrations is a continuum. Setting a cut-off value can be considered rigid and clinical judgement is vital when more patients receive the diagnosis of myocardial injury or infarction (92). The current consensus is that the 99th percentile is evidence-based in analytical and clinical terms. While not perfect, the 99th percentile cutoff value is the best alternative (93).

1.4.3 Differences between troponin isoforms

Several cTnI assays are available with different LoDs and URLs. Due to patent protection, there is only one cTnT assay (Roche Diagnostics). Diagnostic accuracy is considered equal between the cTnT and cTnI assays by both ESC, The American Heart Association (AHA), The American College of Cardiology Foundation (ACCF), and World Heart Federation (WHF) (31). However, cTnT and cTnI have several differences, both genetically, kinetically, biochemically, and analytically.

First, cTnT is released from cardiomyocytes and degrades slower than cTnI whose concentration in serum increases very rapidly immediately after a myocardial infarction and is gradually degraded in the following days. The kinetics of cTnT kinetics are characterized by a very rapid drop in biomarker concentrations during the first two days, followed by a plateau period for three days and an accelerated decreasing curve after the fifth day (57, 58, 94). Analytically, the LoD is lower for cTnI assays than the cTnT assay, and the number of patients with detectable cTnI is higher than for cTnT (95). The concentration of cTnI after an AMI is up to 10 times higher than that of cTnT and can be explained by differences in the release kinetics or properties of the assays (96).

Second, some patients without cardiac disease, but with skeletal muscle injury, may have elevated cTnT. Neither cTnT nor cTnI are present in healthy adult skeletal muscle, but cTnT is present in fetal skeletal muscle (97). During chronic skeletal muscle injury in adults, embryogenic myogenesis occurs and fetal isoforms of cTnT are reexpressed (98-100). cTnI, which is never expressed in skeletal muscle, may have higher precision for the identification of coronary artery disease in patients with Duchenne Muscular Dystrophy and other chronic muscle diseases (101). In addition to muscle injuries, cTnI can be falsely elevated due to cross-reaction with skeletal cTnI (102).

Third, interference with antigen-antibodies may provide a false cTn result (103, 104). Heterophilic antibodies interfere with some cTn assays and cause false positive results that can remain elevated in the circulation for years (105). Several studies have shown that the presence of macrotroponins (large immunoglobulin-troponin complexes) may interfere with the measured concentration of both cTnI and cTnT. (106-108)

Fourth, direct comparisons of cTnT and cTnI assays have shown weak correlation and may differ in association to certain risk factors (109). Chronically elevated cTnI might be more strongly associated with future myocardial infarction and coronary artery disease, while cTnT appear more strongly associated with all-cause mortality (95).

Fifth, the measured concentration of cTn is affected by kidney function. cTnT is elevated more frequently than cTnI in patients with renal disease (110). It is not fully understood whether the elevation of cTn is caused by decreased renal excretion or increased cardiac release. The kidneys may favor the secretion of the 24 kDa cTnI molecule compared to the larger 37 kDa cTnT molecule. Differences can also be associated with cTnT fragments that remain in the circulation in patients with renal disease that differ from complete molecules released and identified by the cTnT assay after an AMI (79).

1.5 Troponin algorithms

High-sensitivity troponin assays can detect concentrations more than ten times lower than contemporary assays and have a much higher precision. Since the first hs-cTn studies showed improved diagnostic precision in 2009 (111, 112) and were commercially available a year later, hs-cTn assays have been the preferred method for cTn quantification in Europe and Asia. In 2017, the first assay was approved for use in the USA. The term high sensitivity is rewarded with assays capable of detecting cTn concentrations in ≥50% of healthy men and ≥50% of healthy women with CV_A <10% at the 99th percentile (113, 114). The last generations of some hs-cTnI assays can detect circulating cTn in >95% of healthy adults. The cTnT assay, on the other hand, appear to have lower detection rate (115).

High sensitivity and low imprecision have made it possible to develop rapid protocols for early detection of AMI (91, 116-118). While hospitals using contemporary cTn assays are recommended to wait 3-6 hours between the first and second blood samples (45, 119), hs-cTn assays can 'rule out' or 'rule in' AMI one, two, or three hours after presentation. The rationale behind the new algorithms is that patients with a history of coronary symptoms of more than three hours and blood samples with low and stable cTn concentrations a few hours apart will also have a stable cTn concentration later, for example, after 6 or 12 hours. In patients with a longer history of symptoms, a low cTn concentration at presentation is enough to rule out AMI (120, 121).

Sensitivity, specificity, and positive and negative predictive values (PPV and NPV) are important statistical terms when assessing diagnostic algorithms. To safely rule out patients in the emergency department, a high negative predictive will ensure that patients who are 'ruled out' and possibly discharged do not have an AMI. Sensitivity describes the rate of patients with AMI correctly identified as non-rule-out by the algorithms. The optimal sensitivity and NPV is not established, but the National Institute for Health and Care Excellence (NICE) in the United Kingdom has by consensus recommended early rule-out pathways where the negative predictive value is ≥99.5 and the sensitivity is ≥97% (122).

For the 'rule-in' algorithms, a high PPV indicates that most patients who are classified as 'rule-in' do have an AMI. A high specificity indicates that few patients without AMI are categorized as ´rule-in´.

1.5.1 The ESC algorithms and High-STEACS

The ESC has endorsed a 0/3-hour algorithm that may effectively and safely rule out myocardial infarction in patients with one or two low cTn values depending on the duration of symptoms. Myocardial infarction is considered unlikely if the time from onset of symptoms is >6 hours, the ECG is nonischemic, and the cTn concentration at the time of presentation is below the assay-specific 99th percentile. If a patient has a GRACE (Global Registry of Acute Coronary Events) score below 140, he or she is eligible for stress testing and/or early discharge. In patients with shorter duration (<6 hours), a retest is recommended 3 hours after presentation with AMI ruled out if cTn is below the sex-neutral 99th percentile or without significant change defined as >50% of URL. The 0/3h algorithm is recommended in both the 2015 and 2020 ESC guidelines, although the 0/1h algorithm is recommended as the first line option when available in the 2020 guidelines (21, 123).

As an alternative, the High-STEACS algorithm was developed by a research group in Edinburgh, Scotland (121). The rule-out algorithms use the low risk of AMI found in patients with very low levels of cTn at presentation and can rule out AMI in patients with non-ischemic ECG with symptom debut >2 hours before presentation and serum levels of cTnI or cTnT <5 ng/L. In early presenters (symptoms debut <2 hours before presentation), a second blood sample is collected 3 hours later. Myocardial infarction is excluded if the change in cTn concentration is <3 ng/L and still below the gender neutral 99th percentile of 14 ng/L for cTnT (Roche Diagnostics) or sex specific 99th percentiles of 16 ng/L (women) and 34 ng/L (men) for cTnI (Abbott Architect).

1.5.2 The 0/1-hour troponin algorithm

Studies find that the reduction in the 'troponin-blind' period from 6 hours to 1, 2 or 3 hours is safe with NPV exceeding 99% in most studies; see **Table 1**. The ESC

recommendation from 2015 and 2020 to assess cTn concentration at presentation and after 2 or 3 hours was uncontroversial (123). The one-hour algorithm was initially the subject of more debate. The class 1 recommendation from the 2015 guidelines was based on three studies and a meta-analysis assessing patients with undetectable cTn levels at presentation (124-127) and five studies evaluating a 0/1h algorithm (112, 128-131). The five 0/1h studies were carried out in cohorts from the same study population. Publication bias is a concern in the field of rapid diagnostic protocols (117), but most so when results have not yet been reproduced in other cohorts.

Before the following ESC guidelines were published in 2020, more evidence was published of the safety of the 0/1h rule-out and rule-in algorithms (132, 133), including studies in patients with renal disease (134) and older age (135). A meta-analysis of 15 high-quality studies found that a concentration of cTnI at presentation <6 ng/L and an absolute change of <4 ng/L after 45 to 120 minutes had a NPV for AMI of 99.5% (136).

Some arguments against the 0/1h algorithm remain, and clinical implementation has been slow (137). Most centralized laboratories have a turnaround time of 60-90 minutes, and physicians may than not possess results from the first blood sample before the next sample is to be obtained (138). Suh et al. did not find that the reduced blood sample interval reduces the length of stay (LoS) in the ED (139). The one hour reduction in LoS as seen in the RAPID-TnT trial (140) is half the reduced interval between blood samples (from 3 to 1 hour). In TRAPID-AMI, the mean LoS in the ED was reduced by two hours, but with great variations, since some hospitals saw an increase in the mean LoS after the introduction of the 0/1h protocol (13). The improvement in LoS is greatest in calm periods in the ED, but less visible during busy hours as seen in the RAPID-CPU study (141).

Critics aside, the increasing amount of data shows that rapid algorithms ruling out patients at presentation or 1 hour are safe and improve patient flow in the ED compared to the 0/3h algorithm (142, 143). The 2020 ESC guidelines also highlight three recent real-life implementation studies that confirm the safety and high efficiency of the 0/1h algorithm, including the High-STEACS study (144), the RAPID-TnT trial, and the RAPID-CPU study. (140, 141).

***Table 1**. List of publications on cTn accelerated diagnostic protocols (<3 hours).*

First author, published	Study name	Study design	n	Endpoint	Isotype and cutoff	Algorithm	Sensitivity	NPV	Percent rule-out	Other results
0h algorithms										
Reichlin et al, 2009 (145)	APACE	Prosp.	487	AMI	cTnT	0h + copeptin	N/A	N/A	N/A	AUC 0.86 for AMI by cTnT at presentation alone, 0.97 combined with copeptin.
Reichlin et al, 2009 (112)	APACE	Prosp.	718	AMI	cTnT, hs-TnT and hs-cTnI	0h	N/A	N/A	N/A	AUC 0.95-0.96 for AMI for the high-sensitivity assays vs. 0.90 for the standard assay.
Raskovalova et al, 2014 (146)		Meta-analysis	8740 + 1429 (hs)	AMI	cTnT and cTnI + hs-cTnT <99th perc.	0h + copeptin	87 + 99 (hs)	N/A	N/A	AUC 0.80 for AMI by cTnT at presentation, 0.91 when combined with copeptin.
Bandstein et al, 2014 (126)		Prosp.	14636	Mortality or AMI	hs-cTnT <5 ng/L	0h	N/A	99.8	N/A	0.44% of patients with low hs-cTnT and non-ischemic ECG died or had an AMI within 30 days.
Möckel et al, 2015 (120)		RCT	902	MACE	hs-TnT <14 ng/L TnI <56/45 ng/L	0h + copeptin	N/A	N/A	N/A	Very low MACE-rate (0.6%) in patients with low cTn and copeptin concentrations.
Zhelev et al, 2015 (127)	Meta-analysis	Meta	20 studies	AMI	hs-cTnT <5 ng/L	0h	97.4	N/A	N/A	At the 99th percentile (14 ng/L), the summary sensitivity was 89.5% for AMI.
Body et al, 2015 (147)		Prosp.	463	AMI	hs-cTnT <5 ng/L	0h	98.7	99.0	20.7	100%/100% sensitivity/specificity if no ECG criteria fulfilled.
Shah et al, 2015 (121)	UTROPIA	Prosp.	3799 + 1061	AMI or cardiac death	hs-cTnI <5 ng/L	0h	93.8 + 94.3	99.6 + 99.5	60.8 + 55.9	*Sensitivity calculated based on numbers in Supplemental material*
Neumann et al, 2016 (132)	BACC	Prosp.	5049	1y-AMI/ mortality	hs-cTnI <6 ng/L	0h	92.2	97.1	N/A	
Anand et al, 2021 (148)	HISTORIC	Stepped-wedge cluster RCT	31492	AMI	hs-cTnI <5 ng/L	0h	N/A	N/A	N/A	Safety outcome in 2.7% before 0h algorithm implemented vs. 1.8% after.

1h algorithms

Reichlin et al, 2012 (128)	APACE	Prosp.	872	AMI	hs-cTnT <12 ng/L + delta <3 ng/L	0h + 1h	100.0	100.0	60.0	
Gimenez et al, 2015 (131)	APACE	Prosp.	906 + 905	AMI	hs-cTnI <5.2 ng/l + delta <1.9 ng/L	0h + 1h	97.6 + 98.8	99.2 + 99.6	56.0 + 50.5	Patients were excluded if final diagnosis remained unclear after adjudication (n=69)
Reichlin et al, 2015 (130)	APACE	Prosp.	1320	AMI	hs-cTnT <12 ng/L + delta <3 ng/L	0h + 1h	99.6	99.9	16.4	
Neumann et al, 2016 (132)	BACC	Prosp.	5049	AMI or mortality 1 year	hs-cTnI <6 ng/L + delta <12 ng/L	0h + 1h	97.6	99.0	39.0	
Pickering et al, 2016 (149)	Five different studies	Prosp.	2222	AMI	hs-cTnT0 <5 ng/L hs-cTnI0 <2 ng/L or hs-cTnT <12 ng/L + delta <3 ng/L hs-cTnI <5 ng/L + delta <2 ng/L	0h + 1h	97.1 (TnT) + 98.8 (TnI)	99.5 (TnT) + 99.8 (TnI)	64.1 (TnT) + 54.2 (TnI)	
Mueller et al, 2016 (150)	TRAPID-AMI	Prosp.	12a82	AMI	hs-cTnT <12 ng/L + delta <3 ng/L	0h + 1h	96.7	99.1	63.4	
Jaeger et al, 2016 (151)	APACE	Prosp.	750 + 750	AMI	hs-cTnI <5 ng/L + delta <2 ng/L	0h + 1h	97.1+ 100.0	98.9+ 100.0	47.9+ 57.1	
Twerenbold et al, 2018 (152)	JACC	Prosp.	4368 + 3500	AMI	hs-cTnT0 <5 ng/L hs-cTnI0 <2 ng/L or hs-cTnT <12 ng/L + delta <3 ng/L hs-cTnI <5 ng/L + delta <2 ng/L	0h + 1h	99.3 (TnT) + 99.1 (TnI)	99.8 (TnT) + 99.7 (TnI)	57.1(TnT) + 43.8(TnI)	*Sensitivity calculated based on numbers in material.*
Boeddinghaus et al, 2018 (133)	APACE	Prosp.	1755	AMI	hs-cTnT <3 ng/L or <6 ng/L + delta <3 ng/L	0h + 1h	99.1	99.7	46	

Badertscher et al, 2018 (143)	APACE	Prosp.	2547	AMI	hs-cTnT0 <5 ng/L hs-cTnI0 <2 ng/L or hs-cTnT <12 ng/L + delta <3 ng/L hs-cTnI <5 ng/L + delta <2 ng/L	0h + 1h	N/A	99.8 (TnT) + 99.6 (TnI)	60 (TnT) + 51 (TnI)	The 0/1h algorithm had equal/better safety and higher/equal efficacy than the 0/3h algorithms, NPV 99.7/97.8 (TnT/TnI) and perc. rule-out 44/52% (TnT/TnI).
Chapman et al, 2019 (144)	High-STEACS	Prosp.	1920	AMI + CV death 30 days	hs-cTnI <5 ng/L or hs-cTnI<99th perc + delta <3 ng/L	High-STEACS 0h + 1h	98.0	99.5	63.4	High-STEACS performed similar to the ESC 0/1 algorithm (sens. 99.2, NPV 99.0 and perc. rule-out 64.5%) and better than the 0/3h algorithm (sens. 90.8, NPV 98.0 and perc. rule-out 65.0%)
2h algorithm										
Than et al, 2012 (153)	ADAPT	Prosp.	1975	MACE 30 days	cTnI 0h and 2h <30 ng/L (Abbott) or <40 ng/L (Beckman Coulter)	0h + 2h +ECG +TIMI	99.7	99.7	19.8	
Cullen et al, 2013 (154)	ADAPT	Prosp.	1635 + 909	MACE 30 days	hs-cTnI 0h and 2h <26.3 ng/L	0h + 2h + ECG + TIMI 0/1	100.0/99,2 (TIMI 0/1) + 100.0/99.4 (TIMI 0/1)	100.0/99.7 (TIMI 0/1) + 100.0/99.7 (TIMI 0/1)	19.6/41.5 (TIMI 0/1) + 25.3/38.6 (TIMI 0/1)	Including non-ischemic ECG and TIMI 0 or 1.
Reichlin et al, 2014 (155)	APACE	Prosp.	1148 + 517	AMI	hs-cTnT <14 ng/L +delta <4 ng/L	0h + 2h	99.5 + 96.0	99.9 + 99.5	59.5 + 77.8	
Meller et al, 2015 (156)	APACE	Prosp.	1085 + 1590	MACE 30 days	hs-cTnT 0h and 2h <14 ng/L	0h + 2h + ECG + TIMI	100.0 + 99.1	100.0 + 97.4	34.5 + 40.3	Including TIMI <2 and normal ECG
Boeddinghaus et al, 2016 (157)	APACE	Prosp.	1435 + 1194		hs-cTnI 0h and 2h <6 ng/L + delta <2 ng/L	0h + 2h	99.2 + 98.7	99.8 + 99.7	56.0 + 59.9	

N is defined as number of study participants; prosp., prospective study; NPV, negative predictive value; prosp., prospective study; RCT, randomized controlled study; AMI, acute myocardial infarction; cTnT, cardiac Troponin T; cTnI, cardiac Troponin I; hs-cTnT, high-sensitivity cardiac Troponin T; hs-cTnI, high-sensitivity cardiac Troponin I; N/A, not available; MACE, major adverse cardiac event; 0h, 0 hour; 1h, 1 hour; 2h, 2 hour.

1.5.3 High-risk ACS criteria

ESC or High-STEACS algorithms can safely rule out AMI, but many patients with low and stable cTn values have unstable angina pectoris (UAP) with prognostic benefit of intensified medical treatment and/or early coronary revascularization. The 2015 ESC guidelines classified patients with ACS as low, intermediate, high, or very high risk according to the risk of short-term adverse events (123). Patients with very high risk (e.g., due to hemodynamic instability or arrythmias) should be revascularized immediately (<2 hours), patients with high risk (e.g., dynamic cTn, ischemic ECG, or Grace score >140) within 24 hours, and intermediate risk (e.g., diabetes, kidney failure, established coronary disease, or Grace score >109) with suspected ACS should have an invasive coronary evaluation within 72 hours. Patients without any risk factors were considered low risk and should be evaluated with non-invasive strategies either in-hospital or as outpatients.

The treatment recommendations in the 2020 guidelines were largely unchanged, although early presenters that warranted extra caution had a symptom debut <3 hours before presentation instead of <6 hours in the previous guidelines (21). Intermediate and low risk groups were combined into a larger group where an invasive strategy should be selectively considered based on previous diseases and symptom specificity, see **Figure 6**.

1.5.4 Choosing patients for further cardiac examinations

Only a minority of patients presenting to an ED with chest pain, have ACS, e.g., 5.1% in the USA (119). The rate is higher in countries where patients have been evaluated by primary care physicians or ambulance personnel before referred to the ED, (112, 142, 158), but 70% or more of patients will have noncardiac causes of chest pain that do not require urgent care. Admitting patients with a low probability of ACS to the hospital will lead to unnecessary and potentially harmful diagnostic procedures, decrease patient flow in busy EDs, and potential relocation of resources from patients with more life-threatening diseases.

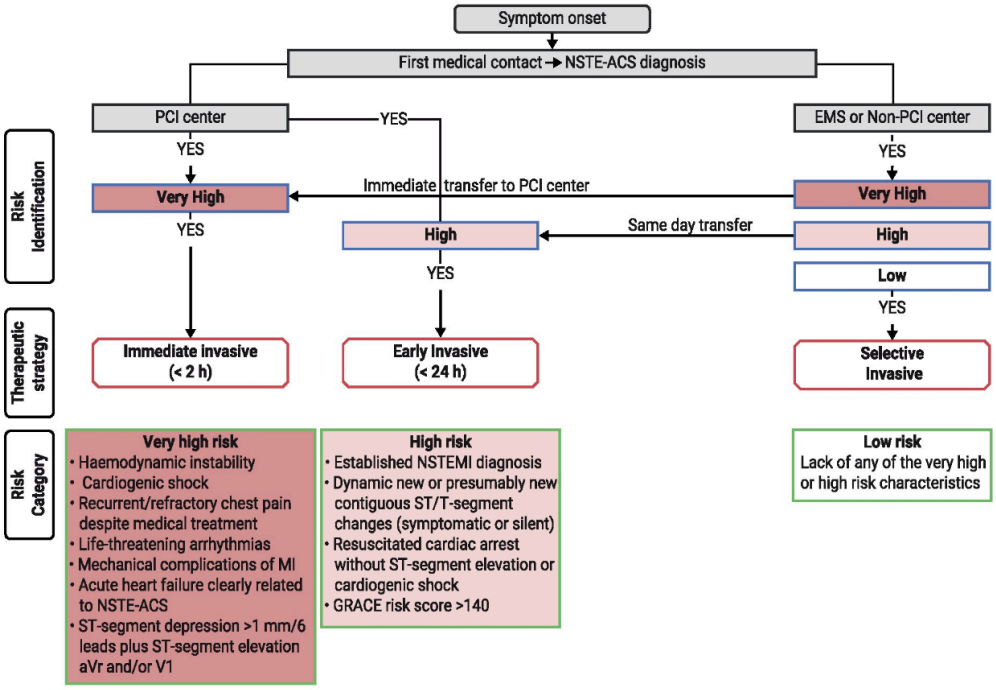

Figure 6. *Selection of treatment strategy and timing according to initial risk stratification in the 2020 ESC guidelines for ACS management without persistent elevations of the ST segment. J.-P. Collet et al., 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent elevation of the ST segment, European Heart Journal. 2020 Aug 29;00:1–35, permission to reprint by Oxford University Press* (21).

ESC risk definitions were developed to identify patients with suspected ACS and an increased risk of short-term cardiovascular mortality or morbidity. When AMI and other serious conditions are excluded, no high-risk criteria are present and the short-term prognosis is good, the physician faces a new dilemma: Continue with cardiac examinations to exclude UAP with maximal certainty or discharge from the ED to no or out-of-hospital follow-up. To correctly identify patients with UAP and discharge low-risk patients, two strategies can be applied: gestalt or clinical risk scores.

1.5.4.1 Clinical gestalt

Interpreting symptoms based on clinical knowledge and experience has been a part of the diagnostic process since the dawn of medicine. Adding subjective assessment to a cTn algorithm improves the diagnostic precision of ACS (159, 160). However, a physician's objective impression of risk, often called the clinical gestalt, should be used with caution. Some studies have found that gestalt alone is too inaccurate to safely identify the presence or absence of ACS (161, 162). The precision of gestalt in studies is likely as diverse as the clinical experience among physicians on a cardiac ward. The current consensus is that gestalt should be one of several pillars for which a diagnosis is made, which is particularly important for less experienced physicians.

1.5.4.2 Clinical risk scores

Clinical risk scores have been developed to assess the risk of coronary disease more objectively. Risk scores combine clinical and biological data to quantify the risk of ACS in patients with chest pain or adverse events in patients with confirmed ACS. Some risk scores also include evaluation of symptoms or gestalt. Most are developed based on multiple logistic regression in large cohorts, while others are developed based on the authors' opinion on risk factors and later validation in patient cohorts. Some risk scores are meant to be calculated bedside, while others are complex and require computer calculations. Supporters of clinical risk scores argue that they can force physicians to structure the evaluation based on all available data (163).

TIMI was one of the first risk scores to be developed (year 2000) and has been validated in several studies (164). Calculates the risk of death or ischemic events in patients with confirmed AMI or UAP based on factors such as age, changes in the ECG, risk factors and cTn concentration. Total score of 0-1 points is considered low risk, and 2 points or more are considered non-low risk, see **Figure 7.** A large meta-analysis showed a strong linear relationship between TIMI score and cardiac events, but 9.4% of patients considered low risk (TIMI 0-1) had a cardiac event within 30 days (165). Hence, low risk based on the TIMI score should not be used as the sole criterion for early discharge in patients with suspected ACS.

The GRACE score was developed in 2003 and 2004 based on multiple logistic regression and requires a computer for calculation (166, 167). It estimates the risk of mortality during hospitalization or within 6 months after discharge based on factors such as age, sex, changes in ECG, cTn concentration, systolic blood pressure, pulse, and kidney function. It is the only risk score recommended in the ESC guidelines for risk stratification (21).

HEART score is probably the most widely used risk score to determine the probability of ACS in patients with chest pain or other symptoms that suggest ACS (168). It can be calculated bedside and awards 0, 1 or 2 points for each of the five factors in the HEART acronym: History, ECG, Age, Risk factors, and cTn concentrations. Clinical gestalt is included in the score as physicians add 0, 1 or 2 risk points for symptom typicality (History). Randomized studies have shown high safety when the decision of early discharge is based on HEART score ≤3 (169, 170) and increased rate of early discharge, reduced length of stay and need for extra cardiac examinations (171). In a meta-analysis, however, 3.3% of patients considered low risk (HEART score 0-3) had a MACE within 30 days (172). Hence, the question is whether HEART score alone safely can identify patients eligible for early discharge from the ED.

Some newer risk scores, such as EDACS (173) and T-MACS (174), are developed to assess the risk of adverse events in patients with suspected ACS. They award risk points for typical symptoms such as diaphoresis, pain radiation and vomiting, and retract points if atypical symptoms such as pain associated with palpation or radiation are present.

Table 1 Components of 10 different risk scores and mHEART

	History	Age	ECG	Risk factors	Troponin levels	Known CAD	Angina	SBP	Other	Low risk
HEART (2008)	Typical = 2p Atypical = 1p	>65 = 2p >45 = 1p	ST-dep = 2p Other = 1p	≥3 or CAD = 2p ≥1 = 1p	≥3 × 99th = 2p ≥99th = 1p					≤3p
mHEART (2017)	Typical = 2p Atypical = 1p	>65 = 2p >45 = 1p	ST-dep = 2p Other = 1p	≥3 or CAD = 2p ≥1 = 1p	≥99th = 2p Measurable = 1p					≤3p
CARE (2018)	Typical = 2p Atypical = 1p	>65 = 2p >45 = 1p	ST-dep = 2p Other = 1p	≥3 or CAD = 2p ≥1 = 1p						≤1p
TIMI (2000)		>65 = 1p	ST-changes >0.5 mm = 1p	≥3 = 1p	>99th = 1p	1p	Severe = 1p		Aspirin used within 7 days = 1p	≤1p
GRACE (2003/2004)		0–100p	ST-changes >0.5 mm = 17p		>99th = 14p			0–40p	Pulse = 0–34p Creatinine = 0–28p Cardiac arrest = 30p Killip class = 0–44p	≤108p ≤89p
EDACS (2014)	Diaphoresis = 3p Radiation[a] = 5p Resp. pain = -4p Reproduced by palpation = -6p	2–20p		≥3 or CAD[b] = 4p					Male gender = 6p	≤15p
sEDACS (2016)	Radiation[a] = 1p	0–6p		≥3 or CAD = 1p					Male gender = 1p	≤3p
T-MACS[c] (2017)	Diaphoresis = d Radiation[e] = r Vomiting = v		Ischaemia = i		By degree of elevation = t		Crescendo = c	<100 = h		≤0.02
sT-MACS (2018)	Diaphoresis = 1p Radiation[e] = 1p Vomiting = 1p		Ischaemia = 1p		TnT >9 ng/L = 1p		Crescendo = 1p	<100 = 1p		≤0p
Geleijnse–Sanchis (2005)	>10 symptom points = 1p	≥67 = 1p		DM[d] = 2p		1p	Severe = 1p			≤1p
Goldman (1996)			Ischaemia = high risk				Crescendo = 1p	<110 = 1p	Bilateral pulmonary rales = 1p	≤1p

CAD, coronary artery disease; CARE, characteristics, age, risk factors, EGG; EDACS, Emergency Department Assessment of Chest Pain Score and MI, myocardial infarction; GRACE, Global Registry of Acute Coronary Events; HEART, History, ECG, Age, Risk factors, Troponin; mHEART, modified HEART score with troponin points given if hs-Tn is measurable; SBP, systolic blood pressure; TIMI, Thrombolysis In Myocardial Infarction; T-MACS, troponin-only Manchester Acute Coronary Syndromes.
[a]To *any* shoulder/arm/jaw.
[b]Age 18–50 years.
[c]Percentage risk of ACS calculated using the following formula: p = 1/(1 + e^ - (1.713i + 0.847c + 0.607r + 1.417v + 2.058d + 1.208h + 0.089t - 4.766)), where hs-TnT is continuous and the other factors dichotomous.
[d]Demanding insulin.
[e]To *right* arm/shoulder.

Figure 7. *Components of 11 different clinical risk scores. Illustration by Steiro et al., Clinical risk scores identify more patients at risk for cardiovascular events within 30 days as compared to standard ACS risk criteria: the WESTCOR study. European Heart Journal: Acute Cardiovascular Care. 2020 Oct 2;10(3):287–301, published under Open Access and reprinted under the terms of the Creative Commons CC BY license.* (158).

1.5.4.3 Accelerated diagnostic protocols

For most physicians, identifying very high-risk patients with ACS is easier than selecting patients for early discharge. Knowing that many patients will not benefit from extended cardiac examinations, identifying true low-risk patients has been a topic for decades (175). Fear of malpractice and loss of respect from colleagues may still lead to unnecessary examinations and admissions to hospitals (176, 177).

Accelerated diagnostic protocols (ADPs) are designed to improve diagnostic speed and precision by combining biomarkers with diagnostic tools, such as a clinical risk score. Examples such as ADAPT and HEART Pathway combine serial cTn measurements, ECG findings, and TIMI or HEART score to predict the risk of coronary artery disease (178, 179). The protocols use evidence-based methods to decrease the rate of false positive results and unnecessary examinations, including exposure to radiation.

1.6 Symptoms of ACS

The character and intensity of symptoms differ between the three subgroups of ACS. As the relative prevalence of STEMI and NSTEMI have changed and more patients have been reclassified from NSTEMI to UAP due to increasingly sensitive cTn assays during the past 20 years, the distinct symptom characteristics of AMI and UAP may have changed accordingly (89, 180, 181). Symptoms of UAP are described by the very definition of the disease: chest pain during activity that subsides during rest, with increasing symptom burden to the point where limited or even no activity triggers symptoms (182). The two forms of AMI have slightly different symptom character and intensity. Patients with NSTEMI more often present without chest pain (183, 184), and pain intensity might be lower compared to patients with STEMI (185).

Symptoms of ACS were first described by William Heberden in 1768 (186). Heberden described 'a disorder of the breast marked with strong and peculiar symptoms' that he called angina pectoris. The sensation was more pronounced walking uphill or shortly after a meal and could disappear as soon as the patient rested. Heberden described radiating pain to the left or sometimes to the right arm and additional symptoms, such as nausea.

In the twentieth century, several additional symptoms of ACS were described. The Canadian physicist William Osler in 1910 described 'vasomotor phenomena, pain radiation, cardiac, respiratory, and gastric symptoms' that could accompany chest pain (187). The American physician James B. Herrick connected angina pectoris with AMI

when he described myocardial infarction as chest pain that resembles angina pectoris, but with the addition of nausea and vomiting suggesting an occluded artery (188).

Acute myocardial infarction may occur without the patient having chest pain. The very first patient diagnosed with coronary artery embolism that was later confirmed by autopsy was a 34-year-old male patient of the German physician Adam Hammer in 1878 (39). The patient had rheumatic aortic valve disease and an embolism that occluded the right coronary artery. He experienced complete heart block and cyanosis, but no chest pain or shortness of breath when assessed by Hammer. Since then, physicians have continued to investigate the typical and more atypical symptoms that can be caused by ACS. Harvard cardiologist Samuel A. Levine studied body language and in 1929 described Levine´s sign: When asked to describe the symptoms of AMI, patients tend to hold a clenched fist over the sternum (189).

During the past 40 years, studies established what is today considered typical signs of AMI: a pressure-like sensation with radiation to the left arm, left shoulder, jaw, or neck often accompanied by vomiting and diaphoresis (190-194). Pain radiation has received more attention as the likelihood ratio of AMI increases if pain radiates to the right arm (195) or both arms (196). STEMI is more often associated with nausea, vomiting, dizziness, diaphoresis, and jaw pain (185, 197, 198) and appears to have a more abrupt appearance of symptoms with maximum intensity after only a few minutes (185).

1.6.1 Sex differences in prevalence and symptoms

Coronary artery disease was long considered a 'man´s disease', and women have been underrepresented in clinical trials on most cardiovascular diseases (199).
During the 1980s and 1990s studies found that myocardial infarctions were more likely to be unrecognized in women than in men (200, 201). After an AMI, younger women may have higher mortality rates than younger men (202, 203), although this difference appears to be smaller in a follow-up study (204). Sex differences in outcomes after AMI have been extensively studied, particularly from the late 1990s. Women with myocardial infarction are older than men, and some studies have not been able to find differences in mortality after adjustment for age and comorbidities

(205-207). A study from Norway found a lower case fatality rate in women ≥60 years compared with men ≥60 years and no significant differences in women and men <60 years (208). Women, however, have more complications after revascularization, possibly due to smaller coronary arteries, older age, and more comorbidities (209-211). Differences in mortality after coronary interventions remain disputed, as studies show various results (212-214).

Symptoms can be difficult to interoperate, creating possible pitfalls if diagnostic decisions are made on the typicality of symptoms alone (215). At the same time, fear of discharge of patients with low probability of ACS based on symptoms can cause an unwanted increase in upstream diagnostic tests. Previous studies found that women with AMI more often than men have other main complaints than chest pain (216-219). Due to heterogeneity in the study samples, metanalyses have not been able to clearly state if large differences occur. No symptoms appear to be mutually exclusive based on sex (220). More recent prospective studies in patients with suspected rather than confirmed coronary disease find fewer differences in the presenting symptoms (221-225).

1.7 Troponin as a prognostic marker

Elevated cTn concentration is an independent predictor of future cardiovascular mortality and adverse events, even in the absence of overt myocardial injury as assessed by cTnT (226-229) or cTnI assays (230-235). Being an independent predictor, identifying a decision limit for cTn concentrations for where to consider increased cardioprotective measurements, could be of clinical importance. Such a limit is difficult to identify due to differences between assays entailing assay-specific cutoff values but even more due to heterogeneity between clinical studies determining the cutoff values.

The risk of adverse events is elevated at concentrations close to the LoD (236). Using such low concentrations as an intervention threshold would be problematic since biological and analytical variations are 50-60% at low cTn concentration (31). The risk of mortality and cardiovascular events are proportional to cTn concentrations,

and exploring a decision limit at or close to the assay-specific 99th percentile could be an alternative.

Chronic myocardial injury, defined as chronically elevated cTn concentrations above the 99th percentile URL, has received more attention after being highlighted in the fourth UDMI (31). Several studies have found that patients with CMI have a mortality risk similar to type 1 and type 2 myocardial infarction (37, 38, 237-239). A major challenge in using the 99th percentile for prognostic evaluation is the discrepancy in rate of CMI depending on cTn assay and the possible non-harmonized 99th percentile URLs found by the different assay manufactures. The optimal cut-off value for the condition is debated, in part due to questions whether the URLs of different assays are sufficiently harmonized (86).

1.7.1 cTn concentration and preventive treatment

Treatment and secondary preventive measurements are well established for patients with AMI, but there is no consensus on specific treatments or follow-up for patients with chronically elevated troponin concentrations. Even though the increased risk of future cardiovascular events has been highlighted in the fourth UDMI (31), the intensity or outcome of treatment has not changed since the updated definition was published (235). Chronically elevated cTn concentrations are caused by a range of different conditions, and attempts to lower the cTn values by preventive measurements may not automatically reduce the risk of adverse events. Even so, measurements that reduce cTn concentrations deserve attention.

Cholesterol-lowering treatment reduces the risk of mortality or CV events in patients with established cardiovascular disease (240-244), even in older patients (245, 246), and in subjects with very high risk of future coronary artery disease (247). Two studies have found that statin treatment reduces cTn concentration (234, 248) including an association between reduced cTn concentration and the risk of AMI and death from coronary artery disease (234). Although observational, a study by Kadesjö et al. found an association between CMI, prognosis, and the number of prescribed medications with cardioprotective effects (249). cTn concentrations are also associated with

physical activity as found in a study of elderly from the general population (250). An RCT by the same authors showed that moderate exercise intervention in older sedentary adult slowed down the age-expected increase in cTnT concentrations (251).

The use of antiplatelet inhibitors, antihypertensive agents, and cholesterol lowering agents as primary and secondary prophylactic treatment has increased over time, but women and older patients are less frequent users (252). Implementing high-sensitivity cTn assays with sex-specific 99th percentiles has increased the rate of women diagnosed with myocardial injury, but without an increase in prescribed prophylactic treatments (253). Future studies are warranted to assess the relationship between elevated sex-specific cTn concentration, preventive measurements, and potential protective effect on future risk of adverse cardiac events for women and men.

1.8 Gaps in knowledge

Most studies on symptoms of acute myocardial infarction were performed in a time when far more patients had ischemic ECGs. These cohorts and the identified typical symptoms of AMI may not represent today´s patient populations where non-ischemic ECGs and NSTEMI is far more common than STEMI.

High-sensitivity cTn assays have improved the diagnostic efficiency in the ED, but low and stable cTn concentrations do not rule out CAD, with possible prognostic implications if left untreated. The potential increase in safety of adding a clinical risk score for the evaluation of ACS is not well investigated in the literature.

Elevated cTn increase the risk of cardiovascular death or adverse events. Chronic myocardial injury has received more attention in the last version of UDMI (31), but the clinical utility of the condition for risk assessment is not well examined. The diagnostic and prognostic challenges caused by low to moderate correlation between cTnT and cTnI needs to be addressed before CMI can be further evaluated as a condition with prognostic utility.

2. Aims of the thesis

2.1 General aims

The general objective of the WESTCOR study was to explore new ways for early, easy and safe identification of patients with suspected ACS through rapid high-sensitivity troponin algorithms and clinical risk scores. Secondly, the thesis aimed to evaluate the long-term prognostic value of elevated cTn concentrations measured by three different cTn assays.

2.2 Specific aims

Paper 1

Assess the prevalence of specific symptoms in patients with non-ST segment elevation myocardial infarction (NSTEMI), whose relative prevalence compared to STEMI is increasing. Furthermore, evaluate the diagnostic precision of specific symptoms based on sex and age.

Paper 2

Replace the ACS risk criteria recommended in the ESC guidelines with standardized clinical risk scores in a double rule out accelerated diagnostic protocol. The study aimed to evaluate two troponin-based rule-out algorithms (the ESC 0/3h and the high-STEACS algorithms) combined with 11 different clinical risk scores to identify patients with high risk of mortality, AMI or revascularization within 30 days.

Paper 3

Assess whether chronic myocardial injury (CMI) identified by three different cTn assays (cTnT and cTnI) could serve as a uniform and relevant marker of elevated cardiovascular risk by evaluating cTnT and cTnI correlation, prevalence of CMI and long-term outcome if CMI (cTn above the 99th percentile) or lower cTn concentrations were used as prognostic cutoff value.

3. Materials and methods

3.1 Study design

The WESTCOR study (Aiming Towards Evidence Based Interpretation of Cardiac Biomarkers in Patients Presenting With Chest Pain) study is a dual-center cross-sectional prospective observational study conducted at the two university hospitals within the Western Norway Regional Health Authority, Haukeland University Hospital and Stavanger University Hospital. The main purpose of the study was to evaluate rapid ´rule-in´and ´rule-out´ protocols such as the ESC 0/3h and 0/1h algorithms. The clinical information collected at the presentation allowed us to calculate the risk of cardiovascular mortality and morbidity based on clinical risk scores.

The enrollment period lasted from September 2015 to March 2020. The patients were divided into a derivation cohort (WESTCOR-D) and two validation cohorts; see **Figure 8**. As part of the study protocol, patients in the internal validation cohort (WESTCOR-CT) underwent cardiac computed tomography angiography (CCTA) unless contraindicated. In the remaining cohorts, CCTA, coronary angiography, or exercise electrocardiograms were performed at the discretion of the treating physician.

Paper 2 uses blood samples and clinical data from the local derivation cohort at Haukeland University Hospital (WESTCOR-D), while paper 1 and 3 are based on patients from WESTCOR-D and patients in the internal validation cohort at Haukeland University Hospital (WESTCOR-CT).

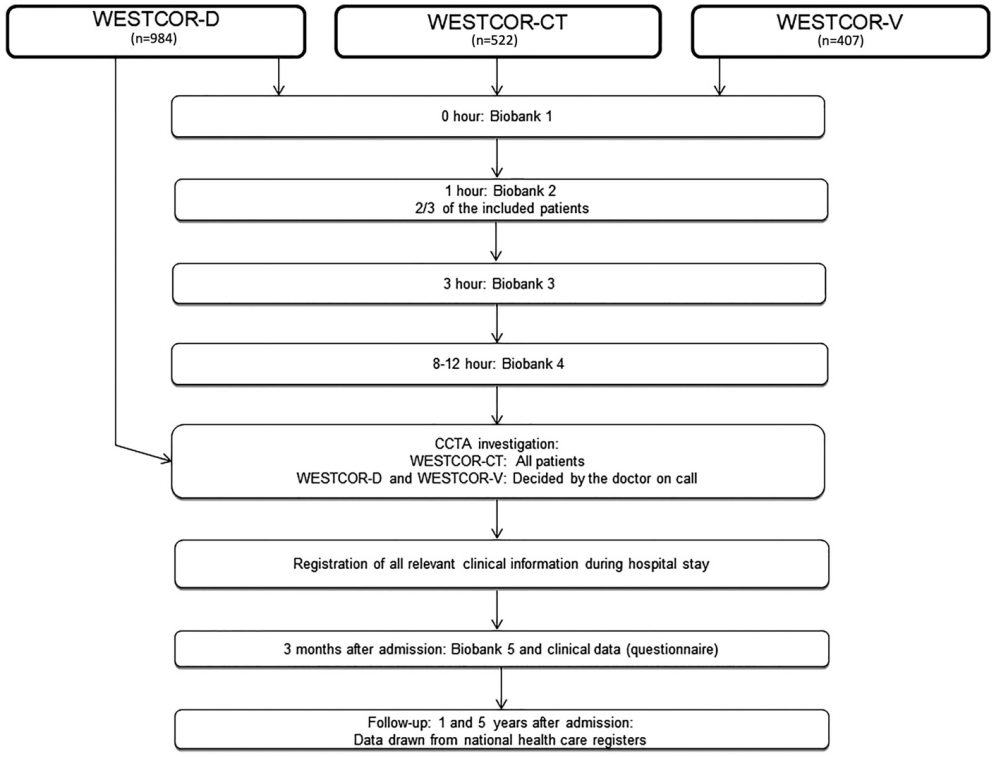

Figure 8. *Study flow chart of the WESTCOR study. Slightly revised figure from Tjora et al., Aiming toWards Evidence baSed inTerpretation of Cardiac biOmarkers in patients pResenting with chest pain-the WESTCOR study: study design. Scandinavian Cardiovascular Journal. Taylor & Francis; 2019 Aug 8;53(5):280–5, published under Open Access and reprinted under the terms of the Creative Commons CC BY license (254).*

3.2 Patient population and biobanking

All patients ≥18 years of age admitted to the emergency department with symptoms suggestive of ACS were eligible for inclusion. Patients unable to consent, patients with ST elevation or short life expectancy were excluded; see **Table 2**.

INCLUSION CRITERIA
Patients admitted with chest pain suspicious of NSTE-ACS
Age >18 years
EXCLUSION CRITERIA
Patients with STEMI
Patients transferred from other wards or hospitals for second opinion
Comatose or other reasons for not being able to consent
Terminal patients, short life expectancy

Table 2. *Inclusion and exclusion criteria. Table by Tjora et al., Aiming toWards Evidence baSed inTerpretation of Cardiac biOmarkers in patients pResenting with chest pain-the WESTCOR study: study design. Scandinavian Cardiovascular Journal. Taylor & Francis; 2019 Aug 8;53(5):280–5, published under Open Access and reprinted under the terms of the Creative Commons CC BY license* (254).

The decision to enroll a patient was made by nurses or emergency department physicians on call. Oral consent was collected immediately, and written consent was obtained within the next day. Serum samples were collected at the time of presentation, after 3 hours and 8-12 hours as part of standard clinical care, and the results were available to the treating physician. Extra sample materials were collected simultaneously and stored in a biobank. After a period of implementation, all enrolled patients (2/3 of the total cohort) received an additional blood sample 1 hour after presentation. Biobanked serum samples from patients who withdrew consent were removed from the biobank.

3.3 Biochemical analyses

All blood samples were left for 30 minutes to allow clotting and centrifuged for ten minutes. The material for biobanking was frozen at -80°C while fresh serum samples for standard care were continuously analyzed by a Roche Diagnostics hs-TnT assay using nine different reagents and caliber lots. The biobanked material was transported under frozen conditions to two other laboratories for cTnI analysis (Abbott Diagnostics and Siemens Healthineers).

Standard care material and frozen 1-hour samples were analyzed by Roche Diagnostics' high sensitivity assay with a limit of blank (LoB) of 3 ng/L, a limit of detection (LoD) of 5 ng/L and coefficient of variation (CV_A) of 10% or lower for concentrations >4.5 ng/L. The 99th percentile URL is 14 ng/L in both sexes combined, 9 ng/L in women, and 16 ng/L in men.

The Abbott high-sensitivity assay had a LoD of 1.9 ng/L and 10% CV_A at a concentration of 5.2 ng/L. The 99^{th} percentile URL is 15.6 ng/L in women and 34.2 ng/L in men. The Siemens hs-cTnI assay had a LoD of 1.6 ng/L and 10% CV_A at 6 ng/L. The 99^{th} percentile URL is 38.6 ng/L in women and 53.5 ng/L in men.

Cobas e602 or Cobas 8000 from Roche Diagnostics were used for all other biochemical analyzes. The glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration formula on cobas 8000 from Roche Diagnostics (255).

3.4 Baseline characteristics and symptoms

Medical history and clinical information such as blood pressure, pulse, and body mass index were collected from medical records by a chart reviewer who knew of the study hypothesis but was blinded to the final diagnosis. Symptoms at presentation used in paper 1 were collected from electronic medical records provided by ambulance personnel, referring physicians, and hospital physicians at presentation. The department's routines are to report both positive and negative symptoms, but available information was dependent on the level of detailed information provided by health

personnel. In the <5 cases where pre-hospital and in-hospital personnel provided conflicting information, hospital physician data was used. A description of the character, location, and duration of the pain was available for >80% of the patients. When this information was missing, patients were excluded from specific analyzes, but not from the study. Additional symptoms like shortness of breath and nausea not recorded at presentation were considered negative, in accordance with similar studies (256).

3.5 Adjudication

Two independent cardiologists adjudicated diagnoses based on symptoms descriptions, biochemical results, ECGs, and image results of echocardiography, CCTA, and invasive coronary angiography. A third adjudicator was consulted in cases of disagreement. Acute myocardial injury and infarction were defined according to the third UDMI as elevated and dynamic cTn concentration in a clinical setting consistent with myocardial ischemia in the form of symptoms of ischemia, changes in ECG, imaging evidence of loss of viable myocardium or confirmed intracoronary thrombus (45). Biochemical criteria were a concentration of one or more cTn above the common 99th percentile URL and a 20% increase and/or decrease in the baseline value (if first cTn value >99th percentile) or 50% (if first cTn value <99th percentile). UAP was defined as symptoms suggestive of ACS with stable concentration of cTn (21). Diagnostic criteria for 20 other medical conditions were predefined, including arrythmias, myocarditis, pneumonia, gastroesophageal reflux syndrome, and myalgia.

3.6 Follow-up and endpoints

The study and biobank were approved by the Regional Committees for Medical and Health Research Ethics (2014/1365 REK West and 2014/1905 REK West). The study has permissions to follow included patients through three different national health care registries, Norwegian Patient Registry (NPR), Norwegian Cause of Death Registry (NCDR), and Norwegian Prescription Database (NorPD).

Paper 1 was a retrospective analysis of symptoms at presentation with an adjudicated diagnosis of NSTEMI as the primary endpoint. Paper 2 included short-term diagnostic and prognostic endpoints with a primary composite endpoint of acute fatal or nonfatal myocardial infarction, all-cause mortality, and unplanned revascularizations (including intention to treat) collected from NPR and NCDR. The secondary endpoint was an adjudicated diagnosis of NSTEMI during index hospitalization. Paper 3 evaluated the prognostic value of cTn assays in patients without acute myocardial injury with a primary composite endpoint of cardiovascular death, acute myocardial infarction (AMI), or revascularization within follow-up (median 4.1 years). The secondary endpoints were all cause mortality, AMI, revascularization, hospitalization due to heart failure or stroke. The tertiary endpoint was all-cause mortality, and all information was collected through NPR and NCDR.

CVD included all causes of death coded I00 to I99 or R96 according to the ICD-10 code system. Information was collected through the NCDR, where the cause of death is determined by autopsy or clinical postmortem assessment. The cause of death was determined by the principal condition that caused the death and not the immediate mode of death.

3.7 Statistical methods

3.7.1 Power calculations

The necessary sample size for the WESTCOR study was calculated based on the main goal of the study to compare different ´rule-out´/´rule-in´-algorithms. The study designers aimed for results with statistical significance <0.05 and a power of >80%. Power calculations showed that a clinically significant difference of 5% for sensitivity or specificity using McNemar's test would require 355 patients. 80% of the power to detect a difference in AUC of 0.03 by Delong test would require a total of 828 patients (92 with the condition and 735 without).

3.7.2 Statistical analysis

Statistics were performed using IBM SPSS Statistics version 26.0.0.1, Medcalc version 17.6 and R version 4.0.3, programs that each have distinct features and disadvantages. SPSS was used for most standard calculations and is an easy-to-learn program with a user-friendly interface. The disadvantage of SPSS is the lack of some features available in other programs. Medcalc was therefore used as a supplement, e.g., for the comparison of AUC by different ROC curves using Delong's test. R is open-source software with a large selection of freely available statistical packages and was used to create figures like radar plots (Paper 2) and Venn diagrams (Paper 3).

In the three articles, baseline characteristics were analyzed using nonparametric tests (Mann-Whitney U test) for continuous variables and the Chi-square or Fisher's exact test (if n<5 per group) for categorical variables. Baseline characteristics were reported as means (±2 SD) for normally distributed data and median with 25 and 75 percentiles for nonnormally distributed data. All hypothesis testing was two-tailed with *P*-values <0.05 considered statistically significant.

Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated in all articles but presented with different emphasis based on the research question; see **Table 3**.

In Paper 1, the association between symptoms and sex or age was assessed using a multivariate regression model that contains the symptom, sex/age, and the combined variable of symptom+sex/age. The p-value for the interactions was calculated using the Wald-Chi square. The age of 70 years was chosen as the cutoff value since the median age of the *first* myocardial infarction is close to 70 years in the United States (257) and 72 years for all myocardial infarctions in Norway (258). In Paper 2, combinations of troponin-based algorithms (categorical variable) and risk scores (continuous variable) were assessed by creating a combined variable using binominal logistic regression later compared by the Delong test. In Paper 3, the cTn values were transformed to logarithmic values due to the nonnormal distribution. The correlation between different assays was assessed by Pearson's correlation test. The calculation of the equivalent cTn values was performed through linear regression.

Table 3. Overview of statistical methods used to answer the scientific questions.

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Odds ratio	Other statistical analysis
Paper 1	Rate of patients with a given symptom that *do* have NSTEMI divided by all patients with NSTEMI (true positive rate).	Rate of patients *without* a given symptom that *do not* have NSTEMI divided by all patients without NSTEMI (true negative rate).	**Proportion of patients with a given symptom that *do* have NSTEMI.**	**Proportion of patients with a given symptom that *do not* have NSTEMI.**	Odds of having a specific symptom given NSTEMI divided by the odds of having the symptom given not having NSTEMI.	AUC: Area under the curve when true positive rate (having symptom and NSTEMI) and false positive rate (having symptom but not NSTEMI) are plotted for various thresholds. Accuracy: Sensitivity + specificity adjusted for prevalence of the measured parameter. Logistic regression: Association between sex/age and symptoms.
Paper 2	**Rate of patients correctly identified as *non-rule out* (due to MACE) divided by all patients with MACE (true positive rate)**	Rate of patients correctly identified as *rule out* (due to non-MACE) divided by all patients without MACE (true negative rate).	Proportion of non-ruled out patient that *do* have a MACE.	**Proportion of ruled out patient that *do not* have a MACE.**		AUC: Area under the curve when true positive rate (non-rule-out and MACE) and false positive rate (non-rule-out but not MACE) are plotted for various thresholds. Accuracy: Sensitivity + specificity adjusted for prevalence of the measured parameter.
Paper 3	**Rate of patients with cTn concentration above a given threshold reaching an endpoint divided by all patients reaching the endpoint.**	Rate of patients with cTn above a given threshold *not* reaching an endpoint divided by all patients not reaching the endpoint.	**Proportion of patients *with* cTn concentration above a given threshold reaching an endpoint.**	Proportion of patients *without* cTn concentration above a given threshold *not* reaching an endpoint.	Odds of having elevated cTn given endpoint reached divided by the odds of elevated cTn given not endpoint not reached.	AUC: Area under the curve when true positive rate (elevated cTn and endpoint reached) and false positive rate (elevated cTn but endpoint not reached) are plotted for various thresholds.
Test of difference	The McNemar test					AUC: Delong test

4. Summary of results

4.1 Paper 1

The aim of Paper 1 was to identify the symptoms of myocardial infarction with the highest predictive value and to evaluate potential differences based on the sex or age groups. The study population of WESTCOR-D and the internal validation cohort (WESTCOR-CT) consisted of 1506 patients (60% male) with a mean age of 62 years. A total of the 11.6% of patients had NSTEMI as adjudicated diagnosis. NSTEMI patients were 5.4 years older than patients without AMI, and women were 4.7 years older than men.

The character of chest pain traditionally considered atypical was present in a higher fraction of men than in women (21.8% vs 18.3%, p=0.041), but atypical chest pain *location* was present in a borderline higher fraction of women (9.4% vs 6.7%, p=0.059), see **Figure 9**. A higher fraction of younger (<70 years) than older patients (≥70 years) presented with chest pain with atypical character (22.5% vs. 15.4%, p=0.006) while atypical chest pain *location* were present in a higher fraction of older patients (10.3% vs. 6.7%, p=0.018).

The symptom with the highest odds ratio to represent an NSTEMI was radiating pain to both arms (OR 9.4) followed by typical angina prodromes (exertional chest pain present during the last week, OR 3.0) and pain occurring during activity as a reason for seeking medical attention (OR 2.9). Men had significantly lower odds of having an NSTEMI compared to women if pain was dependent on position, respiration, or palpation (OR 0.17 vs 0.53, p-value for interaction 0.047). For age groups, patients <70 years had a higher OR for having an NSTEMI if exertional chest pain had been present during the past week (OR 4.08 vs 1.81, 95%, p-value for interaction 0.025) and a lower OR if pain radiated to the left arm (OR 0.73 vs 1.67, p-value for interaction 0.045).

The study was unable to demonstrate that women or older patients had a higher risk of having an NSTEMI if atypical symptoms were present. The differences in the presentation of symptoms and the risk of NSTEMI between the sex and age groups were small

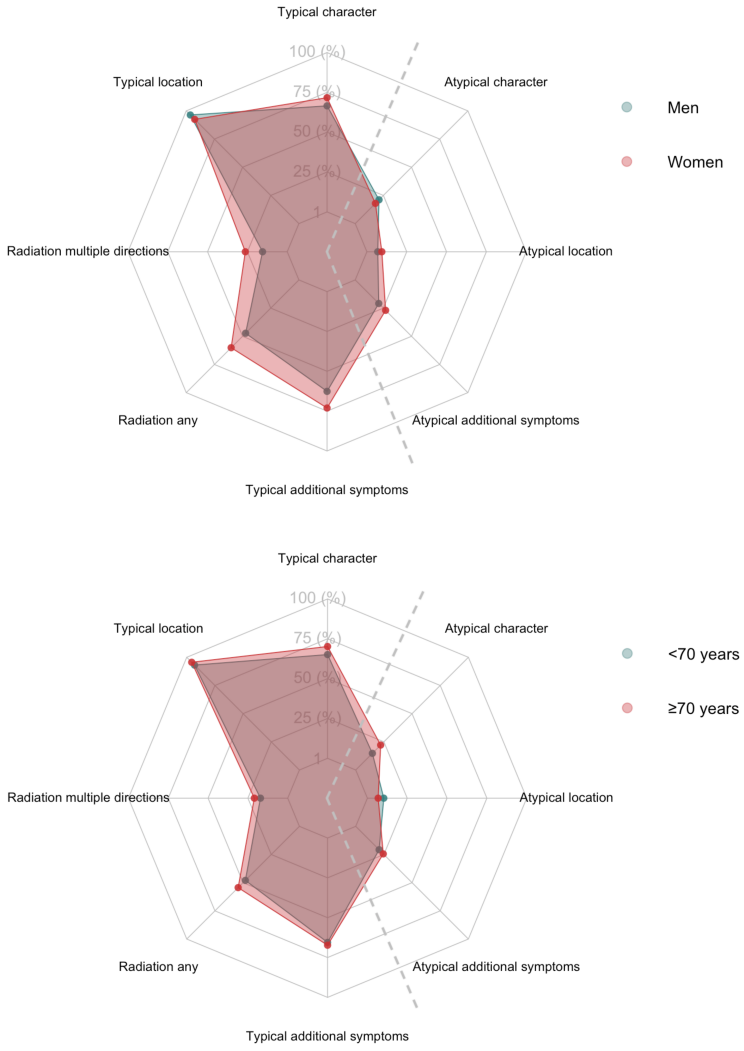

Figure 9. *Incidence of traditionally considered typical and atypical chest pain symptoms in women/men and younger/older patients who present with suspected ACS. Illustration by Steiro et al., Association between symptoms and risk of non-ST segment elevation myocardial infarction according to age and sex in patients admitted to the emergency department with suspected acute coronary syndrome: a single-centre retrospective cohort study. BMJ Open. 2022;12:1–12, published under Open Access and reprinted under the terms of the Creative Commons CC BY license* (259).

4.2 Paper 2

The objective of Paper 2 was to assess the ability of troponin-based algorithms and clinical risk scores to predict mortality, myocardial infarction, or coronary revascularization within 30 days in patients admitted to the emergency department with symptoms suggestive of ACS. The troponin-based algorithms (ESC 0/3h and the High-STEACS algorithm) were combined with the ACS risk criteria of the 2015 ESC guidelines or one of 11 different clinical risk scores in a double rule out ADP strategy.

The 932 patients (60% male) had mean age of 63 years. Having ACS was associated with higher age, male sex, hypertension, hyperlipidemia, diabetes mellitus, prior AMI or revascularization, and peripheral vascular disease.

The patients were evaluated in the emergency department median eight hours after symptom onset. A total of 21% reached the primary endpoint of non-fatal myocardial infarction, all-cause mortality, or unplanned revascularization.

The four cTn algorithms combined with the ACS risk criteria showed a similar AUC (0.70-0.71), sensitivity (90-93%) and NPV (95-96%) for the primary endpoint. ESC algorithms ruled out slightly more patients as low risk than High-STEACS algorithms (40.3 vs 39.4 percent, $p<0.01$ for ESC cTnT vs. High-STEACS cTnT). The primary endpoint rate among low-risk patients was 4.0-4.9% (ESC 0/3h) and 3.8-4.3% (High-STEACS); see **Figure 10**.

HEART ≤3, mHEART ≤3 or T-MACS ≤0.02 were the three clinical risk scores with the highest precision in identifying patients who reached the primary endpoint. HEART score with a cutoff value of >3 points identified the most patients (85%) who underwent unplanned revascularization, and the combination of a HEART score ≤3 and the ESC 0/3h or High-STEACS algorithm had the highest diagnostic precision. Only 2.2%-2.7% of patients ruled out by this ADP reached the primary endpoint, almost exclusively due to coronary revascularizations. Efficacy was maintained, as 38-40% of patients were considered low-risk and eligible for early discharge.

A cTn algorithm (ESC 0/3 or High-STEACS) combined with the risk criteria for ASC in the ESC guidelines, HEART score or T-MACS identified almost all patients with myocardial infarction (secondary endpoint).

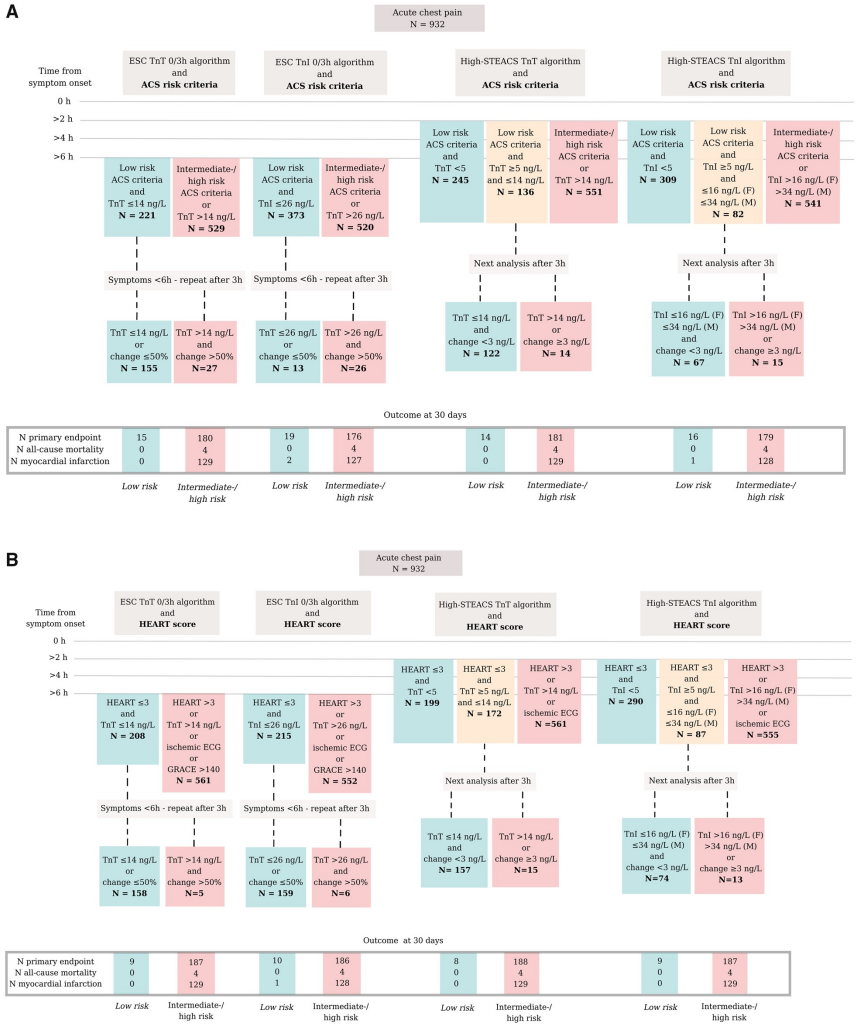

Figure 10. *(A) Summary of the ESC 0/3 h and High-STEACS algorithms, number of patients assigned to rule-out or none-rule-out at presentation or 3 h and outcome within 30 days. (B) Summary of ESC 0/3 h and High-STEACS algorithms combined with HEART score. Illustration by Steiro et al., Clinical risk scores identify more patients at risk for cardiovascular events within 30 days as compared to standard ACS risk criteria: the WESTCOR study. European Heart Journal: Acute Cardiovascular Care. 2020 Oct 2;10(3):287–301, published under Open Access and reprinted under the terms of the Creative Commons CC BY license. (158)*

4.3 Paper 3

The objective of Paper 3 was to assess possible differences in prevalence of CMI (chronically elevated cTn concentrations) and prognostic implications when cTn were measured by three different hs-cTn assays.

The hs-Tn assays were able to detect cTn in more men than women (cTnT Roche, men/women: 75.3/55.8%; cTnI Abbott, 71.2/59.1%; cTnI Siemens 97.5/90.4%, all p-values for diff. <0.001). The correlation between the two hs-cTnI assays was good (r=0.730 in blood samples from women; r=0.752 in men), but lower between the cTnT vs. cTnI assays (in women, r=0.699 for Roche vs. Abbott; r=0.640 for Roche vs. Siemens; in men, r=0.737 for Roche vs. Abbott; r=0.674 for Roche vs. Siemens), see **Figure 11**. A total of 218 patients (19.0%) had CMI by any assay, but with large differences between the hs-cTnT (207 patients) and the hs-cTnI assays (Abbott hs-cTnI, 46 patients; Siemens hs-cTnI, 53 patients).

The prognostic precision for the primary endpoint was similar between the hs-cTnT assay and the Abbott hs-cTnI assay when cTn concentrations were analyzed as continuous variables. However, the utility CMI as a condition with possible prognostic implications was higher when patients were assessed with the hs-cTnT assay (AUC 0.583; cTnI Abbott, AUC 0.531, p-value 0.021 for difference; cTnI Siemens, AUC 0.522; p-value 0.008 for difference). Based on linear regression and using the cTnT 99th percentile URL as reference (9.0 ng/L in women and 16.8 ng/L in men), equivalent cTnI concentration were found to be 4.1/8.7 ng/L (women/men) with the Abbott assay and 6.9/16.5 ng/L (women/men) with the Siemens assay. The calculated optimal prognostic cutoff values were found to be below the 99th percentile and not far above the LoD for all three assays (cTnT, 8/9 ng/L in women/men; cTnI Abbott, 2.9/3.4 ng/L in women/men; Siemens cTnI, 3.6/3.5 in women/men).

Overall, the upper reference limits of cTnT and cTnI appeared unharmonized when analysed in a cohort of hospitalized patients without acute myocardial injury.

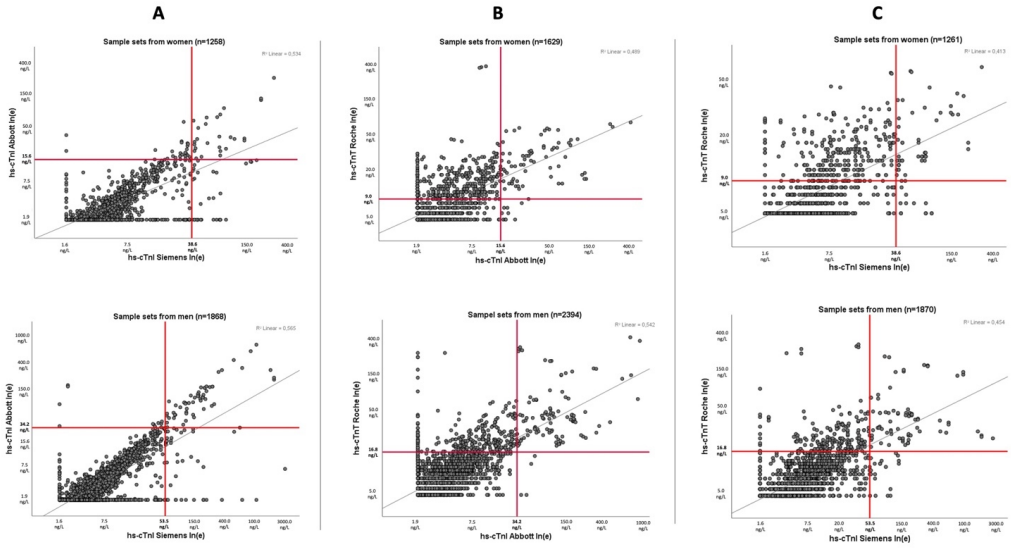

Figure 11. *Distribution of cardiac troponin T and I (cTnT and cTnI) below and above the upper reference limit of the 99th percentile (red line) provided by manufacturers in women and men without acute myocardial injury comparing (**A**) cTnI Abbott vs. cTnI Siemens, (**B**) cTnT Roche vs. cTnI Abbott, and (**C**) cTnT Roche vs. cTnI Siemens.*

5. Discussion

Early, safe, and effective identification of coronary artery disease depends on cTn measurements and correct clinical assessments. cTn can also be used as a prognostic marker of cardiovascular risk. In this thesis, we evaluated tools to improve precision in triage, treatment, and risk assessment of patients who present to an emergency department with symptoms suggesting ACS.

5.1 Methodological considerations

The WESTCOR study is a prospective cohort study. The prospective design was used to observe patients over a long period to assess the risk of an outcome after exposure. The effect of exposure can then be effectively measured as relative risk (260). The prospective design has several advantages. One single study cohort can be used to measure multiple exposure factors in different outcome variables, compared to a case-control study in which outcome is given at inclusion. The design is favorable when the outcome of interest is likely to occur in a sufficient number of participants, which was the case in the WESTCOR study assessing future cardiovascular disease within years of follow-up in patients admitted to a hospital due to chest pain (261). A disadvantage of the prospective design is the risk of sampling bias and the long observation time often necessary to assess the effect of exposure. On the other extreme, too long observation time may affect the relationship between exposure and outcome. Prospective studies are most often unable to separate cause and effect, which means that only associations rather than causality can be assessed.

In Paper 1, information collected by non-study affiliates at inclusion was retrospectively analyzed. A common problem with retrospective analysis is that all relevant information may not have been rigorously collected. Symptom information was not collected by study personnel but retrospectively reviewed from charts written by ambulance personnel, physicians referring patients to the emergency department, and hospital physicians evaluating patients at presentation. Missing information may be handled by exclusion, but exclusion introduces potential selection bias, as patients

with lacking information may differ from patients where all information has been gathered.

Although prospective in study design, the WESTCOR study used data for cross-sectional analysis. A cross-sectional study does not follow patients over time but analyzes data from a population at one given time point. The design is most often used to assess the prevalence of a disease but can also be used to assess exposure and outcome in shorter time frames. As in a prospective study, the relationship between cause and effect can be obscured (262). In the WESTCOR study, patient with shortness of breath (SoB) as the sole actual symptom of NSTEMI could develop chest pain due to SoB anxiety rather than chest pain caused by NSTEMI itself. Even though it is highly probable that both shortness of breath and chest pain were symptoms caused by NSTEMI, the risk of cause/effect misinterpretation is present.

5.2 Bias

To ensure reliable and valid results in a study, it is important to avoid skewed data due to systematic errors. Biases are often classified into two main categories: Selection bias and information bias. Selection biases occur when systematic errors are made during the selection of the study group so that participants differ from the population it is supposed to represent (263). Information biases occur when systematic errors in the handling of data may lead to wrong conclusions. Confounding is sometimes classified as a bias but should more precisely be considered a misinterpretation of cause and effect. A factor that can influence both the explanatory variable and the outcome may create false assumptions but can be identified and corrected for through statistical calculations.

5.2.1 Selection bias

Selection bias will occur in all studies that recruit patients by informed consent, like in the WESTCOR study. Examples of selection biases like exclusion bias, migration bias, self-selection and consent bias will be discussed shortly, while consecutive

recruitment, nonresponse bias, referral bias, and Berkson´s bias are discussed separately.

Exclusion bias occurs when subjects are exposed to rigorous screening before entering a trial, i.e., if only the more physically robust patients are invited to test a new medication. The WESTCOR study excluded patients <18 years, patients with STEMI and those unable to consent, which may have introduced exclusion bias.

Migration bias occurs when included patients who are lost to follow-up due to migration differ from the rest of the participants, for example, by being younger, healthier, and more likely to relocate than the remaining participants. The problem is most prominent in studies that perform follow-up consultations in person, for example, only in patients who are able and willing to travel to a particular site for follow-up examinations. In the WESTCOR study, some patients (n<5) migrated to another country and were lost to follow-up, which introduces a small, but existing risk of migration bias. Follow-up data on remaining participants were collected through national registers, ensuring an almost complete set of follow-up data.

Self-selection bias may occur if decision to participate in a study is decided entirely by the participants, for example if an observational study aiming to assess the health benefits of a new diet recruit volunteers with a greater interest in nutrition than the general population. Consent bias is a form of self-selection bias that occur when participation in a study relies on consent by the participants (264). Patients in the WESTCOR study were recruited in the ED and with high acceptance rate. However, if patients not willing to participate differ from those in the final cohort, consent bias have occurred. Also, studies recruiting participants by active consent, like in the WESTCOR study, is more vulnerable to consent bias than studies recruiting through passive consent (265).

5.2.1.1 Bias due to non-consecutive sampling

Consecutive sampling of a prospective cohort is considered the optimal way to minimize selection bias, since all available subjects are asked to participate. The WESTCOR study included patients with chest pain consecutively 24 hours a day, 7 days a week, but the study was vulnerable to selection bias for two reasons. In periods

of overcrowding, fewer patients were recruited. Malaise in recruiting personnel may have favored the inclusion of younger and more healthy patients.

Additionally, not all patients with chest pain seek medical attention or is transferred to hospital by the first responders. Selection bias may have been introduced to the WESTCOR cohort if patients presenting to the ED were more concerned about chest pain symptoms than the population in general, for example, by having family members with cardiac diseases. In Paper 1, the rate of family history of early coronary artery disease was not higher in patients with ACS than in those without ACS (with ACS 18.6%; without 20.7%, p-value for the difference 0.497), which suggests that patients with chest pain and a family history of cardiac disease more often than others seek medical attention. The difference could also be due to a higher referral rate by first responders knowing the patients´ family history, known as referral bias. However, the pattern was opposite for the remaining main risk factors (hypertension, hyperlipidemia, diabetes, and current smoking), where prevalence was highest in patients with ACS.

5.2.1.2 Non-response bias

Even studies that actively select the study population may be at risk of not including patients important for a representative cohort. Non-response bias occurs when patients not willing to participate in a study differ systematically from those who choose to participate. Inclusion in the WESTCOR study was dependent on oral and later written consent and may have not included all eligible patients, e.g., due to language barriers since the consent form was written in Norwegian, or due to very high frailty.

An alternative study design to ensure the maximum response rate is cluster-randomized studies, which compare the outcome before and after a new procedure or treatment has been implemented. Cluster-randomized studies should be limited to the evaluation of treatments and diagnostic strategies that are so established that participants are not exposed to a major risk or side effects. Novel algorithms for early discharge of patients might be challenging to implement before observational and randomized studies have been performed.

5.2.1.3 Referral bias

Referral bias occurs when patients referred from a primary care unit to a secondary or tertiary care unit differ systematically from the population of interest, i.e., by having more or specific risk factors, more complex disease, or worse outcomes. The WESTCOR study specifies that the population of interest is those referred to a hospital, but there is still a risk of bias if preconceptions make the referred population skewed. For example, both female patients with AMI and their healthcare providers are less likely to attribute the symptoms to AMI, which can explain why female patients arrive later to hospital compared to men (266, 267). If the presentation and pathophysiology of a disease differ between sexes and scientific knowledge is not equally distributed for female and male patients, the referred patients can be skewed compared to the actual population.

5.2.1.4 Berkson's bias

Berkson's bias is a systematic error that can occur if included patients are recruited from a specific segment that has a different risk of an outcome compared to the general population. In Paper 3, the risk of a future event is calculated in patients with elevated cTn concentrations. Secondary outcome is all-cause mortality, coronary event, or hospitalization due to heart failure or stroke. Hospitalized patients are at increased risk for new hospitalizations even in the absence of the suspected cause of admission, such as acute coronary syndrome in the WESTCOR study. The risk of mortality or hospitalization may not be directly transferable to patients with elevated cTn concentrations who are not admitted to the hospital.

5.2.2 Information bias

Information biases occur due to systematic errors in data handling and can affect the generalizability of the results (268). Examples include recall bias, misclassification bias, and reporting bias.

5.2.2.1 Recall bias

Recall bias is a potential systematic error in retrospective self-reporting analysis when participants may not recall past experiences in detail. The bias is of greatest importance when participants are asked to recall experiences over a long period of time. Undesirable habits, such as a history of smoking, may also be under-reported due to recall bias (269).

Even though chest pain information in the WESTCOR study was reported at the time of presentation with a median time from the onset of symptoms of 8 hours, the data may have been incorrectly reported or registered. Symptoms during the past days and week were also recorded, and Paper 1 compared symptoms based on age under and over 70 years of age. Recall bias may have been introduced if older patients had more difficulties remembering symptoms that occurred days before presentation compared to the younger patients.

5.2.2.2 Misclassification bias

Misclassification occurs when a study participant is categorized into an incorrect category. If the probability of misclassification is similar in all study groups (non-differential misclassification), the risk of affecting the outcome is smaller than if the probability is unequally distributed (differential misclassification) (270). The latter may occur if the precision of a diagnosis is affected by factors such as the educational level. Systematic reviews and meta-analyzes are at increased risk of misclassification bias since included studies may use different classification systems.

AMI is a diagnosis with clear diagnostic criteria, particularly objective biochemical cut-off limits of cTn concentration. However, the results of the WESTCOR study have been subjected to differential misclassification if the available information differs between subgroups. For example, the potential benefit of invasive coronary angiography is often considered lower in older or more frail patients with concomitant increased risk of procedural complications. A less thorough investigation of coronary anatomy may introduce a possible higher imprecision in categorization of the oldest or most frail patients.

5.2.2.3 Reporting bias

Reporting bias occurs when authors underreport undesirable or unexpected study results if they attribute the results to errors in sampling or measurements (271). Similarly, authors may be more susceptible to report findings consistent with previous studies, even though these results are subject to the same potential errors. Reporting bias may be self-enhancing if investigators discover and discard the same results, ultimately making new investigators justify their reporting bias by the strong evidence for the opposite results found in previous studies.

In Paper 1, we hypothesized that typical and atypical symptoms representing NSTEMI would be unequally distributed between younger and older patients and between men and women. We were unable to prove this pattern but found the results worthy of being published.

5.3 Choosing the endpoints

The endpoints differed between the three articles. In Paper 1, NSTEMI during index hospitalization was the natural endpoint as the study aimed to assess the risk of NSTEMI before admission based on specific symptoms. Paper 2 had the primary endpoint of mortality, AMI, or revascularization within 30 days in order to identify all patients with ACS. Since revascularization can be delayed in patients with stable cTn concentrations, some patients with ACS could have been missed if a shorter follow-up period had been chosen, i.e., events within index hospitalization. A longer follow-up period, that is, 6 or 12 months, could have affected whether the findings at presentation were associated with the outcome. Most risk scores are intended to identify patients with a high risk of cardiovascular events in the near future and not as a prognostic tool for events several months or a year ahead.

Paper 3 had a primary, secondary, and tertiary endpoint. We aimed to assess the prognostic relevance of chronic myocardial injury (elevated, but stable cTn concentrations) on a composite cardiovascular endpoint consisting of cardiovascular death, AMI, or revascularization. The chosen endpoint components are all associated with modifiable risk factors such as hypertension, smoking, and dyslipidemia.

The secondary endpoint added all-cause mortality and two diagnoses associated with elevated cTn concentrations, heart failure, and stroke. When an endpoint contains up to five components, the risk of misinterpretation increases. Composite endpoints are increasingly popular in randomized clinical trials (RCT) when a single component endpoint is likely to produce few outcomes (272). The chances of discovering significant differences between two treatments increase in parallel with the number of outcomes during follow-up. Since components have different consequences for patient quality of life, for example, the risk of readmission versus death is not equally important to the patient, the author must be careful when making conclusions, particularly when the least important outcome occurs more frequently than mortality. This was not the case in Paper 3, where all-cause mortality occurred 3.5 times more often than heart failure and stroke combined.

One might question whether all-cause mortality belongs in a secondary outcome where all other components are more strongly associated with modifiable risk factors. The reason is the difference in prognostic utility of cTnT and cTnI, where cTnT is more strongly associated with all-cause mortality and elevated cTnI might be a stronger predictor of cardiovascular morbidity.

Finally, all-cause mortality was chosen as a tertiary endpoint even though the study aimed to assess outcomes with modifiable risk factors. It would however be a limitation to compare cTn assays based only on endpoints less established in the literature. If prognostic differences were found between assays, the study had to address whether the differences were caused by the cTn assays or the selected endpoints.

5.4 Measuring diagnostic and prognostic performance

All three articles contain calculations of sensitivity, specificity, NPV, PPV, and area under the receiver-operator curve, while Paper 2 also contains calculations of accuracy. The optimal way to measure the performance of an cTn rule-out algorithm, symptom, or biomarker is debated.

The abstract of Paper 2 highlights the high NPV for troponin-based algorithms. NPV is a useful parameter when evaluating the safety of rule-out algorithms, as it is

closely related to the clinical dilemma physicians face when deciding to discharge a patient from the emergency department. It denotes the probability that a rule-out patient does not have an AMI. Some have suggested that 99.5% is the acceptable NPV for a test to safely exclude myocardial infarction (121). NPV is often reported as a safety measure but depends on the prevalence of the disease. A higher prevalence of AMI will decrease NPV and increase PPV, and therefore NPV only indirectly reflects the diagnostic or prognostic sensitivity of the test (273). The safety of all algorithms and ADPs are supplemented by sensitivity, which denotes the percentage of patients with AMI that correctly have not been ruled out. A study has shown that most physicians accept a 0.5% miss rate for short-term MACE, which means a sensitivity of 99.5% (274).

The three papers measure accuracy as AUC of ROC curves with both single point thresholds and as continuous variables. These ROC curves cannot be compared. That is, an ROC curve based on the rule-out criteria for NSTEMI (single-point threshold) cannot be compared with the ROC of the HEART score (continuous score from 0 to 10). AUCs of different tests with a single point threshold should also be compared with great caution, as the clinical utility is dependent on the purpose. Using cTnT or cTnI in the ESC algorithm for AMI performs equally well based on AUC (0.75 vs 0.77). Sensitivity to identify patients with ACS is non-significantly higher for the cTnT assay compared to the cTnI assay (75.8 vs 66.5), and specificity is significantly lower (74.3 vs. 86.9). So, if the purpose of a test is to identify all patients with a disease (at the expense of lower specificity), the AUC alone is not sufficient to identify the best test.

In Paper 1, accuracy is used as a supplementary measure of diagnostic precision. Accuracy is the proportion of correctly classified patients (true positive and true negative) among all patients (true positive, true negative, false positive and false negative), but does not discriminate between true positive and true negative. The usefulness depends on sufficiently high rate of the classifier (symptom). Radiation to the right arm has 87.5% accuracy despite neutral AUC of 0.499 and only slightly lower accuracy than radiation to both arms, which has significantly higher AUC (accuracy 88.6% and AUC 0.585). The reason for the high accuracy is the very low

number of patients reporting radiation to the right arm (20 persons) and a high number of true negatives. Since only 10% of patients with radiation to the right side have NSTEMI (PPV 0.10) compared to an almost similar prevalence of 11,6% in the cohort, the high precision does not reflect the diagnostic utility of radiation to the right side as a diagnostic marker.

It should be noted that accuracy as a statistical measurement is affected by the prevalence of the disease. If very few patients develop the disease, accuracy will be higher than if the same test with identical sensitivity and specificity were used to identify a highly prevalent disease. This potential pitfall affects all symptoms in an analysis but may provide a very high accuracy if both prevalence of a symptom and prevalence of the disease are low.

In Paper 1, both odds ratios and likelihood ratios are reported. The odds ratio is the ratio between two odds, which is defined as the probability of the occurrence of an event given a certain condition divided by the probability of an event not occurring given the same condition (275). It is sometimes confused with risk, which is the probability of an outcome given a certain condition divided by *both* occurring and non-occurring outcomes. Positive likelihood ratio is defined as sensitivity divided by 1-spesificity and can be used to describe the change in probability of having a disease if a test is positive, in other words, the change in probability going from pre- to post-test. Similarly, the negative likelihood ratio is 1-sensitivity divided by specificity and describes the change in probability if a test is negative.

5.5 Ethical considerations

The patients gave oral consent to participate in the study upon presentation and a written consent during admission. Blood samples from the few patients who later withdrew their consent, were removed from the biobank. Participants of the study had some more blood samples drawn compared to non-participating patients, but participation were otherwise not associated with any risk. The pace and content of treatment were not affected by the study. The study and associated biobank were approved by the Regional Committees for Medical and Health Research Ethics

(2014/1365 REK vest and 2014/1905 REK vest) and carried out in accordance with the Declaration of Helsinki.

5.6 Discussion of main findings

During the past 10 years, the initial workup of patients with suspected ACS has changed. Adoption of high-sensitivity troponin assays have made it possible to detect AMI earlier. Patients without ACS might be identified and discharged earlier. New objective tools for risk assessment have been developed and validated. The composition of patient characteristics has changed. The aim of the thesis is to increase understanding of all phases of the initial workup of patients with suspected ACS and assess new ways for early identification of CAD.

Phase 1: Presentation and triage.

The typical patient with ACS in high-income countries has changed. The relative prevalence of NSTEMI has increased from 14.2% to 59.1% between 1990 and 2006 in the USA (276) and has surpassed 70% in Norway (277). The proportion of women with ACS has increased from 32.4% to 37.0%, and patients with AMI less often report previous myocardial infarction and angina pectoris, but more often have a history of revascularization, diabetes, hypertension, and current smoking (276).

Participants in older landmark studies on typical symptoms of AMI more often had ST segment deviations (190-192). STEMI is a cardiac condition with a grim prognosis if left untreated but is most often characterized by typical symptoms and classic findings on the ECG, making it easy to identify. Patients with NSTEMI or unstable angina, on the other hand, may have a normal ECG and can be more difficult to diagnose in the early phase after presentation. Updated knowledge of typical symptoms of NSTEMI in women, men, elderly, and young patients is warranted to ensure correct triage, as is the topic of Paper 1.

Paper 1 identified 17 independent symptoms and pain characteristics with a significant positive or negative OR for having an NSTEMI in patients with suspected ACS. Minor differences in presentation and risk of NSTEMI between women, men,

younger and older patients were identified, but symptoms and odds of NSTEMI were more similar than different.

Phase 2: Identifying NSTEMI

When ST-elevation myocardial infarction has been excluded by one or more electrocardiograms, physicians assess the probability of non-STE-ACS. High-sensitivity cTn assays have been available in Europe for fourteen years, but adoption varies significantly throughout the world, also in the USA where the FDA approved the use of the hs-cTnI and hs-cTnT assays five and six years ago. High-sensitivity assays have allowed development of faster algorithms for excluding acute myocardial infarction. A single very low hs-cTn measurement or two non-elevated values might be sufficient to rule out AMI. Paper 2 assesses the diagnostic precision of a 0/3-hour algorithm based on two different hs-cTn assays for the rapid identification of AMI, as well as identification of patients with low risk of having the disease. The results show that troponin-based algorithms (ESC or High-STEACS) identify almost all patients with NSTEMI during admission (secondary endpoint).

Phase 3: Identifying ACS.

High-sensitivity cTn algorithms have not been developed to identify patients with unstable angina, who, by definition, have stable and often low cTn concentrations. When STEMI and NSTEMI are excluded, physicians must assess whether the patient has unstable angina and can benefit from admission to a ward despite stable cTn values. Some clinicians decide based on gestalt, which might be sufficient given experience in identifying typical symptoms and knowledge of possible pitfalls in subgroups of patients. Even though the ESC guidelines define which ACS patients who have increased risk of unfavorable outcomes based on comorbidities and clinical findings, some physicians could benefit from using a structured tool for risk assessment, particularly physicians with less experience.

Paper 2 explores the possible benefits of using a clinical risk score rather than the high-risk criteria of the ESC guidelines for the identification of patients with ACS. Both methods increased the sensitivity for NSTEMI from 94.4-98.4 (depending on hs-

cTn assay) to 100%, but clinical risk scores identified more patients in need of coronary revascularization compared to the ESC high-risk criteria. HEART score and T-MACS were the two out of eleven assessed risk scores with best balance between precision and efficacy.

Phase 4: Future risk assessment

Patients with ACS are usually admitted for additional coronary examinations, antiplatelet treatment, and possibly coronary revascularization. Most patients admitted to the emergency department with chest pain do not have ACS, but many have cardiovascular risk factors and an increased risk of future mortality or cardiovascular disease.

Decades of research have provided physicians with knowledge on preventable causes of future ACS and possible treatments. As in medicine in general, most efforts should be directed at patients with the highest risk of future adverse events. Patients with chronically elevated cTn above the 99th percentile carry significant risk of future adverse cardiac events. The term CMI is seldom used in daily clinical practice compared to AMI and UAP for several reasons. Apart from management of risk factors, no specific treatments have been identified to reduce the elevated risk. Possible diagnostic discordancy is also a concern.

Paper 3 assesses the possible differences between the prevalence of CMI based on three different cTn assays and find large differences. Only 13% of patients with CMI were identified by all three assays.

5.6.1 Symptoms of NSTEMI

Paper 1 assesses the prevalence of different characteristics of symptoms in patients presenting to the emergency department admitted with suspected ACS and the odds ratio for each symptom to be caused by coronary artery disease. Men more often than women reported pain at typical locations (defined as thorax, shoulders, arms, jaw, or neck), but there was no significant difference in OR for actually having an NSTEMI based on those locations. Likewise, women less often reported atypical pain character (defined as burning or stinging character) and more often had radiating pain, shortness

of breath, nausea, palpitations, and dizziness, but the OR for having an NSTEMI were similar.

Only one difference in OR was identified. Men had significantly lower OR for NSTEMI if chest pain depended on position, respiration, or palpation compared to women. The reason might be the coexistence of NSTEMI and other causes of chest pain, as ORs were not adjusted for existing musculoskeletal disorders such as rheumatoid arthritis, polymyalgia rheumatica and fibromyalgia, which is more prevalent in women (278, 279). Atypical chest pain symptoms in female study participants with NSTEMI and concomitant muscular disease would not necessarily be caused by the NSTEMI, and the ORs could be overestimated.

Likewise, there were only minor differences between symptoms and OR for NSTEMI based on age groups older or younger than 70 years. Presenting with a non-chest pain symptom as the main complaint, e.g., shortness of breath, nausea, or palpitations, was more common in older patients. However, the OR for actually having an NSTEMI when such non-pain main complaints were present, was similar between age groups. Younger patients reported more often radiating pain in any direction, but with a similar OR for having an NSTEMI when radiation was present.

Two differences in OR between age groups were identified. Pain radiating pain to the left arm was reported equally often in younger and older patients but was stronger associated with NSTEMI in older patients. There are at least two possible explanations for the difference. One explanation could be that older patients with NSTEMI actually have pain radiating to the left arm more often than younger patients. However, selection bias can affect which patients end up in the emergency department. Pain radiating to the left arm has been found to be a typical and strong sign of AMI in several early studies (190). Newer studies that contain fewer patients with ischemic ECGs, find only a moderate likelihood ratio of around 1.5 for AMI if radiation to the left side is present (222, 225). Successful information campaigns and media articles can increase knowledge about typical symptoms of AMI in the population. An online search for typical symptoms of AMI will return several sites that describe radiation to the left arm as a typical sign of AMI. As a result, patients with non-coronary chest pain experiencing radiation on the left side might be more

inclined to seek medical attention, even though they have few risk factors for AMI. If access to information is skewed between generations, that is, if younger patients are more likely to search for and gather more information online, the association between NSTEMI and left-sided radiation may be diluted more in younger than older patients.

Paper 1 also finds that exertional chest pain during the last week before presentation is a typical finding in both younger and older patients but is more strongly associated with NSTEMI in young patients. The symptom is reported non-significantly more often in older patients, so the difference in activity level is not the sole cause. A possible explanation is that older patients often have exertional chest pain due to non-coronary causes, such as myalgia or poor posture. Since the endpoint is NSTEMI and not ACS (including angina), another explanation is that older patients in the study more frequently requested medical attention due to increased intensity of angina pectoris caused by pathophysiological stable atherosclerosis, while the younger patients more often experienced plaque rupture or erosion prior to admission.

5.6.2 Combining risk scores with cTn algorithms

During the past decade, much has happened in the development of rapid algorithms for the identification of myocardial infarctions. Paper 2 found that the troponin-based algorithms performed acceptable with a sensitivity for NSTEMI of 94.4-98.4% which increased to 100% when combined with the ACS high-risk criteria from ESC guidelines, HEART score, TIMI or T-MACS.

When AMI is excluded by troponin-based algorithms, patients can still suffer from UAP and benefit prognostically from being coronary revascularized. Risk assessment has traditionally been performed using clinical gestalt and the ACS risk criteria described by the ESC guidelines (21, 123). Over the past 10 years, several clinical risk scores have been developed and validated as a tool to assist in risk assessment.

In Paper 2, the use of an ADP containing a troponin-based algorithm and a clinical risk score identified more patients with MACE within 30 days, without reduced efficacy. The combination of a troponin-based 0/3-hour algorithm and HEART score ≤3 had higher accuracy than the ACS risk criteria combined with the

same troponin-algorithm, without a significantly reduction in number of patients considered low risk. Another risk score, T-MACS had a similar AUC as HEART score, both alone and in combination with a troponin-based algorithm. However, more patients identified as non-low risk by T-MACS were already identified by the troponin-based algorithms, and the sensitivity was non-significantly lower.

The use of clinical risk scores in the evaluation of patients with possible ACS was not mentioned in the latest ESC guidelines for NSTE-ACS from 2020 (21). This decision is discussed by the IFCC Committee on Clinical Applications of Cardiac Biomarkers, a consortium of scientists from laboratory medicine, cardiology, and emergency medicine (163). The comments resemble the argument made in Paper 2. Although the ESC guidelines recommend clinical evaluation of all patients, there is a risk that too much emphasis is placed on troponin-based algorithms. Using clinical risk scores routinely would be a way to force a clinical component into the diagnostic process and could be useful for less experienced physicians in particular. Subjective judgments are part of the medical evaluation but may not be sufficient if risk factors and the typicality of symptoms is misinterpreted.

5.6.3 Prognostic value of CMI

In Paper 3, a total of 19.0% of the patients had CMI by any assay, but the prevalence was much higher according to the hs-cTnT assay compared to the two hs-cTnI assays. Assay-dependent differences in prevalence are concerning as they imply that different patients can be diagnosed with CMI in different health care institutions depending on the cTn assay used for analysis.

During myocardial damage, cTnI and cTnT are released as part of the same cTn complex consisting of one cTnI, cTnT, and TnC molecule (77). The concentration should hence be equal and the correlation high as seen in patients with confirmed ACS (280, 281). cTnT assays are manufactured by Roche only, the 99th percentile URL is quite reproducible between studies (282). The URLs for the many different cTnI assays are less robust due to the variety of monoclonal antibodies used to detect different epitopes in cTnI molecules, and with different incubation conditions and blocking reagents (283). cTnI measured by the same antibodies and the same

manufacturer may even differ when analyzed on a different detection platform (284, 285).

The topic of potential differences in the 99th percentile URLs of cTn may seem confusing. On the one hand, the ability to correctly diagnose AMI is high and similar in both isoform assays (112, 286). With regards to prognostic precision, paper 3 finds no differences between the cTnI and cTnT assay when comparing ROC curves of cTn values as continuous variables. Patients with elevated but stable cTn concentrations measured by a cTnT or cTnI assay have an increased risk of cardiovascular death, AMI, or revascularization.

On the other hand, the 99th percentile URLs provided by the manufacturers appear unharmonized. Manufacturers of cTnI assays have identified a 99th percentile that can be twice or higher the numerical value of the cTnT 99th percentile, i.e., 15.6 ng/L in women measured by the Abbott cTnI assays compared to 9.0 ng/L measured by the Roche cTnT assay. External studies, however, indicate that the 99th percentile of cTnT and cTnI is numerically more similar when measured in the same patient cohorts (285, 287).

5.6.4 Release of cTn in the low normal range

The cTnI assays exhibit more ´extreme´ cTn values than the cTnT assay. In adults with cTn values in the lowest quartile, cTnI tends to be much lower than cTnT (288). In patients with AMI and elevated cTn, however, cTnI can be more than 10 times higher than cTnT (289).

In the WESTCOR cohort, where a majority of patients did not have coronary disease, median cTnI values were lower than cTnT (Abbott TnI, 2.7 ng/L; Siemens TnI 4.4 ng/L; Roche TnT 6 ng/L). The reasons for the low cTnI/cTnT ratio during low-level cTn leakage remain speculative, but differences in release and clearance could influence the balance relatively more when the levels of circulating cTn are low.

Several important differences in cTn kinetics are known. First, the concentration of free cTnT in the cytosol is slightly higher than that of cTnI, which could alter the correlation if cTn released during troponin leakage is recruited from the cytosol (48). Second, the stability of cTnI and cTnT in serum may differ as certain

regions if the cTnI molecule is highly susceptible to proteolysis (290, 291). Third, the secretion of the 24 kDa TnI molecule and the 37 kDa TnT through the kidneys favors cTnI excretion (292). Finally, analytic differences, particularly between cTnI assays, could influence correlation in healthy adults, as the assays quantify cTn based on different epitopes of the molecule (293).

5.6.5 Release of cTn in the high normal range

A protruding question that needs to be addressed is whether extrinsic or intrinsic factors have influenced the calculations of the established 99th percentiles. If so, the 99th percentile of the cTnT assay by Roche (based on blood samples from 500 healthy adults) could be underestimated, or the 99th percentile of the cTnI assays (most often calculated in 1500-2000 healthy adults) could be overestimated. Poorly defined cohorts with different sample sizes and a mix of sex, age groups, ethnicity, and possible unknown underlying conditions may also affect the 99th percentile measured (49). When more stringent inclusion criteria are applied excluding volunteers with possible comorbidities based on pro-BNP, GFR or imaging, the 99th percentile is lower (115, 294-296). In a recent study, macrotroponins affecting cTn concentration were found in 53% of blood samples, and the diagnostic precision of the analyzed cTnI assay improved after immunoglobulin depletion (297).

The cTnI/cTnT ratio is not linear across the spectrum from healthy adults to patients with subclinical conditions or cardiovascular disease. At what level of cardiac malfunction the concentration of cTnI begin to exceed cTnT is unknown. Calls for standardization of cTn assays have yet to be performed (284), and the potential pitfalls in calculation of the 99th percentile URLs of cTn assays is an ongoing challenge (86).

5.7 Clinical implications and future perspectives

Correct interpretation of symptoms and biomarkers is important to ensure early diagnosis and treatment of patients with suspected ACS and early discharge of patients without the need for admission. The thesis addresses three stages of patient care.

Although the epidemiologic panorama of AMI subgroups has changed, typical symptoms such as radiation to both arms still warrant extra vigilance from emergency department physicians during triage. Women and older patients have the same risk of NSTEMI if they present with typical or atypical symptoms compared to men and older patients and should be treated with the same attention and determination.

The combination of a clinical risk score and troponin-based algorithm identifies slightly more patients who die, have an AMI or are being revascularized within 30 days of follow-up. The study did not compare clinical risk score and gestalt, but the promising results should be of interest for hospitals who search for an ADP to identify both AMI and UAP with as objective criteria as possible.

Of 11 clinical risk scores, the HEART score had the best balance between safety and rule-out rate and should be favored. The use of risk scores for the identification of ACS was not incorporated into the latest ESC guidelines in 2020, but the thesis supports voices in the scientific environment that advocate a more objective risk assessment than clinical gestalt (163).

The prevalence of chronic myocardial injury was several times higher when using a cTnT assay compared to a cTnI assay. The findings should encourage more studies on potential differences and ways to harmonize the 99th percentiles to avoid differences in risk assessment and treatment. Chronic myocardial disease could be established as a condition that requires extra vigilance of the treating physicians to ensure proper prophylactic treatment against the elevated risk of CV disease. However, if CMI is to be used for research or in clinic, voices in the scientific society may suggest a lower URL for CMI than for AMI, corresponding to the threshold where CVD risk increases the most based on sex and age.

Elevated cTn is not specific for acute myocardial infarction. Patients with diseases such as pulmonary embolism, atrial fibrillation, myocarditis, or Takotsubo cardiomyopathy can present with similar symptoms and elevated concentrations of

cTn. The analysis and quantification of cTn fragments is an interesting but less studied topic. Some studies indicate that the ratio of long/intact cTn fragments vs total cTn can distinguish elevated cTn due to AMI from non-cardiac causes (80). cTn fragment analysis is the topic of several awaited, but unpublished studies. If the composition of cTn fragments compared to complete molecules is specific for certain conditions, the diagnostic precision of the cTn concentration might increase significantly.

Increased specificity may also be achieved by comparing cTn assays that detect and capture different epitopes of the cTn molecules. When a cTn molecule is degraded into fragments, the cTn will still be identified by assays that detect and capture epitopes in the central region, which is less susceptible to degradation. Patients with chronically elevated cTn values due to kidney disease and a high proportion of cTn fragments may have a higher concentration of cTn in assays using epitopes in proximity in the central molecule region, like the Roche cTnT assay and Abbott cTnI assay. Siemens has developed a cTnI assay with two detection antibodies: one that targets an epitope in the central molecule and one more distal epitope. It has been speculated that the Siemens assay may identify less fragmented molecules and relatively more complete molecules, making it a more specific test for acute myocardial injury (298). As interest in cTn fragments increases, more assays targeting both central and peripheral epitopes may be developed to increase cTn specificity.

Lastly, artificial intelligence may play an important role in risk assessments and outcome predictions in the coming decades. Coronary artery disease will probably be first in line when machine learning technology is adopted into clinical use, since CAD is a well-defined condition diagnosed by techniques highly suitable for machine learning algorithms such as ECG (299), coronary CT angiography (300) and echocardiography (301). Machine learning algorithms may be able to incorporate factors previously not considered of major importance and improve the accuracy for the prediction of AMI (302) and long-term outcome after the disease (303, 304).

6. Conclusions

- Chest pain that radiates to both arms has the highest odds ratio for NSTEMI of 9.4 followed by 3.0 if exertional chest pain has been present during the past week and 2.9 if pain occurred during activity.

- The difference in odds ratio for NSTEMI based on specific symptoms vary little between women, men, younger, and older patients.

- An accelerated diagnostic protocol of a troponin-based algorithm combined with a clinical risk score identify more patients with high risk of mortality, AMI or revascularization within 30 days compared to a troponin-based algorithm and low-risk criteria for ACS recommended by the ESC guidelines.

- Of 11 risk scores combined with the ESC 0/3-hour and High-STEACS algorithms, the HEART score had the best balance between safety and efficacy.

- The prevalence of chronic myocardial injury (cTn above the 99th percentile without rise and/or fall) was 3.9-4.5 times higher using a cTnT assay compared to a cTnI assay.

- Overall, there were no large differences in prognostic precision between cTnT or cTnI assays, but the cTnI assay had lower precision at the 99th percentile cutoff value used as diagnostic cutoff value for chronic myocardial injury. When the upper cTnI reference limits (URL) were lowered to harmonize the cTnT URL, the prognostic precision became close to similar.

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Association between symptoms and risk of non-ST segment elevation myocardial infarction according to age and sex in patients admitted to the emergency department with suspected acute coronary syndrome: a single-centre retrospective cohort study

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ABSTRACT

Objectives Evaluate the association between symptoms and risk of non-ST segment elevation myocardial infarction (NSTEMI) in patients admitted to an emergency department with suspected acute coronary syndrome based on sex and age.

Design Post hoc analysis of a prospective observational study conducted between September 2015 and May 2019.

Setting University hospital in Norway.

Participants 1506 participants >18 years of age (39.6% women and 31.0% 70 years of age or older).

Findings The OR for NSTEMI was 9.4 if pain radiated to both arms, 3.0 if exertional chest pain was present during the last week and 2.9 if pain occurred during activity. Men had significantly lower OR compared with women if pain was dependent of position, respiration or palpation (OR 0.17 vs 0.53, p value for interaction 0.047). Patients <70 years had higher predictive value than older patients if they reported exertional chest pain the last week (OR 4.08 vs 1.81, 95%, p value for interaction 0.025) and lower if pain radiated to the left arm (OR 0.73 vs 1.67, p value for interaction 0.045).

Conclusions Chest pain with radiation to both arms, exertional chest pain during the last week and pain during activity had the strongest predictive value for NSTEMI. The differences in symptom presentation and risk of NSTEMI between sex and age groups were small.

Trial registration number WESTCOR study ClinicalTrials.gov (NCT02620202).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our large cohort of prospectively included patients with suspected acute non-ST segment elevation myocardial infarction (NSTEMI) is among the very few using a high-sensitivity troponin assay in establishing the final diagnoses.
⇒ The diagnostic performance of symptoms predicting NSTEMI was assessed in a real-life setting including patients with and without NSTEMI, compared with earlier register studies which only included NSTEMI patients.
⇒ The study investigated the important topic whether women with atypical symptoms have higher risk of myocardial infarction than men and assessed the impact of age in the same cohort.
⇒ Information about symptom presentation was gathered retrospectively and not based on a standardised symptom assessment form. Symptom descriptions in the electronic charts may have been influenced by the hospital physicians' risk assessment as they were not blinded for ECGs and first troponin measurements.
⇒ The results may not be representative for STEMI patients and those with non-chest pain NSTEMI.

INTRODUCTION

The epidemiological panorama of acute myocardial infarction (AMI) has changed during the past decades with a lower rate of ST-segment elevation myocardial infarction (STEMI) versus non-STEMI (NSTEMI).[1] The decline in STEMI incidence has been attributed to improved awareness of coronary risk factors and early primary preventive measurements. Why the incidence of NSTEMI has increased in the same period may be due to demographic changes and higher prevalence of concomitant conditions like diabetes and obesity that promote

NSTEMI more than STEMI. Moreover, increasingly sensitive troponin assays tend to reclassify patients from the diagnosis of unstable angina pectoris (UAP) to NSTEMI,[2] which can explain the decline in the frequency of ECG changes in AMI patients over the last 50 years.[3]

The recent epidemiological shift may affect what symptoms we consider to be representative of AMI. Earlier studies of symptom presentation where 50%–90% of patients had ischaemic ECGs[4–6] probably do not represent the AMI patients in today's emergency departments. The new high-sensitivity troponin assays (hs-Tn) are very sensitive, but less specific as they detect slightly increased troponin concentrations in a substantial number of non-AMI patients. Correct triage based on symptoms may help ensure early treatment in high-risk patients and possibly reduce unnecessary examinations and overtreatment in low-risk patients.

Studies suggest that symptom presentation differs by sex and age, which can influence the rate of misdiagnosis and affect prognosis. Most studies identifying sex differences are based on AMI registries, and do not compare presenting symptoms in patients with AMI to patients with non-coronary disease.[7–11] Newer prospective studies including patients with suspected rather than confirmed coronary disease find less sex differences,[12–16] questioning the assumption that presenting symptoms of AMI are different in men compared with women. Furthermore, women with AMI are older than men. Although most newer studies on sex differences adjust for age, few studies have compared the OR for different symptoms based on sex and age in the same cohort.

To address these unresolved issues, we assessed typical symptoms of NSTEMI in a contemporary cohort of patients presenting with suspected NSTE-acute coronary syndrome (ACS) and the potential impact of sex and age on these associations.

METHODS

Study design and population

The Aiming Towards Evidence-Based Interpretation of Cardiac Biomarkers in Patients Presenting with Chest Pain is a prospective observational study conducted at two university hospitals in Norway.[17]

The current article is a post hoc analysis of a subset of 1506 patients >18 years admitted to Haukeland University Hospital between September 2015 and May 2019 with suspected NSTE-ACS. Suspected NSTE-ACS was defined as chest pain or discomfort that triggered a cardiac evaluation consisting of ACS risk assessment, an ECG and troponin measurements. Participants gave oral consent to participate in the study at arrival, and written consents were obtained when the clinical situation was stabilised. Blood samples from patients who did not provide written consent were destroyed. Patients with ST segment elevations where excluded, as well as patients transferred from other hospitals, those unable to provide informed consent or with a short life expectancy, for example, terminal cancer.

Data collection

Information about symptoms at presentation was collected from electronic medical records provided by ambulance personnel, referring physicians and hospital physicians at presentation. The chart reviewers were not blinded to the study hypothesis. The treating hospital physicians are instructed to report both positive and negative symptoms as part of the department's routine. However, since a symptom checker is not routinely used, the amount of available information was to some extent dependent of the treating physician's accuracy. In the very few incidences (<5 cases) where prehospital and in-hospital personnel gave conflicting information, data provided by hospital physicians were used.

Blood samples were analysed using the high-sensitivity troponin T assay from Roche Diagnostics with a limit of blank of 3 ng/L, a limit of detection of 5 ng/L and a sex-neutral 99th percentile of 14 ng/L, CV_A were 10% or lower for concentrations >4.5 ng/L. The final diagnosis was adjudicated by two independent cardiologists based on clinical data, high-sensitivity troponin T, 12-lead ECG and additional coronary examinations.[17] AMI was defined according to the third universal definition for MI.[18] A 20% or 50% change in troponin concentration was regarded significant if baseline cTnT concentration were >14 ng/L or ≤14 ng/L, respectively.

Chest pain characteristics

Detailed information on character, location and duration of pain was available for >80% of patients. Patients with missing information about character, location or duration were excluded from specific analyses when that information was needed, but not from the study. Additional symptoms like shortness of breath and nausea not registered at presentation were regarded negative, in line with similar studies.[7] The fraction of unregistered symptoms (then considered negative) is available in online supplemental table 1. The additional symptoms most often not reported were pain dependent of position (85.5% unreported), palpitations (81.1%) and pain dependent of respiration (77.5%). Shortness of breath were left unregistered in 24.3%, while nausea and vomiting were not registered in 49.3% and 56.0% of patients. The majority of positive or negative symptoms were reported equally often in patients with a later diagnosis NSTEMI versus non-NSTEMI, with five exceptions: Positive or negative presence of diaphoresis/clamminess and effect of nitroglycerines were reported more often for patients with a later diagnosis of NSTEMI. Positive and negative presence of dizziness and pain triggered by respiration or palpation were reported more often in patients given a non-NSTEMI diagnosis.

Traditionally, several studies have chosen to define typical location and pain character as pain or

discomfort in chest, arm or jaw, with character being dull, heavy, tight or crushing. Atypical pain has been defined as pain located in the epigastrium, abdomen, back or any other location with character being burning, stabbing, stinging or any other character.[12 19] When combined, pain is regarded atypical if either character or location is atypical, and typical only when both are classified as typical. The term typical and atypical symptoms of ACS is debated and should be used with caution since the frequency of reported symptoms may differ between sexes and age groups.[20] For simplicity reasons, we have still included these terms according to definitions described above.

Statistical analysis

Baseline characteristics for patients with and without NSTEMI was reported as means (±2 SD) for normally distributed data, median with 25- and 75-percentiles for non-normally distributed data and frequencies with percentages for categorical data. Differences between groups were compared using two-sample t-test or Wilcoxon rank-sum test for continuous variables and Pearson χ^2 test or Fisher's exact for categorical data.

Patients were grouped by gender and age, using ≥70 years as the cut-off limit for age based on median age of first myocardial infarction close to 70 years in the USA[21] and 72 years for all myocardial infarctions in Norway.[22]

ORs with 95% CIs were calculated for all specific symptoms within sex and age groups. Sensitivity, specificity, positive and negative predictive value (PPV and NPV), positive and negative likelihood ratio (LR), accuracy and area under receiver operating characteristic curve (ROC-AUC) were calculated for selected variables. To assess the association between symptoms and sex we made a multivariable regression model containing symptom, sex and the combined variable of symptom/sex. Age effect was similarly evaluated using symptom, age group and the combined variable of symptom/age. The p value for interactions was calculated using Wald χ^2. The degree of interaction for sex and age was compared in order to evaluate which factor influenced the odds of having an NSTEMI if presentation was typical or atypical for NSTEMI.

Hypothesis testing were two tailed, and p values <0.05 were considered statistically significant. Analyses were performed using IBM SPSS Statistics V.26.0.0.1 and R V,4.0.3.

Patient and public involvement

The study was discussed in the patients' user committee at Haukeland University Hospital in January 2016.This committee include one representative from the national patient organisation for lung and heart diseases. The user committee was positive to the study and gave important input to the planning and implementation. Information describing the progression and data reported from the study is available for patients online.

RESULTS

Baseline characteristics are shown in table 1. A total of 175 patients (11.6%) were classified with NSTEMI, of which 96% had a type 1 infarction and 4% type 2 infarction. Women accounted for 39.6% of the included patients and 30.3% of those with NSTEMI. Corresponding numbers for patients≥70 years of age was 31.0% and 43.4%. Patients with NSTEMI was on average 5.4 years older than non-myocardial infarction patients, and women were 4.7 years older than men.

Presenting symptoms are outlined in online supplemental table 2. If both pain location and character were in line with what has usually been described as typical, the sensitivity and NPV for NSTEMI was 84.6 (95% CI 77.4 to 90.2) and 92.0 (95% CI 88.4 to 94.5) (see table 2). The specificity was low, and the AUC was only slightly better than neutral, 0.532.

Patients in the total cohort had significantly increased OR for NSTEMI if chest pain radiated to both arms, was triggered by physical activity or if chest pain had occurred multiple times during the last week (tables 3 and 4). In total, 50% of patients with radiation to both arms were diagnosed with NSTEMI (PPV 50.0, 95% CI 38.8 to 61.2), the highest fraction of the assessed symptoms (see table 2). Negative ORs were observed if the pain was located precordial, occurred during rest or was accompanied by dizziness.

Sex differences

Chest pain character traditionally regarded atypical was present in a higher fraction of men than women (21.8% vs 18.3%, p=0.041). On the other hand, chest pain location regarded atypical were present in a borderline higher fraction of women (9.4% vs 6.7%, p=0.059) (see figure 1 and online supplemental table 2). In patients with either atypical character or location, there were no difference between women and men (19.5% of women vs 18.0% of men, p=0.494). Women significantly more often than men reported radiating pain and additional symptoms.

The OR for having an NSTEMI based on specific symptoms differed slightly between women and men. Men had lower OR for NSTEMI than women if additional symptoms like pain dependent on position, respiration or palpation were present (OR 0.17, 95% CI 0.07 to 0.39 vs OR 0.53, 95% CI: 0.25 to 1.11, p value for interaction 0.047) (see table 3). The difference was driven by a lower OR for positional pain (OR 0.17, 95% CI 0.04 to 0.71 for men vs OR 1.10, 95% CI 0.42 to 2.90 for women, p value for interaction 0.033).

Longer symptom duration (60 min to 24 hours) was associated with NSTEMI in women but not in men, with interaction being borderline significant (p=0.050).

Age differences

A higher fraction of younger (<70 years) than older patients (≥70 years) presented with what has traditionally been

Table 1 Baseline characteristics by sex and age group

	All patients, (n=1506)	Women, (n=597)	Men, (n=909)	P value	Age <70, (n=1039)	Age ≥70, (n=467)	P value
Baseline characteristics							
Age, years	62.3±33.1	65.1±28.6	60.4±35.2	<0.001 (T)	54.6±20.9	79.3±29.5	<0.001 (T)
Symptom to arrival time, hours	8.6 (3.1–52.7)	8.6 (2.8–51.2)	8.9 (3.2–56.25)	0.266 (W)	9.1 (3.1–55.0)	8.3 (3.1–50.8)	0.449 (W)
Hospital stay, hours	28.0 (22–69)	26.0 (22–50)	32.0 (22–73)	<0.001 (W)	26.0 (21–62)	44.0 (24–78)	<0.001 (W)
Acute MI	175 (11.6)	53 (8.9)	122 (13.4)	0.007 (C)	99 (9.5)	76 (16.3)	<0.001 (C)
Risk factors							
Hypertension, %	616 (40.9)	266 (44.6)	350 (38.5)	0.019 (C)	337 (32.4)	279 (59.7)	<0.001 (C)
Hyperlipidaemia, known %	303 (20.1)	121 (20.3)	182 (20.0)	0.907 (C)	193 (18.6)	110 (23.6)	0.026 (C)
Hyperlipidaemia, new,* %	142 (9.4)	71 (11.9)	71 (7.8)	0.008 (C)	98 (9.4)	44 (9.4)	0.995 (C)
Diabetes mellitus, %	181 (12.0)	62 (10.4)	119 (13.1)	0.114 (C)	105 (10.1)	76 (16.3)	0.001 (C)
Insulin-dependent	51 (3.4)	18 (3.0)	33 (3.6)	0.518 (C)	26 (2.5)	25 (5.4)	0.005 (C)
Family history, %	275 (18.3)	117 (19.6)	158 (17.4)	0.276 (C)	224 (19.8)	51 (10.9)	<0.001 (C)
Current smoker, %	284 (18.9)	118 (19.8)	166 (18.3)	0.466 (C)	206 (19.8)	78 (16.7)	0.152 (C)
Previous smoker, %	658 (43.7)	248 (41.5)	410 (45.1)	0.173 (C)	445 (42.8)	213 (45.6)	0.314 (C)
Medical history							
Prior MI, %	289 (19.2)	76 (12.7)	213 (23.4)	<0.001 (C)	141 (13.6)	148 (31.7)	<0.001 (C)
Prior PCI, %	293 (19.5)	73 (12.2)	220 (24.2)	<0.001 (C)	159 (15.3)	134 (28.7)	<0.001 (C)
Prior CABG, %	111 (7.4)	18 (3.0)	93 (10.2)	<0.001 (C)	45 (4.3)	66 (14.1)	<0.001 (C)
Heart failure, %	52 (3.4)	18 (3.0)	34 (3.7)	0.451 (C)	20 (1.9)	32 (6.9)	<0.001 (C)
Stroke, %	42 (2.8)	12 (2.0)	30 (3.3)	0.137 (C)	17 (1.6)	25 (5.4)	<0.001 (C)
Peripheral vascular disease, %	29 (1.9)	9 (1.5)	20 (2.2)	0.339 (C)	11 (1.1)	18 (3.9)	<0.001 (C)
Vital parameters at admission							
Systolic BP, mm Hg	145.9±41.0	147.2±47.3	143.8±40.1	0.003 (T)	142.9±41.0	150.1±46.4	<0.001 (T)
Diastolic BP, mm Hg	84.3±25.3	81.5±26.7	85.4±24.9	<0.001 (T)	85.2±24.6	80.8±27.5	<0.001 (T)
Heart rate, bpm	72.7±32.9	75.9±32.3	74.2±38.1	0.069 (T)	74.1±31.0	76.6±25.0	0.012 (T)
BMI†	27.4±9.2	26.4±9.6	28.0±8.8	<0.001 (T)	28.0±9.4	26.2±8.3	<0.001 (T)
ECG findings							
ST segment depression, %	47 (3.1)	22 (3.7)	25 (2.8)	0.307 (C)	21 (2.0)	26 (5.6)	<0.001 (C)
T-wave inversion, %	47 (3.1)	18 (3.0)	29 (3.2)	0.848 (C)	33 (3.2)	14 (3.0)	0.854 (C)

Values are median (IQR), mean±2 SD, or n (%).
*Total cholesterol ≥6.5 ng/L at presentation.
†Data missing in 50.6% (762/1506).
BMI, body mass index; BP, blood pressure; C, chi-square; CABG, coronary artery bypass grafting; FE, Fischer's exact; MI, myocardial infarction; PCI, percutaneous coronary intervention; T, two-sample t-test; W, Wilcoxon.

regarded atypical character (22.5% vs 15.4%, p=0.006). Traditionally considered atypical chest pain location was present in a higher fraction of older patients (10.3% vs 6.7%, p=0.018) (see figure 1 and online supplemental table 2). As seen with sexes, a similar fraction of younger and older patients presented with either atypical character or location (18.2% of younger patients vs 19.5% of older patients, p=0.582).

A few differences in the OR for NSTEMI based on specific symptoms were evident. In patients presenting with exertional chest pain during the past week, younger patients had higher OR for NSTEMI compared with older patients (OR 4.08, 95% CI 2.63 to 6.34 vs OR 1.81, 95% CI 1.03 to 3.15, p value for interaction 0.025) (see table 4). For pain radiating to the left arm, the ORs for NSTEMI were lower in younger than older patients (OR 0.73, 95% CI 0.42 to 1.28, vs OR 1.67, 95% CI 0.93 to 3.00, p value for interaction 0.045).

DISCUSSION

Our study of suspected ACS in patients without ST elevations showed that chest pain radiating to both arms has the highest predictive value for NSTEMI regardless of sex and age. Retrosternal location, vomiting, diaphoresis, onset during physical activity and exertional chest pain prior to admission are other symptoms found to be representative of AMI. This is in line with previous studies with high percentage of patients with ST elevations, who were diagnosed with less sensitive troponin assays. The presence of symptoms like chest pain dependent of

Table 2 Diagnostic precision of selected chest pain characteristics

	Sensitivity	Specificity	PPV	NPV	Pos. LR	Neg. LR	Accuracy	AUC
Location*								
Retrosternal	61.1 (53.3–68.4)	57.1 (54.4–59.8)	15.9 (14.2–17.8)	91.7 (90.1–93.1)	1.42 (1.24–1.63)	0.68 (0.56–0.83)	57.6 (55.0–60.1)	0.591
Precordial	7.6 (4.1–12.6)	76.5 (74.1–78.8)	4.1 (2.5–6.8)	86.2 (85.6–86.8)	0.32 (0.19–0.55)	1.21 (1.15–1.27)	68.5 (66.0–70.8)	0.421
Sum typical† location	95.9 (91.8–98.4)	5.4 (4.2–6.8)	11.9 (11.5–12.2)	90.9 (82.4–95.5)	1.01 (0.98–1.05)	0.75 (0.35–1.61)	16.0 (14.2–18.0)	0.507
Sum atypical‡ location	6.4 (3.2–11.2)	92.1 (90.4–93.5)	9.7 (5.5–16.3)	88.1 (87.7–88.5)	0.80 (0.44–1.47)	1.02 (0.97–1.06)	82.0 (80.0–84.0)	0.492
Character								
Sum typical§ character	89.5 (83.0–94.1)	14.8 (12.8–17.1)	11.5 (10.9–12.2)	91.9 (87.2–95.0)	1.05 (0.99–1.12)	0.71 (0.42–1.19)	23.1 (20.7–25.6)	0.522
Sum atypical¶ character	21.8 (15.2–29.8)	74.8 (72.1–77.4)	9.7 (7.1–13.1)	88.5 (87.5–89.5)	0.87 (0.62–1.21)	1.05 (0.95–1.15)	69.0 (66.3–71.6)	0.483
Typical pain**	84.6 (77.4–90.2)	21.8 (19.4–24.3)	11.7 (10.9–12.6)	92.0 (88.4–94.5)	1.08 (1.00–1.17)	0.71 (0.47–1.17)	28.6 (26.1–31.2)	0.532
Atypical pain††	15.4 (9.8–22.6)	78.2 (75.7–80.6)	8.0 (5.5–11.6)	88.3 (87.4–89.1)	0.71 (0.47–1.07)	1.08 (1.00–1.17)	71.4 (68.8–73.9)	0.468
Radiation								
Multiple directions	27.8 (21.2–35.2)	80.9 (78.6–83.0)	15.8 (12.5–19.7)	89.7 (88.7–90.5)	1.45 (1.11–1.90)	0.89 (0.81–0.98)	74.8 (72.5–77.0)	0.543
Both arms	19.5 (13.8–26.3)	97.5 (96.5–98.3)	50.0 (38.8–61.2)	90.4 (89.7–91.0)	7.76 (4.92–12.23)	0.83 (0.77–0.89)	88.6 (86.9–90.2)	0.585
Left arm	20.7 (14.9–27.6)	80.1 (77.8–82.2)	11.8 (8.9–15.5)	88.7 (87.8–89.5)	1.04 (0.76–1.42)	0.99 (0.91–1.07)	73.3 (71.0–75.6)	0.504
Right arm	1.18 (0.1–4.2)	98.6 (97.8–99.2)	10.0 (2.53–32.2)	88.6 (88.4–88.7)	0.86 (0.20–3.68)	1.00 (0.98–1.02)	87.5 (85.7–89.1)	0.499
Any radiation	48.1 (45.4–50.9)	48.1 (45.4–50.9)	13.8 (12.4–15.4)	91.3 (89.5–92.9)	1.24 (1.10–1.41)	0.74 (0.60–0.91)	50.0 (47.4–52.6)	0.563
Additional symptoms‡‡								
Sum typical§§	66.3 (58.8–73.2)	33.2 (30.7–35.8)	11.5 (10.4–12.7)	88.2 (85.7–90.3)	0.99 (0.89–1.11)	1.02 (0.81–1.27)	37.1 (34.6–39.6)	0.497
Sum atypical¶¶	8.6 (4.9–13.7)	74.8 (72.3–77.1)	4.3 (2.7–6.8)	86.2 (85.5–86.8)	0.34 (0.21–0.56)	1.22 (1.16–1.29)	67.1 (64.6–69.4)	0.417
Last 24 hours								
Exc. chest pain >once	5.1 (2.4–9.5)	97.1 (96.0–97.9)	18.8 (10.2–31.9)	88.6 (88.3–89.0)	1.76 (0.87–3.56)	0.98 (0.94–1.01)	86.4 (84.6–88.1)	0.511
Last week								
Exertional chest pain	35.4 (28.4–43.0)	84.5 (82.5–86.4)	23.1 (19.2–27.6)	90.9 (89.9–91.8)	2.29 (1.81–2.90)	0.76 (0.68–0.85)	78.8 (76.7–80.9)	0.6

*In patients having chest pain at presentation.
†Summation of traditionally considered typical pain location like retrosternal, precordial, other parts of thorax, shoulder, arms, jaw or neck.
‡Summation of traditionally considered atypical pain location like epigastrium, abdomen, back or other locations.
§Summation of traditionally considered typical pain character like tight, crushing, dull or heavy.
¶Summation of traditionally considered atypical pain character like burning, stinging or other.
**Typical pain is defined as the combination of traditionally considered typical location and typical character.
††Atypical pain is defined as either atypical location or atypical character, or both.
‡‡If not stated considered negative.
§§Summation of traditionally considered typical additional symptoms like shortness of breath, nausea, vomiting, diaphoresis, clamminess, palpitations or dizziness.
¶¶Summation of traditionally considered atypical additional symptoms like pain dependent of position, respiration or palpation.
Accuracy, Sensitivity x prevalence + specificity x (1 - prevalence); AUC, Area under receiver operating characteristics curve; LR, likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

Table 3 Positive OR (95% CI) for NSTEMI by symptoms in all patients and by sex

	N of total (%)	All (n=1506)	Men (n=909)	Women (n=597)	P value for interaction
Presenting symptom					
Chest pain	1468 (97.5)	1.55 (0.47–5.09)	2.05 (0.48–8.75)	0.97 (0.12–7.76)	0.565
Location*					
Retrosternal	661 (45.0)	2.09 (1.51–2.89)	2.24 (1.51–3.34)	1.75 (0.98–3.10)	0.48
Precordial	317 (21.5)	0.27 (0.15–0.48)	0.24 (0.12–0.46)	0.30 (0.09–0.98)	0.734
Thorax, other parts	396 (27.0)	0.95 (0.67–1.37)	1.05 (0.68–1.64)	0.85 (0.45–1.60)	0.579
Shoulders or arms	34 (2.3)	0.72 (0.22–2.40)	0.74 (0.17–3.26)	0.73 (0.09–5.65)	0.989
Jaw or neck	25 (1.7)	1.45 (0.49–4.26)	3.88 (0.91–16.4)	0.64 (0.08–4.89)	0.156
Sum typical† location	1391 (94.8)	1.35 (0.61–2.98)	1.60 (0.48–5.32)	0.97 (0.33–2.83)	0.543
Epigastrial or abdominal	81 (5.5)	1.07 (0.54–2.11)	0.81 (0.31–2.09)	1.67 (0.62–4.49)	0.298
Other location‡	34 (2.3)	0.22 (0.03–1.65)	–	0.56 (0.07–4.30)	0.999
Sum atypical§ location	77 (5.2)	0.79 (0.42–1.51)	0.57 (0.22–1.45)	1.29 (0.53–3.18)	0.217
Character					
Tight/crushing	960 (63.7)	1.33 (0.82–2.14)	1.44 (0.80–2.59)	1.18 (0.51–2.75)	0.706
Dull/heavy	81 (5.4)	1.16 (0.59–2.32)	0.73 (0.28–1.89)	2.37 (0.85–6.58)	0.098
Sum typical¶ character	1033 (68.6)	1.48 (0.83–2.64)	1.18 (0.62–2.26)	3.37 (0.80–14.3)	0.194
Burning	89 (5.9)	2.21 (1.27–3.83)	3.14 (1.61–6.10)	1.14 (0.39–3.38)	0.12
Stinging	218 (14.5)	0.42 (0.23–0.77)	0.34 (0.16–0.73)	0.57 (0.20–1.64)	0.448
Other atypical	2 (0.1)	–	–	–	0.999
Sum atypical** character	299 (19.9)	0.83 (0.54–1.28)	0.82 (0.49–1.37)	0.78 (0.35–1.74)	0.932
Unknown	263 (17.5)	1.40 (0.96–2.06)	1.58 (1.01–2.47)	0.95 (0.43–2.08)	0.273
Typical pain††	981 (66.8)	1.52 (0.94–2.48)	1.39 (0.78–2.50)	1.99 (0.76–5.19)	0.609
Atypical pain‡‡	224 (15.3)	0.66 (0.40–1.07)	0.72 (0.40–1.29)	0.50 (0.19–1.31)	0.609
Radiation					
Multiple directions	298 (19.8)	1.63 (1.13–2.34)	1.62 (1.00–2.61)	2.06 (1.14–3.73)	0.532
Both arms	66 (4.4)	9.40 (5.62–15.7)	8.28 (4.44–15.4)	11.7 (4.68–29.1)	0.543
Left arm	296 (19.7)	1.05 (0.71–1.56)	1.05 (0.65–1.69)	1.08 (0.54–2.17)	0.939
Right arm	20 (1.7)	0.86 (0.20–3.74)	1.65 (0.35–7.87)	–	0.999
Both shoulders	25 (1.7)	1.97 (0.73–5.31)	0.64 (0.08–5.01)	4.49 (1.36–14.9)	0.114
Left or right shoulder	92 (6.1)	0.16 (0.04–0.67)	0.14 (0.02–1.04)	0.21 (0.03–1.58)	0.776
Jaw	321 (21.3)	1.41 (0.98–2.03)	1.70 (1.06–2.70)	1.34 (0.74–2.46)	0.551
Epigastrium or abdomen	38 (2.5)	1.18 (0.46–3.07)	0.36 (0.05–2.71)	2.96 (0.95–9.29)	0.075
Back	189 (12.5)	1.42 (0.92–2.20)	1.71 (0.95–3.07)	1.41 (0.71–2.80)	0.677
Numbness upper extremities	128 (8.5)	1.12 (0.65–1.94)	1.07 (0.55–2.08)	1.21 (0.46–3.22)	0.827
Any radiation	789 (52.4)	1.69 (1.21–2.35)	1.82 (1.22–2.70)	1.77 (0.93–3.34)	0.937
Unknown	26 (1.7)	2.33 (0.92–5.88)	2.02 (0.65–6.29)	3.01 (0.61–14.9)	0.69
Additional symptoms§§					
Shortness of breath	628 (41.7)	1.06 (0.77–1.45)	1.11 (0.75–1.64)	1.05 (0.60–1.85)	0.875
Nausea	318 (21.1)	0.93 (0.63–1.37)	1.01 (0.61–1.68)	0.95 (0.50–1.80)	0.88
Vomiting	43 (2.9)	2.38 (1.15–4.93)	2.33 (0.97–5.64)	2.45 (0.68–8.89)	0.951
Diaphoresis or clamminess	287 (19.1)	1.79 (1.25–2.56)	2.01 (1.32–3.06)	1.19 (0.58–2.45)	0.218
Palpitations	174 (11.6)	0.69 (0.40–1.20)	0.90 (0.47–1.75)	0.47 (0.16–1.33)	0.298
Dizziness	226 (15.0)	0.38 (0.21–0.70)	0.43 (0.21–0.91)	0.35 (0.12–0.98)	0.732
Sum typical¶¶ add. symptoms	1005 (66.7)	0.98 (0.70–1.37)	1.11 (0.75–1.66)	0.84 (0.45–1.56)	0.452

Continued

Table 3 Continued

	N of total (%)	All (n=1506)	Men (n=909)	Women (n=597)	P value for interaction
Dependent of position	124 (8.2)	0.43 (0.20–0.94)	**0.17 (0.04–0.71)**	**1.10 (0.42–2.90)**	**0.033**
Dependent of respiration	149 (9.9)	0.19 (0.07–0.52)	0.13 (0.03–0.55)	0.33 (0.08–1.39)	0.384
Pain on palpation	177 (11.8)	0.38 (0.19–0.75)	0.21 (0.07–0.69)	0.69 (0.29–1.66)	0.117
Sum atypical*** add. symptoms	351 (23.3)	0.28 (0.16–0.48)	**0.17 (0.07–0.39)**	**0.53 (0.25–1.11)**	**0.047**
Effect of NG	268 (17.8)	1.78 (1.24–2.57)	1.49 (0.71–3.13)	1.57 (0.57–4.31)	0.936
Onset of symptoms					
During physical activity	285 (18.9)	2.91 (2.06–4.10)	2.63 (1.74–3.96)	3.29 (1.75–6.19)	0.559
After physical activity	72 (4.8)	1.27 (0.64–2.52)	1.02 (0.42–2.47)	1.86 (0.62–5.60)	0.405
Acute/chronic stress	115 (7.6)	0.26 (0.10–0.72)	0.10 (0.01–0.71)	0.62 (0.19–2.07)	0.118
During rest	1027 (68.2)	0.50 (0.36–0.69)	0.56 (0.38–0.83)	0.41 (0.23–0.73)	0.4
Unknown	18 (1.2)	2.98 (1.05–8.45)	5.30 (1.40–20.0)	1.29 (0.16–10.5)	0.264
Symptom duration					
<30 min	377 (25.0)	0.91 (0.62–1.33)	0.98 (0.62–1.55)	0.77 (0.39–1.53)	0.559
30–60 min	84 (5.6)	1.36 (0.73–2.53)	2.87 (1.45–5.69)	–	0.997
60 min to 24 hours	482 (32.0)	1.44 (1.02–2.04)	1.12 (0.74–1.71)	2.37 (1.28–4.39)	0.05
>24 hours	155 (10.3)	0.13 (0.04–0.40)	–	0.60 (0.18–2.00)	0.996
Terminated by NG	88 (5.8)	1.55 (0.86–2.78)	1.53 (0.76–3.05)	1.50 (0.50–4.50)	0.979
Terminated by morphine	37 (2.5)	0.88 (0.31–2.51)	1.26 (0.36–4.44)	0.52 (0.07–3.95)	0.463
Unknown	283 (18.8)	0.77 (0.50–1.18)	0.85 (0.51–1.42)	0.61 (0.27–1.38)	0.491
Intensity of pain in intervals†††	1506 (100)	1.56 (1.19–2.04)	1.84 (1.28–2.63)	1.21 (0.80–1.84)	0.141
Last 24 hours					
Exertional chest pain >once	48 (3.2)	1.80 (0.86–3.77)	1.12 (0.42–2.94)	4.36 (1.32–14.4)	0.083
Last week					
Exertional chest pain	268 (17.8)	3.00 (2.13–4.26)	2.77 (1.84–4.18)	3.25 (1.73–6.10)	0.679
Shortness of breath	60 (4.0)	1.36 (0.66–2.82)	1.20 (0.45–3.19)	1.77 (0.59–5.30)	0.607
Pain similar to previous AMI	57 (3.8)	0.72 (0.29–1.84)	0.45 (0.14–1.47)	2.09 (0.45–9.82)	0.12

Statistically significant differences highlighted
*In patients having chest pain at presentation.
†Summation of traditionally considered typical pain location like retrosternal, precordial, other parts of thorax, shoulder, arms, jaw or neck.
‡Summation of pain in the back and all other non-typical locations.
§Summation of traditionally considered atypical pain location like epigastrium, abdomen, back or other locations.
¶Summation of traditionally considered typical pain character like tight, crushing, dull or heavy.
**Summation of traditionally considered atypical pain character like burning, stinging or other.
††Typical pain is defined as the combination of traditionally considered typical location and character.
‡‡Atypical pain is defined as either atypical location or character, or both.
§§ If not stated considered negative.
¶¶ Summation of traditionally considered typical additional symptoms like shortness of breath, nausea, vomiting. diaphoresis, clamminess, palpitations or dizziness.
*** Summation of traditionally considered atypical additional symptoms like pain dependent of position, respiration or palpation.
†††Four groups; no pain; Visual analogue scale (VAS) 1–3.5; VAS 3.5–6.5; VAS >6.5.
AMI, acute myocardial infarction; NG, Nitroglycerin; NSTEMI, non-ST segment elevation myocardial infarction.

position, palpation or respiration reduced the OR for NSTEMI significantly more in men than women. Similarly, prodromes of exertional chest pain during the last week before admission was more predictive of NSTEMI in younger than older patients.

Despite improvements in biochemical diagnostics and imaging, symptom evaluation is the cornerstone in early risk stratification of patients admitted with suspected ACS. Hs-Tn is highly efficient in identifying AMI. However, given the assays' ability to detect even slightly elevated troponin concentrations in a substantial numbers of non-AMI patients, withholding further cardiac examinations in some selected patients with low clinical suspicion of ACS could reduce the number of unwarranted complications and side effects of unnecessary investigations or treatment.

Table 4 Positive OR for NSTEMI by age group

	N of total (%)	<70 years(n=1039)	≥70 years (n=467)	P value for interaction
Presenting symptom				
Chest pain	1468 (97.5)	1.98 (1.28–3.04)	2.67 (1.60–4.44)	0.374
Location*				
Retrosternal	661 (45.0)	1.98 (1.28–3.04)	2.67 (1.60–4.44)	0.374
Precordial	317 (21.5)	0.33 (0.16–0.66)	0.20 (0.07–0.56)	0.444
Thorax, other parts	396 (27.0)	1.05 (0.65–1.70)	0.75 (0.43–1.32)	0.382
Shoulders or arms	34 (2.3)	1.00 (1.00–4.37)	0.41 (0.05–3.18)	0.485
Jaw or neck	25 (1.7)	0.79 (0.10–6.15)	1.68 (0.44–6.36)	0.546
Sum typical† location	1391 (94.8)	2.32 (0.55–9.73)	1.09 (0.41–2.94)	0.398
Epigastrial or abdominal	81 (5.5)	0.21 (0.03–1.53)	1.74 (0.78–3.87)	0.052
Other location‡	34 (2.3)	0.43 (0.06–3.20)	–	0.999
Sum atypical§ location	77 (5.2)	0.27 (0.07–1.13)	1.24 (0.57–2.68)	0.068
Character				
Tight/crushing	960 (63.7)	1.06 (0.67–1.65)	0.92 (0.55–1.52)	0.323
Dull/heavy	81 (5.4)	0.39 (0.09–1.64)	1.90 (0.81–4.45)	0.074
SUM typical¶ character	1033 (68.6)	1.36 (0.68–2.71)	1.76 (0.76–4.06)	0.961
Burning	89 (5.9)	2.01 (0.98–4.10)	2.00 (0.85–4.69)	0.992
Stinging	218 (14.5)	0.41 (0.19–0.86)	0.48 (0.17–1.39)	0.829
Other atypical	2 (0.1)	1.04 (0.99–1.10)	1.02 (0.96–1.09)	0.641
Sum atypical** character	299 (19.9)	0.76 (0.43–1.34)	1.11 (0.55–2.24)	0.407
Unknown	263 (17.5)	1.45 (0.87–2.44)	1.21 (0.67–2.17)	0.638
Typical pain††	981 (66.8)	1.41 (0.75–2.68)	1.83 (0.86–3.90)	0.607
Atypical pain‡‡	224 (15.3)	0.71 (0.37–1.34)	0.55 (0.26–1.16)	0.607
Radiation				
Multiple directions	298 (19.8)	1.84 (1.17–2.89)	1.36 (0.74–2.52)	0.436
Both arms	66 (4.4)	12.50 (6.58–23.75)	5.35 (2.26–12.62)	0.119
Left arm	296 (19.7)	**0.73 (0.42–1.28)**	**1.67 (0.93–3.00)**	**0.045**
Right arm	20 (1.7)	0.73 (0.09–5.62)	1.03 (0.12–8.94)	0.82
Both shoulders	25 (1.7)	0.73 (0.09–5.62)	3.05 (0.87–10.68)	0.242
Left or right shoulder	92 (6.1)	0.14 (0.02–0.98)	0.20 (0.03–1.53)	0.777
Jaw	321 (21.3)	1.53 (0.97–2.41)	1.29 (0.70–2.38)	0.65
Epigastrium or abdomen	38 (2.5)	0.74 (0.17–3.16)	2.30 (0.58–9.09)	0.267
Back	189 (12.5)	1.31 (0.73–2.34)	2.59 (0.23–28.97)	0.792
Numbness upper extremities	128 (8.5)	1.15 (0.59–2.24)	1.31 (0.48–3.60)	0.843
Any radiation	789 (52.4)	1.47 (0.95–2.27)	2.25 (1.33–3.79)	0.223
Unknown	26 (1.7)	2.64 (0.72–9.62)	1.74 (0.46–6.60)	0.662
Additional symptoms§§				
Shortness of breath	628 (41.7)	1.03 (0.68–1.57)	1.14 (0.69–1.88)	0.757
Nausea	318 (21.1)	0.75 (0.43–1.29)	1.23 (0.68–2.20)	0.225
Vomiting	43 (2.9)	1.68 (0.57–4.96)	3.27 (1.15–9.27)	0.386
Diaphoresis or clamminess	287 (19.1)	1.90 (1.21–2.99)	1.86 (1.02–3.38)	0.953
Palpitations	174 (11.6)	0.61 (0.28–1.35)	0.72 (0.33–1.58)	0.777
Dizziness	226 (15.0)	0.39 (0.18–0.86)	0.38 (0.15–0.98)	0.966
Sum typical¶¶ add. symptoms	1005 (66.7)	0.97 (0.63–1.51)	1.01 (0.60–1.70)	0.898

Continued

Table 4 Continued

	N of total (%)	<70 years(n=1039)	≥70 years (n=467)	P value for interaction
Dependent of stature	124 (8.2)	0.41 (0.15–1.15)	0.50 (0.15–1.66)	0.824
Dependent of respiration	149 (9.9)	0.23 (0.07–0.73)	0.15 (0.02–1.11)	0.72
Pain on palpation	177 (11.8)	0.44 (0.19–1.03)	0.29 (0.09–0.97)	0.586
Sum atypical*** add. symptoms	351 (23.3)	0.28 (0.14–0.57)	0.28 (0.12–0.67)	0.995
Effect of NG	268 (17.8)	1.23 (0.56–2.71)	2.18 (0.87–5.50)	0.356
Onset of symptoms				
During physical activity	285 (18.9)	3.32 (2.14–5.16)	2.42 (1.39–4.22)	0.382
After physical activity	72 (4.8)	1.47 (0.64–3.34)	1.06 (0.30–3.76)	0.675
Acute or chronic psychologic stress	115 (7.6)	0.19 (0.05–0.77)	0.60 (0.14–2.63)	0.26
During rest	1027 (68.2)	0.45 (0.30–0.69)	0.52 (0.31–0.87)	0.697
Unknown	18 (1.2)	2.40 (0.50–11.47)	3.17 (0.74–13.57)	0.798
Symptom duration				
<30 min	377 (25.0)	0.86 (0.53–1.39)	1.32 (0.74–2.34)	0.333
30–60 min	84 (5.6)	1.60 (0.73–3.48)	1.18 (0.43–3.22)	0.574
60 min to 24 hours	482 (32.0)	1.36 (0.88–2.09)	1.63 (0.99–2.70)	0.748
>24 hours	155 (10.3)	0.08 (0.01–0.58)	0.20 (0.05–0.85)	0.489
Terminated by NG	88 (5.8)	1.92 (0.94–3.91)	1.24 (0.45–3.40)	0.428
Terminated by morphine	37 (2.5)	1.60 (0.46–5.53)	0.33 (0.04–2.60)	0.196
Unknown	283 (18.8)	0.86 (0.49–1.50)	0.63 (0.32–1.24)	0.494
Intensity of pain in intervals†††	1506 (100)	1.51 (1.05–2.18)	1.70 (1.14–2.55)	0.662
Last 24 hours				
Exertional chest pain >once	48 (3.2)	2.33 (0.86–6.31)	1.15 (0.38–3.50)	0.356
Last week				
Exertional chest pain	268 (17.8)	**4.08 (2.63–6.34)**	**1.81 (1.03–3.15)**	**0.025**
Shortness of breath	60 (4.0)	1.16 (0.40–3.34)	1.46 (0.53–4.06)	0.758
Pain similar to previous infarction	57 (3.8)	0.55 (0.13–2.32)	0.85 (0.25–2.97)	0.652

Statistically significant differences highlighted
*In patients having chest pain at presentation.
†Summation of traditionally considered typical pain location like retrosternal, precordial, other parts of thorax, shoulder, arms, jaw or neck.
‡Summation of pain in the back and all other non-typical locations.
§Summation of traditionally considered atypical pain location like epigastrium, abdomen, back or other locations.
¶Summation of traditionally considered typical pain character like tight, crushing, dull or heavy.
**Summation of traditionally considered atypical pain character like burning, stinging or other.
††Typical pain is defined as the combination of traditionally considered typical location and typical character.
‡‡Atypical pain is defined as either atypical location or atypical character, or both.
§§If not stated considered negative.
¶¶Summation of traditionally considered typical additional symptoms like shortness of breath, nausea, vomiting. diaphoresis, clamminess, palpitations or dizziness.
***Summation of traditionally considered atypical additional symptoms like pain dependent of position, respiration or palpation.
†††Four groups; no pain; Visual analogue scale (VAS) 1–3.5; VAS 3.5–6.5; VAS>6.5.
AMI, acute myocardial infarction; NG, Nitroglycerin; NSTEMI, non-ST segment elevation myocardial infarction.

Since first described as a typical symptom by Heberden,[23] radiation to the left arm has been found to be less predictive of AMI than radiation to right arm or both arms.[24–27] Two recent studies found a relatively low OR just below 1.5 for AMI if left-sided radiation was present.[12 13] Our neutral OR of 1.05 (95% CI 0.71 to 1.56) might be due to the exclusion of STEMI patients, but also seem part of a trend where radiation to the left arm is less predicative of AMI than assumed some decades ago.

International guidelines including the new ESC guidelines state that women more often than men present with atypical symptoms.[28] Indeed, earlier studies found that women with coronary disease more often present without chest pain or report other symptoms as their main

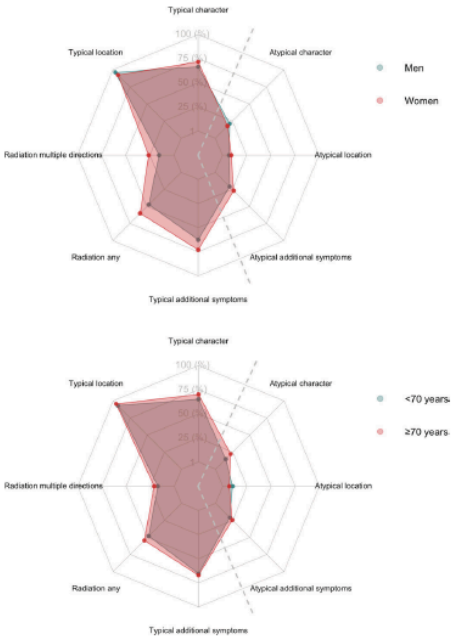

Figure 1 Incidence of traditionally considered typical and atypical chest pain symptoms in women/men and younger/older patients presenting with suspected ACS. ACS, acute coronary syndrome.

complaint.[7 10 29 30] Studies also found that women more often than men have additional symptoms like jaw pain, back pain and nausea.[8 9 31–33] Our study does not support that large sex differences are evident during presentation for NSTEMI, and the frequencies of what has traditionally been regarded typical symptoms in patients presenting with suspected ACS were similar across groups. Moreover, the odds of actually having an NSTEMI if the pain had both typical character and location was not lower in women. We do not find that women have higher odds of NSTEMI compared with men if they report radiating pain or additional symptoms like shortness of breath and nausea. Women with NSTEMI also reported anginal pain prior to their infarction and pain onset was just as often during activity.

In our study, we demonstrate that a few symptoms may be more or less pronounced depending on age groups. One limitation in the earlier studies were the lack of adjustment for age[31] which makes it difficult to assess if any observed difference is a result of age or sex. The women in our study are on average 4.7 years older than men, and some symptoms suggestive of NSTEMI in women also apply for the oldest patient group. However, for most symptoms like location, character, pain prior to admission and trigger factors the interaction between traditionally considered atypical symptoms and age is stronger than the interaction between atypical symptoms and sex. These findings suggest that older patients have higher risk of actually having an NSTEMI if traditionally considered atypical symptoms are present compared with women as a group.

None of the LRs calculated for single symptoms in our contemporary cohort are extremely high or extremely low. This probably reflects the clinical presentation of ACS showing a heterogeneous mix of symptoms being present with different intensity and frequency in individual patients. Some characteristics like chest pain radiating to both arms (LR 7.76) and any additional symptom considered atypical (LR 0.34) seem valuable for initial risk stratification. In line with previous studies our investigation shows that evaluation of symptoms should only be one of several elements to which the decision on further cardiac examinations is based on.

Strengths and limitations

The strength of this study is the inclusion of a large cohort of patients with chest pain being evaluated for AMI rather than having a confirmed diagnosis of AMI. The inclusion criteria were wide ensuring a representative patient population regarding age and co-morbidity. Diagnoses were based on a standard and robust adjudication process, and 89% of patients were observed in hospital for at least 8 hours with three or more high-sensitivity troponin measurements.

The study, however, has some limitations. Information was gathered retrospectively through digital charts. Even though information came from two or more sources (general practitioner and/or ambulance log in addition to hospital physicians at admission), the presence or absence of some additional symptoms were not reported in all patients. Symptoms not mentioned by any source were considered not present, which may have introduced a bias in particular for the five additional symptoms that were unequally reported between patients with and without NSTEMI (online supplemental table 1).

Another limitation is the lack of completely consecutive inclusion. This is a problem notified in similar studies due to the logistic challenges related to an around the clock all week inclusion in the ED. This inclusion procedure ensures that diurnal rhythm or differences between weekends and working days are unlikely to influence the results, but the lack of completely consecutive inclusion could lead to a selection bias as patients with minor disease might be easier to include during busy hours in the ED. If the data are skewed towards more patients with less sever disease (and less pronounce clinical symptoms) being included, this is more likely to underestimate our findings compared with overestimate them for example, the OR for radiation to both arms as a sign of ACS could in reality be higher than 9.4, and minor differences between gender and age groups could also be unnoticed.

The slightly lower rate of AMI seen in our compared with similar studies[12 13] indicating that such selection bias may have influenced our data, but could also be due to not including STEMI patients. Patient characteristics is otherwise similar in our and other studies focusing on a rapid diagnosis of NSTEMI.

Since patients with STEMI were not included in the study, our findings may not be representative for this group. Few studies have compared symptoms of STEMI versus NSTEMI, but some typical signs like central location, nausea and diaphoresis may be less frequent in patients with NSTEMI compared with STEMI.[27] Since 97.4% of patients presented with chest pain or discomfort, our data should not be regarded valid for non-chest pain AMI. Possible sex or age differences in these subgroups should be evaluated in other studies.

We did not correct for multiple testing. If a p value of 0.01 had been regarded significant instead of 0.05, none of the observed interactions between sex and symptoms or age and symptoms had been statistically significant. This should be interpreted as strengthening the assumption that differences in symptom prediction based on group stratification is uncertain.

Finally, many cardiac centres have lately implemented sex-specific troponin T upper reference limits (URLs) for the evaluation of AMI. Our study uses a sex-neutral cut-off since this was recommended when the study was planned in 2012. Only one of the 597 female patients in our study would be reclassified from UAP to NSTEMI if URL was lowered from 14 ng/L to 9 ng/L. No male patients would be reclassified from NSTEMI to unstable angina if URL was raised from 14 ng/L to 16 ng/L. Changing the URL did not affect the observed results.

Conclusion

Chest pain with radiation to both arms has the highest predictive value for identification of NSTEMI regardless of sex and age. Presenting symptoms for NSTEMI are overall similar to those earlier reported for STEMI and vary little between sex and age groups in a contemporary cohort of patients with suspected NSTE-ACS assessed using a hs-Tn.

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Contributors O-TS conceived the research question, collected and analysed the data and drafted the manuscript. O-TS, KMA, KV and TO developed the study design and contributed in data acquisition and analysis. HLT participated in data collection and provided critical revision. ROB, ØS, VVSB and ØRM took part in the early planning of the study design and provided critical revision. JL is the article guarantor, accepts full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish. All acknowledged coauthors revised the article critically for its intellectual content and approved the final manuscript for submission.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s)

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ORIGINAL SCIENTIFIC PAPER

Clinical risk scores identify more patients at risk for cardiovascular events within 30 days as compared to standard ACS risk criteria: the WESTCOR study

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Aims Troponin-based algorithms are made to identify myocardial infarctions (MIs) but adding either standard acute coronary syndrome (ACS) risk criteria or a clinical risk score may identify more patients eligible for early discharge and patients in need of urgent revascularization.

Methods and results Post-hoc analysis of the WESTCOR study including 932 patients (mean 63 years, 61% male) with suspected NSTE-ACS. Serum samples were collected at 0, 3, and 8–12 h and high-sensitivity cTnT (Roche Diagnostics) and cTnI (Abbott Diagnostics) were analysed. The primary endpoint was MI, all-cause mortality, and unplanned revascularizations within 30 days. Secondary endpoint was non-ST-elevation myocardial infarction (NSTEMI) during index hospitalization. Two combinations were compared: troponin-based algorithms (ESC 0/3 h and the High-STEACS algorithm) and either ACS risk criteria recommended in the ESC guidelines, or one of eleven clinical risk scores, HEART, mHEART, CARE, GRACE, T-MACS, sT-MACS, TIMI, EDACS, sEDACS, Goldman, and Geleijnse–Sanchis. The prevalence of primary events was 21%. Patients ruled out for NSTEMI and regarded low risk of ACS according to ESC guidelines had 3.8–4.9% risk of an event, primarily unplanned revascularizations. Using HEART score instead of ACS risk criteria reduced the number of events to 2.2–2.7%, with maintained efficacy. The secondary endpoint was met by 13%. The troponin-based algorithms without evaluation of ACS risk missed three-index NSTEMIs with a negative predictive value (NPV) of 99.5% and 99.6%.

Conclusion Combining ESC 0/3 h or the High-STEACS algorithm with standardized clinical risk scores instead of ACS risk criteria halved the prevalence of rule-out patients in need of revascularization, with maintained efficacy.

Keywords Chest pain • High-sensitivity troponin assay • ESC 0/3 h algorithm • High-STEACS • Risk score • Revascularization

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Introduction

Chest pain is a frequent cause of admittance to the emergency department (ED).[1] Many patients have non-cardiac causes of pain that could be handled outside of hospitals, implying an unnecessary high burden on the healthcare system. Early rule-out of patients unlikely to have acute coronary syndrome (ACS) can ease the pressure on crowded EDs and reduce unnecessary examinations in low-risk patients.

The introduction of high-sensitive troponin assays and rapid rule-out or rule-in algorithms for non-ST-elevation myocardial infarction (NSTEMI) have led to swift and safe identification of these patients[2–6] and are recommended by the European Society of Cardiology (ESC).[7] Patients with unstable angina pectoris (UAP) may present similar history, clinical, and electrocardiographic (ECG) findings. Concentrations of cTn, however, are stable and often low, and troponin-based algorithms are hence less useful. Even though patients with UAP have lower mortality rates than patients with NSTEMI, the possible pitfalls of a troponin-centred evaluation might partly explain the slow implementation of troponin-based rule-out/rule-in algorithms as reported in the literature.[8] Even in Europe, where high-sensitivity troponin assays (cTn) have been available for more than 10 years, only 60% of laboratories use high-sensitivity assays, and only half use serial sampling of ≤3 h.[9]

To avoid patients with UAP being discharged without correct diagnosis (pending further examinations), clinical gestalt may be sufficient in EDs with continuous presence of experienced physicians. A recent study showed that physicians correctly overruled the ESC 0/1 h algorithm in most patients who were in need of revascularization, preventing early discharge of patients with UAP.[10] However, the use of clinical gestalt is questioned, and other studies show fairly low diagnostic accuracy.[11,12] A reasonable supplement might, therefore, be use of standardized clinical risk scores, developed and validated to identify patients with high risk of coronary artery disease.[13] The main goal of this study was to replace the ACS risk criteria recommended in ESC guidelines with standardized clinical risk scores in a double rule-out algorithm and measure the optimal combined diagnostic performance for ACS. We assessed the ESC 0/3 h rule-out algorithms, the High-STEACS algorithms and 11 different clinical risk scores' ability to identify patients in need of immediate follow-up for ACS after hospitalization due to chest pain [composite endpoint of non-fatal myocardial infarction (MI), all-cause mortality or unplanned revascularization]. Furthermore, we evaluated the same diagnostic tools for a secondary endpoint defined as NSTEMI during index hospitalization.

Methods

Study design and population

The Aiming Towards Evidence-Based Interpretation of Cardiac Biomarkers in Patients Presenting with Chest Pain (WESTCOR) is a cross-sectional and prospective observational study conducted at two University hospitals in Norway (Clinical Trial NCT02620202).[14] The current article contain data from the WESTCOR derivation cohort (WESTCOR-D) including 984 patients form Haukeland University Hospital. The study was conducted according to the Declaration of Helsinki and approved by the regional ethics committee (REC number 2014/1365).

Patients >18 years who were admitted to the ED from September 2015 to February 2017 with suspected NSTE-ACS were eligible for inclusion, irrespective of symptom onset. Patients transferred from other hospitals, those unable to provide informed consent or with a short life expectancy, e.g. terminal cancer, were excluded (*Figure 1*). For this analysis, patients missing measurements of either cTnT or cTnI at presentation or after 3 h were excluded.

Data collection

After admittance, all patients underwent clinical assessment including clinical history, risk factors, assessment of vital parameters, physical examination, ECG, and standard blood tests. The treatment was left at the discretion of the attending physician at hospitals adhering to the ESC guidelines for the treatment of acute coronary syndromes (2015) and the third universal definition of MI (2012). Information needed to assess the risk scores was collected retrospectively based on information in electronic medical records provided by ambulance personnel, referring physicians, and hospital physicians at presentation. In cases where pre-hospital and in-hospital personnel gave conflicting information, data provided by hospital physicians were used.

Troponin analysis

Blood samples for routine measurements and biobank were collected at arrival and after 3 and 8–12 h. cTnT analysis was performed in fresh serum samples using the high-sensitivity assay from Roche Diagnostics with a limit of blank (LoB) of 3 ng/L, a limit of detection (LoD) of 5 ng/L, and a 99th percentile of 14 ng/L as described by the manufacturer. The analytical within-series coefficient of variation (CV_A) was 10% at 4.5 ng/L. cTnI was analysed in biobanked first thawed serum samples that had been stored at -80 C until analysis for cTnI from Abbott Diagnostics with an LoB at 0.9 ng/L, LoD at 1.7 ng/L, and a 99th percentile of 26 ng/L.[15]

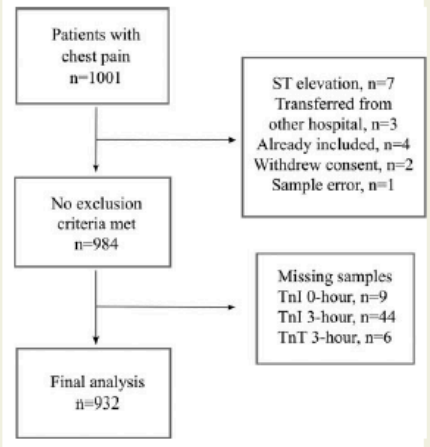

Figure 1 Patients included in final analysis.

Adjudication

The final diagnosis was adjudicated by two independent cardiologists based on all available clinical data, routine laboratory tests including high-sensitivity cTnT as described above (but not cTnI), 12-lead ECG, ultrasound, chest radiography, exercise tests, coronary computed tomography angiography, and conventional angiography. In cases of disagreement, the diagnosis was adjudicated by a third cardiologist. Totally 845 (91%) of patients had three or more cTnT measurements with the last sample drawn at least 8 h after presentation, while only 87 patients (9%) had blood samples drawn at 0 and 3 h only. Specific diagnostic criteria were predefined for 22 different medical conditions based on current guidelines (Supplementary material online).[14] Non-ST-elevation myocardial infarction was defined according to the third universal definition for MI, a definition that remain unchanged in the fourth definition that was published after planning and onset of this study.[16] A 20% (if baseline cTnT concentration were >14 ng/L) or 50% (if baseline cTnT concentration were ≤14 ng/L) change in troponin concentration was regarded significant. Unstable angina pectoris was defined as angina at rest with prolonged duration (>20 min), crescendo angina, recent destabilization of stable angina, or post-MI angina, with stable serial troponin concentrations.

Follow-up and endpoints

This article is a post-hoc analysis with a primary endpoint of CV events: non-fatal MI (Type 1 and Type 2), all-cause mortality, and unplanned revascularization, including intention to treat. Secondary endpoint was NSTEMI during index hospitalization. Information on cardiac events and mortality within 30 days was collected from patient files and the Norwegian Patient Register and Norwegian Cause of Death Registry, which are under Norwegian legislation and register all hospital provided healthcare and deaths in Norway.

Troponin-based rule-out pathways

The ESC 0/3 h algorithm recommends rule-out of MI if the troponin concentration at presentation is below the gender-neutral 99th percentile, onset of symptoms >6 h before presentation and the ECG is non-ischaemic. GRACE (Global Registry of Acute Coronary Events) score is used for prognostic risk stratification, and patients with a score below 140 is eligible for stress testing and/or early discharge[7] (*Figure 2*). Serial sampling with re-testing 3 h after admittance is recommended in patients with onset of symptoms <6 h before presentation. Myocardial infarction is ruled out if cTn is below the gender-neutral 99th percentile or without significant change, defined as >50% of URL.[17]

The High-STEACS pathway rules out MI if levels of troponin I or T is <5 ng/L at presentation, onset of symptoms is >2 h before presentation and the ECG is non-ischaemic.[18] If symptoms appeared <2 h before presentation, a second blood sample is collected 3 h later, with MI ruled out if the change in troponin concentration is <3 ng/L and still below the gender-neutral 99th percentile of 14 ng/L for cTnT (Roche Elecsys) or gender-specific 99th percentiles of 16 ng/L (females) and 34 ng/L (males) for cTnI (Abbott Architect).

For the analysis of High-STEACS we used the same 99th percentiles as used in previous studies[3,19] (gender-specific for cTnI and gender-neutral for cTnT) compared with gender-neutral 99th percentiles for the ESC 0/3 h algorithms.[7]

ESC low risk of ACS criteria and clinical risk scores

According to the ESC guidelines, chest pain patients may be regarded low risk of ACS if they exhibit no very-high/high-risk criteria (haemodynamic instability, recurrent chest pain, life-threatening arrythmias, mechanical complications, acute heart failure, recurrent ST-T wave changes, Tn dynamics, or GRACE score >140) or intermediate-risk criteria (diabetes mellitus, eGFR <60, left ventricular ejection fraction <40%, early post-infarction angina, prior percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), or GRACE score >109).

We included a wide range of standardized clinical risk scores in the evaluation; HEART,[20] CARE,[21] GRACE,[22,23] T-MACS,[24] sT-MACS,[25] TIMI,[26] EDACS,[27] sEDACS,[28] Goldman,[29] and Geleijnse-Sanchis.[30] Components are summarized in *Table 1*. Some of these scores were not developed or validated in low-risk populations (i.e. TIMI), and some are prognostic rather than diagnostic (i.e. GRACE score). Hence, a low accuracy in identifying coronary artery disease (CAD) in low-risk patients do not mean the risk score is less useful in its intended area of use.

The main criteria for being included was population size $n > 1000$ and external validation. Less established risk scores were identified using the search term 'chest pain risk score' in PubMed, but most were dismissed due to small sample size or similarity to other risk score, i.e. several varieties of the TIMI risk score have been developed. Goldman score is chosen as a representative for one of the earliest risk scores, while Geleijnse–Sanchis, although performed in a small cohort ($n = 646$) and not being validated, includes parameters found exclusively in this risk scores, including a thorough symptom evaluation score. CARE score ($n = 650$) is similar to HEART, but without troponin measurements, a potential easy-to-use tool in facilities without access to troponin assays. We also evaluated a modified HEART score (mHEART) where only patients with undetectable troponin values (i.e. cTnT <5 ng/L) would be awarded zero troponin points. Detectable (i.e. cTnT ≥ 5 ng/L), but non-elevated troponins would be given 1 point and elevated troponins (i.e. >14 ng/L) 2 points.[31]

Statistics

The baseline characteristics were reported as means (±2 SD) for normally distributed data and median with 25 and 75 percentiles for non-normally distributed data. Differences between groups were compared using Pearson χ^2 test or Fisher's exact test (if $n < 5$ per group) for binominal distributed data, means with 95% confidence interval (CI) for normally distributed data and Mann–Whitney *U* test for non-normally distributed data. Safety of the troponin-based rule-out algorithms and risk scores were assessed using sensitivity and NPV, and difference in sensitivity was assessed using McNemar's test. Efficacy was quantified as proportion of patients ruled out by the different algorithms. Accuracy for the given threshold was assessed using the formula Sensitivity × Prevalence + Specificity × (1 − Prevalence). Risk scores are continuous variables, and area under the receiver operating characteristics curve (AUROC) served as an additional indicator of accuracy. For the combination of troponin-based algorithms (categorical variable) and risk scores (continuous variable), we created a combined variable using binominal logistic regression. Differences in AUROC were evaluated using Delong test. Hypothesis testing was two-tailed, and *P*-values <0.05 were considered statistically significant. Analysis was performed using IBM SPSS Statistics version 24.0.0.1 for Windows (IBM Statistics, Chicago, IL, USA) and MedCalc version 17.6 for Windows (MedCalc Software bvba, Ostend, Belgium).

Results

Baseline characteristics

The median age of patients was 63 years, and 60% were male. Non-ST-elevation myocardial infarction was diagnosed in 13% of patients ($n = 124$), unstable angina in 11% ($n = 106$), other cardiac diseases in

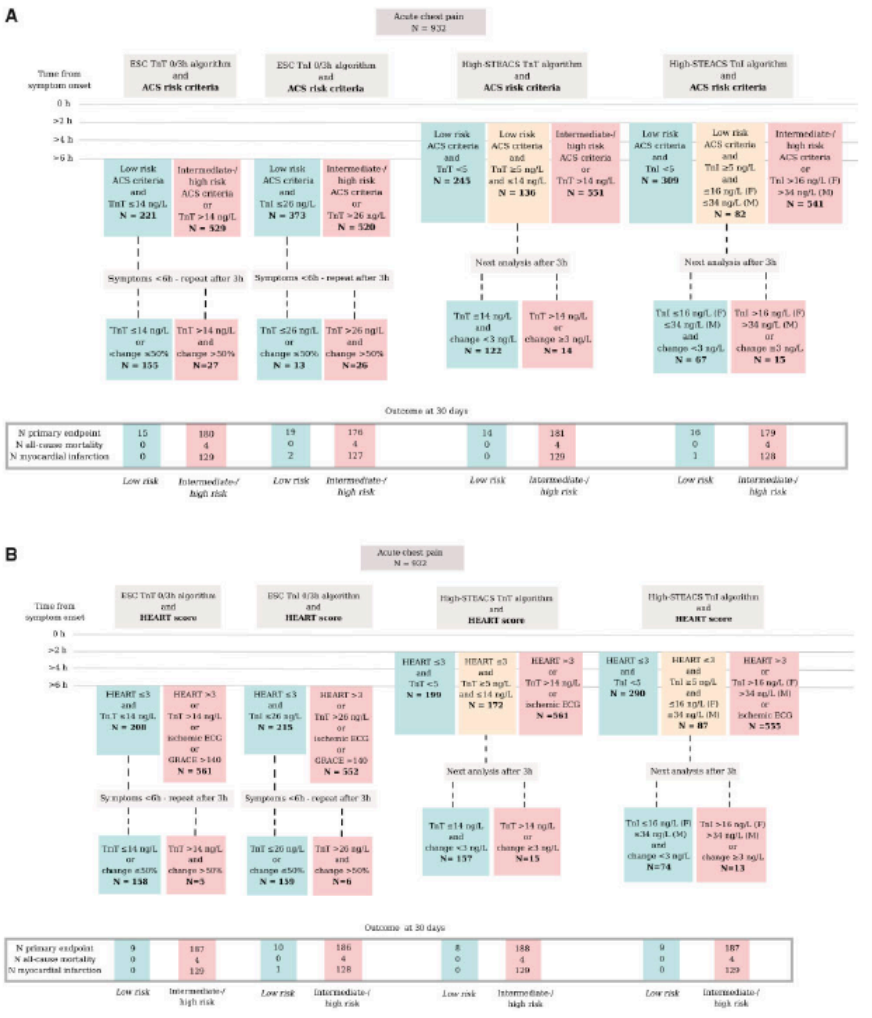

Figure 2 (*A*) Summary of the ESC 0/3 h and High-STEACS algorithms, number of patients allocated to rule-out or none-rule-out at presentation or 3 h and outcome within 30 days. (*B*) Summary of the ESC 0/3 h and High-STEACS algorithms combined with HEART score, number of patients allocated to rule-out or none-rule-out at presentation or 3 h and outcome within 30 days.

Table 1 Components of 10 different risk scores and mHEART

	History	Age	ECG	Risk factors	Troponin levels	Known CAD	Angina	SBP	Other	Low risk
HEART (2008)	Typical = 2p Atypical = 1p	>65 = 2p >45 = 1p	ST-dep = 2p Other = 1p	≥3 or CAD = 2p ≥1 = 1p	≥3 × 99th = 2p ≥99th = 1p					≤3p
mHEART (2017)	Typical = 2p Atypical = 1p	>65 = 2p >45 = 1p	ST-dep = 2p Other = 1p	≥3 or CAD = 2p ≥1 = 1p	≥99th = 2p Measurable = 1p					≤3p
CARE (2018)	Typical = 2p Atypical = 1p	>65 = 2p >45 = 1p	ST-dep = 2p Other = 1p	≥3 or CAD = 2p ≥1 = 1p						≤1p
TIMI (2000)		>65 = 1p	ST-changes >0.5 mm = 1p	≥3 = 1p	>99th = 1p	1p	Severe = 1p		Aspirin used within 7 days = 1p	≤1p
GRACE (2003/2004)		0–100p	ST-changes >0.5 mm = 17p		>99th = 14p			0–40p	Pulse = 0–34p Creatinine = 0–28p Cardiac arrest = 30p Killip class = 0–44p	≤108p ≤89p
EDACS (2014)	Diaphoresis = 3p Radiation[a] = 5p Resp. pain = -4p Reproduced by palpation = -6p	2–20p		≥3 or CAD[b] = 4p					Male gender = 6p	≤15p
sEDACS (2016)	Radiation[a] = 1p	0–6p		≥3 or CAD = 1p					Male gender = 1p	≤3p
T-MACS[c] (2017)	Diaphoresis = d Radiation[e] = r Vomiting = v		Ischaemia = i		By degree of elevation = t		Crescendo = c	<100 = h		≤0.02
sT-MACS (2018)	Diaphoresis = 1p Radiation[e] = 1p Vomiting = 1p		Ischaemia = 1p		TnT >9 ng/L = 1p		Crescendo = 1p	<100 = 1p		≤0p
Geleijnse–Sanchis (2005)	>10 symptom points = 1p	≥67 = 1p		DM[d] = 2p		1p	Severe = 1p			≤1p
Goldman (1996)			Ischaemia = high risk				Crescendo = 1p	<110 = 1p	Bilateral pulmonary rales = 1p	≤1p

CAD, coronary artery disease; CARE, characteristics, age, risk factors, EGG; EDACS, Emergency Department Assessment of Chest Pain Score and MI, myocardial infarction; GRACE, Global Registry of Acute Coronary Events; HEART, History, ECG, Age, Risk factors, Troponin; mHEART, modified HEART score with troponin points given if hs-Tn is measurable; SBP, systolic blood pressure; TIMI, Thrombolysis In Myocardial Infarction; T-MACS, troponin-only Manchester Acute Coronary Syndromes.
[a]To *any* shoulder/arm/jaw.
[b]Age 18–50 years.
[c]Percentage risk of ACS calculated using the following formula: p = 1/(1 + e^ - (1.713i + 0.847c + 0.607r + 1.417v + 2.058d + 1.208h + 0.089t - 4.766)), where hs-TnT is continuous and the other factors dichotomous.
[d]Demanding insulin.
[e]To *right* arm/shoulder.

7.2% ($n = 67$), and non-cardiac chest pain in 68% ($n = 635$). Patients with ACS were older, had more risk factors for cardiovascular disease and used more mediations than patients without ACS (*Table 2*). Time from symptom onset to arrival was median 8 h. About 97 patients (10.4%) had onset of symptoms <2 h before presentation. Coronary computed tomography angiography was performed in 33.0% of the patients, while 8.4% had an angiography without further treatment. About 16.5% were treated with either PCI or CABG. Revascularization was performed in 89/124 (71.8%) of patients with NSTEMI and 58/106 (54.7%) of patients with UAP (Supplementary material online, *Table S1*).

Symptoms indicating ACS ($P < 0.05$) were retrosternal location of chest pain, radiation to both arms, effect of nitroglycerine, debut during physical activity, and pain duration between 1 and 30 min. Symptoms indicating non-ACS was chest pain with stinging character, dependence on stature or respiration, accompanied dizziness, reproducibility upon palpation, history of chronic psychological stress, debut during rest, and pain duration >24 h. Of note, severity of pain (Numeric Rating Scale), pain described as pressing, radiation of pain to the left arm/shoulder or to the jaw, shortness of breath, and nausea were not significantly associated with ACS. A detailed description of patient characteristics including symptoms, medication at admission, and treatment during the ED stay is given in Supplementary material online, *Tables S1* and *S2*.

Patients with NSTEMI had significantly higher cTn values at admission than patients with UAP (median cTnT 50 vs. 9 ng/L, $P < 0.001$, cTnI 121 vs. 5 ng/L, $P < 0.001$; *Table 3*).

Primary endpoint

Within 30 days 194 patients (21%) experienced a composite endpoint of non-fatal MI, all-cause mortality, or unplanned revascularization. Of these, 4 patients died and 128 had a MI (*Figure 2A*). Excluding the 124 patients with index NSTEMI, 70 of 807 patients (8.7%) reached an endpoint. Three patients died, 5 had a non-fatal MI after discharge, and 62 underwent unplanned revascularization.

Troponin-based algorithms and prediction of the primary endpoint

The four troponin algorithms combined with ACS risk criteria showed similar AUC (0.70–0.71), sensitivity (90–93%), and NPV (95–96%) for the identification of MI, mortality, or unplanned revascularization, with slightly more patients regarded low risk by the ESC algorithms (40.3% vs. 39.4%, $P < 0.01$ for ESC cTnT vs. High-STEACS cTnT). Number of primary endpoints among patients with low risk of ACS was 4.0–4.9% (ESC 0/3 h) and 3.8–4.3% (High-STEACS), see *Figure 2A*. In total, no patients died, 0–0.5% experienced an MI (ESC 0/3 h cTnT: 0 patients; ESC 0/3 h cTnI 2 patients; High-STEACS cTnT: 0 patients; High-STEACS cTnI: 1 patient), and 3.8–4.4% underwent unplanned revascularization (ESC 0/3 h cTnT; 15 patients; ESC 0/3 h cTnI 17 patients; High-STEACS cTnT: 14 patients; High-STEACS cTnI: 15 patients).

Risk scores

The risk scores with highest AUC were HEART and T-MACS ($P < 0.05$ compared to the other risk scores). Both had a sensitivity of 91–92% and an NPV of 96% for the primary endpoint (*Table 4*), and the percentages identified as low risk were 39–42%. Number of primary endpoints in the low-risk groups were 4.3% (HEART ≤3) and 4.4% (T-MACS ≤0.02). The algorithms differ in which patients they fail to identify. HEART missed more patients with NSTEMI (8 vs. 1), while T-MACS missed more patients with unplanned revascularization (15 vs. 9). None of the ruled-out patients died. HEART >3 and T-MACS >0.02 identified 85% and 76% of the 62 patients who underwent unplanned revascularization, respectively.

Combination of troponin algorithms and risk scores

When the ACS risk criteria recommended in ESC guidelines were replaced by clinical risk scores, NPV, and sensitivity increased without reduced efficacy. Troponin-based algorithms combined with HEART ≤3, mHEART ≤3, or T-MACS ≤0.02 showed similar AUC ($P > 0.05$). The combinations including HEART score showed a sensitivity of 95–96% and NPV ~97.5%, see *Table 4*. mHEART, which increases at even the slightest rise in troponin values, showed sensitivity of 98%, but allocated less than one-third of patients to low risk. T-MACS had a sensitivity of 92% and allocated <40% to low risk. The combination of ESC 0/3 h algorithms or High-STEACS with any of the eight remaining risk scores showed significantly lower AUC for the primary endpoint.

Replacing the ACS low-risk criteria with HEART score ≤3 resulted in 10–12 less patients being classified as low risk but reduced the number of false negatives by almost the same number (6–9 patients). Low-risk patients (9–10, 2.2–2.7%) experienced a primary event, almost exclusively unplanned revascularizations. HEART combined with the ESC 0/3 h cTnT algorithm or High-STEACS identified all MIs and deaths, while one MI was missed using the cTnI version of ESC 0/3 algorithm. Supplementary material online, *Tables S4* and *S5* for information about the ACS patients missed by the different algorithms.

Secondary endpoint

The ESC 0/3 h cTnT and High-STEACS cTnT algorithms (without evaluation of ACS low-risk criteria) missed 2–3 NSTEMIs, with sensitivity 97.6–98.4% and NPV 99.5–99.7% (*Table 5*). The proportion of low-risk patients ranged from 62% to 76% across the different algorithms. The two cTnI algorithms (ESC 0/3 h cTnI and High-STEACS cTnI) ruled out MI in a larger number of patients than the cTnT-based (ESC 0/3 h cTnT and High-STEACS cTnT) algorithms (71–76% vs. 62–64%, $P < 0.001$).

Most of the clinical risk scores performed worse compared to the troponin-based algorithms. The mHEART, CARE, and T-MACS scores showed comparable sensitivity of 99.2–100%, with fewer patients eligible for rule-out, between 10.3% and 39.1% (*Table 5*).

Discussion

In this post-hoc analysis of a prospective single-centre study of unselected patients presenting with chest pain, we show that the combination of troponin-based algorithms and a clinical risk score is superior to troponin-based algorithms combined with standard ACS risk criteria for detection of the combined endpoint of non-fatal MI, all-cause mortality, and unplanned revascularizations within 30 days. The

Table 2 Baseline characteristics of the study population by cause of chest pain

	All patients, $n = 932$	ACS, $n = 230$	Non-ACS, $n = 702$	*P*-value
Baseline characteristics				
Age, years	63 (52–74)	68 (59–78)	61 (50–73)	<0.001
Male, %	562 (60.3)	163 (70.9)	399 (56.8)	<0.001
Symptom to arrival time, h	8.0 (3–45)	8.0 (3–38)	8.1 (3–47)	0.883
Hospital stay, h	28 (21–68)	74 (52–115)	25 (19–45)	<0.001
Risk factors				
Hypertension, %	383 (41.1)	115 (50.0)	268 (38.2)	0.001
Hyperlipidaemia, known %	180 (19.3)	61 (26.4)	119 (17.0)	0.002
Hyperlipidaemia, new[a], %	85 (9.1)	24 (10.4)	61 (8.7)	0.440
Diabetes mellitus, %	116 (12.4)	49 (21.2)	67 (9.6)	<0.001
Insulin-dependent	37 (4.0)	15 (6.5)	22 (3.1)	0.021
Family history, %	188 (20.2)	43 (18.6)	145 (20.7)	0.497
Unknown	109 (11.7)	30 (13.0)	79 (11.3)	0.481
Current smoker, %	195 (20.9)	49 (21.2)	146 (20.8)	0.901
Previous smoker, %	399 (42.8)	89 (38.5)	310 (44.2)	0.129
Medical history				
Prior MI, %	197 (21.7)	72 (31.3)	125 (17.8)	<0.001
Prior PCI, %	192 (20.6)	77 (33.5)	115 (16.4)	<0.001
Prior CABG, %	79 (8.5)	42 (18.3)	37 (5.3)	<0.001
Heart failure, %	44 (4.7)	15 (6.5)	29 (4.1)	0.143
Stroke, %	29 (3.1)	9 (3.9)	20 (2.9)	0.428
Peripheral vascular disease, %	21 (2.3)	11 (4.8)	10 (1.4)	0.001
Vital parameters at admission				
Systolic BP, mmHg	144 ± 43	149 ± 42	143 ± 42	0.016
Diastolic BP, mmHg	82 ± 26	82 ± 29	83 ± 25	0.588
Heart rate, b.p.m.	76 ± 38	74 ± 41	75 ± 36	0.789
BMI[b]	27.1 ± 9.0	26.7 ± 8.8	27.2 ± 9.0	0.220
Electrocardiography				
ST-segment depression, %	33 (3.5)	20 (8.7)	13 (1.9)	<0.001
T-wave inversion, %	30 (3.2)	15 (6.5)	15 (2.1)	0.001

Values are expressed as median (IQR), mean ± 2 SD, or *n* (%).
BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.
[a]Total cholesterol >6.5 ng/L at presentation.
[b]Data missing in 52.7% (491/932).

clinical risk scores alone missed a fairly large number of MIs but fewer patients with unplanned revascularization. The ESC and High-STEACS algorithms showed excellent diagnostic performance for identifying index NSTEMI, for which they were developed.

Emergency departments around the world have different flow-charts for the treatment of chest pain patients without MI. After initial work-up and exclusion of life-threatening non-cardiac diseases (pulmonary embolism, aortic disease, pneumothorax, etc.) physicians must decide whether or not to admit the patient for further cardiac examinations. Our data confirm that routine use of clinical risk scores instead of standard ACS risk criteria may improve the accuracy of this decision-making process, for one thing, by forcing the physician to structuralize their evaluation. This might prove especially useful for less experienced physicians.

The question of whether physician's gestalt rather than clinical risk scores is sufficient to identify patients with ACS is disputed, and available studies show conflicting results.[10–12,32] Nestelberger *et al.*[33] recently investigated whether clinical gestalt and ECG changes added to the ESC 0/1 h algorithm would better identify chest pain patients with NSTEMI, mortality, and revascularization within 30 days. Based on their numbers, sensitivity increased from 81% (95% CI 78–83%) to 92% (95% CI 90–94%) when gestalt was added to the troponin-based algorithm (without consideration of the ACS low-risk criteria). About 45% (95% CI 42–47%) of patients would still be ruled out as

Table 3 Median (IQR) troponin values in blood samples taken at presentation (0 h), 3 h (3 h), and 8–12 h after presentation (12 h), by adjudicated diagnosis, $n = 932$

cTnT, ng/L	0 h	3 h	12 h
NSTEMI ($n = 124$)	50 (23–180)	129 (50–307)	216 (67–635)
UAP ($n = 106$)	9 (5–18)	9 (5–19)	10 (5–20)
SAP ($n = 7$)	16 (14–48)	17 (15–47)	19 (16–45)
Other cardiac disease ($n = 60$)	18 (9–29)	19 (8–41)	20 (10–43)
Other specified diagnosis ($n = 75$)	9 (3–17)	9 (5–17)	10 (3–21)
NCCP ($n = 560$)	5 (3–9)	5 (3–9)	5 (3–10)
cTnI, ng/L			
NSTEMI ($n = 124$)	121 (27–596)	614 (136–1977)	1262 (212–6458)
UAP ($n = 106$)	5 (3–10)	5 (4–12)	6 (4–12)
SAP ($n = 7$)	11 (6–14)	12 (7–17)	12 (8–29)
Other cardiac disease ($n = 60$)	11 (4–21)	16 (6–38)	18 (7–64)
Other specified diagnosis ($n = 75$)	6 (2–13)	7 (3–14)	9 (4–13)
NCCP ($n = 560$)	3 (2–5)	3 (2–6)	3 (2–6)

NCCP, non-cardiac chest pain; NSTEMI, non-ST-elevation myocardial infarction; SAP, stable angina pectoris; UAP, unstable angina pectoris.

low risk. When using HEART >3 as the additional criteria, we found at least comparable increase in sensitivity from 76% (95% CI 69–81%) to 95% (95% CI 92–98%), and the number of patients still being ruled out was comparable (39%, 95% CI 35–44%).

The classical risk factors of CAD described both in ESC and ACC/AHA guidelines intertwine with elements of the clinical risk scores. One minor difference is history. Although highlighted as an important part of evaluation in both guidelines, the structured evaluation of history and typicality of symptoms (e.g. 0, 1, or 2 points for History in HEART score) might be a major strength, and the reason why risk scores outperform standard ACS criteria in our study.

Another important finding in our study is that assessment of individual symptoms is no definite indicator of ACS. Although some typical signs, such as retrosternal location and radiation to both arms, were significantly more often found in patients with ACS, other typical symptoms like radiation to the left arm, shortness of breath, and nausea were similar frequent in patients with non-ACS. As an example, 30% of patients with a final diagnosis of myalgia reported pain radiating to the left arm as opposed to only 18% of patients with ACS. One might speculate that the reason is a high general knowledge on symptoms of ACS. As information on internet is readily accessible, more patients might contact their general practitioner or call an ambulance if they experience classical symptoms of ACS, even though they may have low risk of coronary disease. The low discriminatory effect of some of the classical symptoms of ACS as found in our and other studies,[34,35] indicate that clinical risk scores through a balanced evaluation of history and risk factors has at least similar safety and is less dependent on physician experience, compared to clinical evaluation used to the best of physician's knowledge.

The importance of identifying all patients with UAP during ED evaluation is unclear. Patients with UAP have increased long term risk of mortality but only a moderate 5% 30-day risk of MI.[36] As high-sensitivity troponin assays identify even very small MIs, it has been argued that the term UAP may in fact disappear and be re-classified as a subgroup of severe stable CAD.[37,38] Knowing that patients with stable CAD has no prognostic benefit of coronary revascularization,[39] mistakenly discharging a UAP patient with low risk of adverse events (perhaps pending further examination) seem safe. However, risk aversion, fear of malpractice, and loss of respect from colleagues may explain why some physicians choose to admit most chest pain patients eligible for early discharge according to the ESC or High-STEACS algorithms and standard ACS risk criteria.[40,41]

The use of clinical risk scores as the sole diagnostic tool could be an option in outpatient clinics without access to high-sensitive troponin assays, as some of the scores do not include such analysis (*Table 1*). Randomized trials applying HEART score alone as a criteria for early discharge have shown more promising results compared to our study.[42,43] However, the non-adherence rate in these studies are not unignorably, and the rate of primary endpoints was much lower. The superior value of HEART over GRACE and TIMI in unselected patients with chest pain has been shown before.[3,44,45] EDACS had lower accuracy than HEART, also in line with earlier findings.[3] T-MACS performed better as compared to HEART for the secondary endpoint, but with slightly lower NPV for the primary endpoint compared to the validation performed by the group who developed the score.[24] The choice between HEART or T-MACS should therefore be done based on local clinical preference.

Although clinical risk scores identify patients in need of revascularizations, their ability to identify MI/death within 30 days is lower compared to troponin-based algorithms.[3,46] In our study, all patients with MI or death within 30 days were already identified by the cTnT versions of ESC 0/3 h or High-STEACS algorithms in combination with ACS criteria, and the additional effect of risk scores were hence non-existing for identification of NSTEMI.

Similarly, and as expected, the ESC and High-STEACS algorithms have high precision in identifying patients with NSTEMI during index hospitalization, with no difference in sensitivity and number of ruled out patients ($P > 0.05$). The results are in line with several studies showing excellent diagnostic performance of troponin-based algorithms for ruling out NSTEMI.[3,18]

Table 4 Primary endpoint

	True pos	False pos	True neg	False neg	NPV (95% CI)	Sens (95% CI)	PPV (95% CI)	Spes (95% CI)	Rule-out/ low-risk, %	Accuracy[a]	AUROC[b]
Troponin-based algorithms											
ESC 0/3 h TnT	147	190	548	47	92.1 (90.1–93.8)	75.8 (69.1–81.6)	43.6 (40.1–47.2)	74.3 (70.9–77.4)	63.8 (61–67)	74.6 (71.7–77.3)	0.75 (0.72–0.78)
ESC 0/3 h TnI	129	97	641	65	90.8 (89.0–92.3)	66.5 (59.4–73.1)	57.1 (51.9–62.2)	86.9 (84.2–89.2)	75.8 (73–79)	82.6 (80.0–85.0)	0.77 (0.74–0.80)
High-STEACS TnT	152	206	532	42	92.7 (90.6–94.3)	78.4 (71.9–83.9)	42.5 (39.1–45.9)	72.1 (68.7–75.3)	61.6 (58–65)	73.4 (70.4–76.2)	0.75 (0.72–0.78)
High-STEACS TnI	137	134	604	57	91.4 (89.5–93.0)	70.6 (63.7–76.9)	50.6 (46.1–55.0)	81.8 (78.9–84.6)	70.9 (68–74)	79.5 (76.8–82.1)	0.76 (0.73–0.79)
Troponin-based algorithms combined with low risk of ACS according to ESC guidelines											
ESC 0/3 h TnT	179	377	361	15	96.0 (93.6–97.5)	92.3 (87.6–95.6)	32.2 (30.4–34.0)	48.9 (45.3–52.6)	40.3 (37–43)	57.9 (54.7–61.1)	0.71 (0.68–0.74)
ESC 0/3 h TnI	175	371	367	19	95.1 (92.6–96.8)	90.2 (85.1–94.0)	32.1 (30.2–33.9)	49.7 (46.1–53.4)	41.4 (38–45)	58.2 (54.9–61.4)	0.70 (0.67–0.73)
High-STEACS TnT	180	385	353	14	96.2 (93.8–97.7)	92.8 (88.2–96.0)	31.9 (30.2–33.6)	47.8 (44.2–51.5)	39.4 (36–43)	57.2 (53.9–60.4)	0.70 (0.67–0.73)
High-STEACS TnI	178	378	360	16	95.7 (93.3–97.3)	91.8 (87.0–95.2)	32.0 (30.3–33.8)	48.8 (45.1–52.5)	40.3 (37–43)	57.7 (54.5–60.9)	0.70 (0.67–0.73)
Risk scores											
HEART ≤3	177	360	378	17	95.7 (93.4–97.2)	91.2 (86.3–94.8)	33.0 (31.1–34.9)	51.2 (47.6–54.9)	42.4 (39–46)	59.6 (56.3–62.7)	0.83 (0.80–0.85)
mHEART ≤3	189	435	303	5	98.4 (96.2–99.3)	97.4 (94.1–99.2)	30.3 (29.0–31.7)	41.1 (37.5–44.7)	33.0 (30–36)	52.8 (49.5–56.0)	0.81 (0.78–0.84)
CARE ≤1	193	643	95	1	99.0 (93.0–99.9)	99.5 (97.2–100.0)	23.1 (22.6–23.6)	12.9 (10.5–15.5)	10.3 (8–12)	30.9 (28.0–34.0)	0.78 (0.75–0.80)
TIMI ≤1	153	305	433	41	91.4 (88.9–93.3)	78.9 (72.4–84.4)	33.4 (31.0–36.0)	58.7 (55.0–62.3)	50.9 (48–54)	62.9 (59.7–66.0)	0.75 (0.72–0.78)
GRACE inhosp ≤108[c]	102	245	491	89	84.7 (82.5–86.6)	53.4 (46.1–60.6)	29.4 (26.0–33.0)	66.7 (63.2–70.1)	62.6 (59–66)	64.0 (60.8–67.1)	0.67 (0.63–0.70)
GRACE 6 months <89[c]	91	203	533	100	84.2 (82.2–86.0)	47.6 (40.4–55.0)	31.0 (27.1–35.1)	72.4 (69.0–75.6)	68.3 (65–71)	67.3 (64.2–70.3)	0.68 (0.65–0.71)
T-MACS ≤0.02	178	390	348	16	95.6 (93.1–97.2)	91.8 (87.0–95.2)	31.3 (29.6–33.1)	47.2 (43.5–50.8)	39.1 (36–42)	56.4 (53.2–59.7)	0.81 (0.79–0.84)
sT-MACS ≤0	178	402	336	16	95.5 (92.9–97.1)	91.8 (87.0–95.2)	30.7 (29.1–32.4)	45.5 (41.9–49.2)	37.8 (35–41)	55.2 (51.9–58.4)	0.78 (0.75–0.80)
EDACS ≤15	140	328	410	54	88.4 (85.7–90.6)	72.2 (65.3–78.4)	29.9 (27.5–32.5)	55.6 (51.9–59.2)	49.8 (47–53)	59.0 (55.8–62.2)	0.68 (0.65–0.71)
sEDACS ≤3	153	397	341	41	89.3 (86.2–91.7)	78.9 (72.4–84.4)	27.8 (25.9–29.9)	46.2 (42.6–49.9)	41.0 (38–44)	53.0 (49.7–56.3)	0.64 (0.61–0.67)
Geleijnse–Sanchis ≤1	69	142	596	125	82.7 (81.0–84.2)	35.6 (28.8–42.7)	32.7 (27.7–38.2)	82.7 (81.0–84.2)	77.4 (75–80)	71.4 (68.3–74.2)	0.66 (0.63–0.69)
Goldman ≤1	40	55	683	154	81.6 (80.5–82.7)	20.6 (15.2–27.0)	42.1 (33.3–51.4)	92.6 (90.4–94.3)	89.8 (88–92)	77.6 (74.8–80.2)	0.63 (0.60–0.66)
Troponin-based algorithms combined with HEART score											
ESC 0/3 h TnT + HEART ≤3	185	381	357	9	97.5 (95.4–98.7)	95.4 (91.4–97.9)	32.7 (31.0–34.4)	48.4 (44.7–52.1)	39.3 (35–42)	58.2 (54.9–61.4)	0.84 (0.81–0.86)
ESC 0/3 h TnI + HEART ≤3	184	374	364	10	97.3 (95.2–98.5)	94.9 (90.7–97.5)	33.0 (31.3–34.7)	49.3 (45.7–53.0)	40.1 (37–43)	58.8 (55.6–62.0)	0.86 (0.84–0.88)
High-STEACS TnT + HEART ≤3	186	390	348	8	97.8 (95.7–98.9)	95.9 (92.0–98.2)	32.3 (30.7–33.9)	47.2 (43.5–50.8)	38.2 (35–41)	57.3 (54.1–60.5)	0.84 (0.81–0.86)
High-STEACS TnI + HEART ≤3	185	383	355	9	97.5 (95.4–98.7)	95.4 (91.4–97.9)	32.6 (30.9–34.2)	48.1 (44.4–51.8)	39.1 (36–42)	57.9 (54.7–61.1)	0.85 (0.83–0.88)
Troponin-based algorithms combined with mHEART											
ESC 0/3 h TnT + mHEART ≤3	190	445	293	4	98.7 (96.5–99.5)	97.9 (94.8–99.4)	29.9 (28.9–31.2)	39.7 (36.2–43.3)	31.9 (29–35)	51.8 (48.6–55.1)	0.83 (0.80–0.85)
ESC 0/3 h TnI + mHEART ≤3	190	444	294	4	98.7 (96.5–99.5)	97.9 (94.8–99.4)	30.0 (28.7–31.3)	39.8 (36.3–43.5)	32.0 (29–35)	51.9 (48.7–55.2)	0.86 (0.83–0.88)
High-STEACS TnT + mHEART ≤3	190	448	290	4	98.6 (96.5–99.5)	97.9 (94.8–99.4)	29.8 (28.5–31.1)	39.3 (35.8–42.9)	31.5 (29–35)	51.5 (48.2–54.8)	0.83 (0.80–0.85)
High-STEACS TnI + mHEART ≤3	190	448	290	4	98.6 (96.5–99.5)	97.9 (94.8–99.4)	29.8 (28.5–31.1)	39.3 (35.8–42.9)	31.5 (29–35)	51.5 (48.2–54.8)	0.85 (0.82–0.87)
Troponin-based algorithms combined with TIMI											

Continued

Table 4 *Continued*

	True pos	False pos	True neg	False neg	NPV (95% CI)	Sens (95% CI)	PPV (95% CI)	Spes (95% CI)	Rule-out/ low-risk, %	Accuracy[a]	AUROC[b]
ESC 0/3 h TnT + TIMI ≤1	181	337	401	13	96.9 (94.8–98.1)	93.3 (88.8–96.4)	34.9 (33.0–37.0)	54.3 (50.7–58.0)	44.4 (41–48)	62.5 (59.3–65.6)	0.80 (0.78–0.83)
ESC 0/3 h TnI + TIMI ≤1	180	332	406	14	96.7 (94.3–97.8)	92.8 (88.2–96.0)	35.2 (33.2–37.2)	55.0 (51.3–58.6)	45.1 (42–48)	62.9 (59.7–66.0)	0.85 (0.82–0.87)
High-STEACS TnT + TIMI ≤1	183	345	393	11	97.3 (95.3–98.5)	94.3 (90.1–97.1)	34.7 (32.8–36.6)	53.3 (49.6–56.9)	43.3 (40–47)	61.8 (58.6–64.9)	0.80 (0.78–0.83)
High-STEACS TnI + TIMI ≤1	183	344	394	11	97.3 (95.3–98.5)	94.3 (90.1–97.1)	34.7 (32.8–36.7)	53.4 (49.7–57.0)	43.5 (40–47)	61.9 (58.7–65.0)	0.84 (0.81–0.86)
Troponin-based algorithms combined with T-MACS											
ESC 0/3 h TnT + T-MACS <0.02	179	390	348	15	95.9 (93.4–97.4)	92.3 (87.6–95.6)	31.5 (29.8–33.2)	47.2 (43.5–50.8)	38.9 (36–42)	56.6 (53.3–59.8)	0.83 (0.80–0.85)
ESC 0/3 h TnI + T-MACS <0.02	179	391	347	15	95.9 (93.4–97.4)	92.3 (87.6–95.6)	31.4 (29.7–33.1)	47.0 (43.4–50.7)	38.8 (36–42)	56.4 (53.2–59.7)	0.83 (0.81–0.86)
High-STEACS TnT + T-MACS <0.02	179	396	342	15	95.8 (93.3–97.4)	92.3 (87.6–95.6)	31.1 (29.5–32.8)	46.3 (42.7–50.0)	38.3 (35–41)	55.9 (52.7–59.1)	0.83 (0.80–0.85)
High-STEACS TnI + T-MACS <0.02	179	398	340	15	95.8 (93.3–97.4)	92.3 (87.6–95.6)	31.0 (29.4–32.7)	46.1 (42.4–49.7)	38.1 (35–41)	55.7 (52.4–58.9)	0.83 (0.81–0.86)
Troponin-based algorithms combined with EDACS											
ESC 0/3 h TnT + EDACS ≤15	180	382	356	14	96.2 (93.9–97.7)	92.8 (88.2–96.0)	32.0 (30.3–33.8)	48.2 (44.6–51.9)	39.7 (37–43)	57.5 (54.3–60.7)	0.80 (0.77–0.82)
ESC 0/3 h TnI + EDACS ≤15	175	363	375	19	95.2 (92.8–96.8)	90.2 (85.1–94.0)	32.5 (30.7–34.5)	50.8 (47.1–54.5)	42.3 (39–45)	59.0 (55.8–62.2)	0.83 (0.80–0.85)
High-STEACS TnT + EDACS ≤15	181	390	348	13	96.4 (94.0–97.9)	93.3 (88.8–96.4)	31.7 (30.0–33.4)	47.2 (43.5–50.8)	38.7 (36–42)	56.8 (53.5–60.0)	0.80 (0.77–0.82)
High-STEACS TnI + EDACS ≤15	178	374	364	16	95.8 (93.4–97.3)	91.8 (87.0–95.2)	32.3 (30.5–34.1)	49.3 (45.7–53.0)	40.8 (38–44)	58.2 (54.9–61.4)	0.82 (0.79–0.84)

Diagnostic precision of troponin-based algorithms alone, in combination with low-risk ACS criteria (ESC guidelines) and in combination with clinical risk scores.
CARE, characteristics, age, risk factors, EGG; EDACS, Emergency Department Assessment of Chest Pain Score; GRACE, Global Registry of Acute Coronary Events; HEART, History, ECG, Age, Risk factors, Troponin; mHEART, modified HEART score with troponin points given if hs-Tn is measurable; MI, myocardial infarction; T-MACS, troponin-only Manchester Acute Coronary Syndromes; TIMI, thrombolysis in myocardial infarction.
[a]Sensitivity × Prevalence + Specificity × (1 - Prevalence).
[b]Calculations based on categorical data for troponin-based algorithms, continuous data for risk scores, and continuous data for the combination of troponin-based algorithms and risk scores.
[c]Excluding five patients with unknown GRACE score.

Table 5 Secondary endpoint

	True pos	False pos	True neg	False neg	NPV (95% CI)	Sens (95% CI)	PPV (95% CI)	Spes (95% CI)	Rule-out/ low risk, %	Accuracy[a]	AUROC[b]
Troponin-based algorithms											
ESC 0/3 h TnT	121	216	592	3	99.5 (98.5–99.8)	97.6 (93.1–99.5)	35.9 (33.3–38.7)	73.3 (70.1–76.3)	63.8 (61–67)	76.5 (73.7–79.2)	0.85 (0.83–0.88)
ESC 0/3 h TnI	117	109	699	7	99.0 (98.0–99.5)	94.4 (88.7–97.7)	51.8 (47.3–56.2)	86.5 (84.0–88.8)	75.8 (73–79)	87.6 (85.3–89.6)	0.90 (0.88–0.92)
High-STEACS TnT	122	236	572	2	99.7 (98.6–99.9)	98.4 (94.3–99.8)	34.1 (31.7–36.6)	70.8 (67.5–73.9)	61.6 (58–65)	74.5 (71.5–77.2)	0.85 (0.82–0.87)
High-STEACS TnI	121	150	658	3	99.6 (98.6–99.9)	97.6 (93.1–99.5)	44.7 (41.1–48.3)	81.4 (78.6–84.1)	70.9 (68–74)	83.6 (81.1–85.9)	0.90 (0.87–0.91)
Troponin-based algorithms combined with low risk of ACS according to ESC guidelines											
ESC 0/3 h TnT	124	432	376	0	100.0	100.0 (97.1–100.0)	22.3 (21.2–23.4)	46.5 (43.1–50.0)	40.3 (37–43)	53.7 (50.4–56.9)	0.73 (0.70–0.76)
ESC 0/3 h TnI	122	424	384	2	99.5 (98.0–99.9)	98.4 (94.3–99.8)	22.3 (21.2–23.6)	47.5 (44.0–51.0)	41.4 (38–45)	54.3 (51.0–57.5)	0.73 (0.70–0.76)
High-STEACS TnT	124	441	367	0	100.0	100.0 (97.1–100.0)	22.0 (20.9–23.0)	45.4 (42.0–48.9)	39.4 (36–43)	52.7 (49.4–55.9)	0.73 (0.70–0.76)
High-STEACS TnI	123	433	375	1	99.7 (98.2–100.0)	99.2 (95.6–100.0)	22.1 (21.0–23.3)	46.4 (42.9–49.9)	40.3 (37–43)	53.4 (50.2–56.7)	0.73 (0.70–0.76)
Risk scores											
HEART ≤3	116	421	387	8	98.0 (96.1–99.0)	93.6 (87.7–97.2)	21.6 (20.3–23.0)	47.9 (44.4–51.4)	42.4 (39–46)	54.0 (50.7–57.2)	0.85 (0.82–0.87)
mHEART ≤3	123	501	307	1	99.7 (97.8–100.0)	99.2 (95.6–100.0)	19.7 (18.8–20.6)	38.0 (34.6–41.4)	33.0 (30–36)	46.1 (42.9–49.4)	0.83 (0.80–0.85)
CARE ≤1	124	712	96	0	100.0	100.0 (97.1–100.0)	14.8 (14.5–15.2)	11.9 (9.7–14.3)	10.3 (8–12)	23.6 (20.9–26.5)	0.76 (0.73–0.79)
TIMI ≤1	96	362	446	28	94.1 (92.0–95.7)	77.4 (69.0–84.4)	21.0 (19.0–23.1)	55.2 (51.7–58.7)	50.9 (48–54)	58.2 (54.9–61.4)	0.73 (0.70–0.76)
GRACE ≤108[c]	76	271	534	46	92.1 (90.2–93.6)	62.3 (53.1–70.9)	21.9 (19.2–24.9)	66.3 (63.0–69.6)	62.6 (59–66)	65.8 (62.7–68.9)	0.69 (0.66–0.72)
GRACE ≤88[c]	70	224	581	52	91.8 (90.1–93.2)	57.4 (48.1–66.3)	23.8 (20.6–27.4)	72.2 (68.9–75.3)	68.3 (65–71)	70.2 (67.2–73.2)	0.70 (0.67–0.73)
T-MACS ≤0.02	123	445	363	1	99.7 (98.1–100.0)	99.2 (95.6–100.0)	21.7 (20.6–22.8)	44.9 (41.5–48.4)	39.1 (36–42)	52.2 (48.9–55.4)	0.91 (0.89–0.93)
sT-MACS ≤0	123	457	351	1	99.7 (98.0–100.0)	99.2 (95.6–100.0)	21.2 (20.2–22.3)	43.4 (40.0–46.9)	37.8 (35–41)	50.9 (47.6–54.1)	0.83 (0.80–0.85)
EDACS ≤15	91	377	431	33	92.9 (90.6–94.6)	73.4 (64.7–80.9)	19.4 (17.5–21.6)	53.3 (49.8–56.8)	49.8 (847–53)	56.0 (52.8–59.2)	0.68 (0.65–0.71)
sEDACS ≤3	99	451	357	25	93.5 (90.9–95.3)	79.8 (71.7–86.5)	18.0 (16.5–19.6)	44.2 (40.7–47.7)	41.0 (38–44)	48.9 (45.7–52.2)	0.64 (0.61–0.67)
Gelejinse–Sanchis ≤1	41	170	638	83	88.5 (87.1–89.7)	33.1 (24.9–42.1)	19.4 (15.4–24.3)	79.0 (76.0–81.7)	77.4 (75–80)	72.9 (69.9–75.7)	0.63 (0.59–0.66)
Goldman ≤1	34	61	747	90	89.3 (88.2–90.3)	27.4 (19.8–36.2)	35.8 (27.7–44.8)	92.5 (90.4–94.2)	89.8 (88–92)	83.8 (81.3–86.1)	0.61 (0.58–0.64)
Troponin-based algorithms combined with HEART score											
ESC 0/3 h TnT + HEART ≤3	124	442	366	0	100.0	100.0 (97.1–100.0)	21.9 (20.9–23.0)	45.3 (41.8–48.8)	39.3 (35–42)	52.6 (49.3–55.8)	0.89 (0.87–0.91)
ESC 0/3 h TnI + HEART ≤3	123	435	373	1	99.7 (98.1–100.0)	99.2 (95.6–100.0)	22.0 (20.9–23.2)	46.2 (42.7–49.7)	40.1 (37–43)	53.2 (50.0–56.5)	0.93 (0.92–0.95)
High-STEACS TnT + HEART ≤3	124	452	356	0	100.0	100.0 (97.1–100.0)	21.5 (20.5–22.6)	44.1 (40.6–47.6)	38.2 (35–41)	51.5 (48.2–54.8)	0.90 (0.88–0.92)
High-STEACS TnI + HEART ≤3	124	444	364	0	100.0	100.0 (97.1–100.0)	21.8 (20.8–22.9)	45.1 (41.6–48.6)	39.1 (36–42)	52.4 (49.1–55.6)	0.93 (0.92–0.95)
Troponin-based algorithms combined with mHEART											
ESC 0/3 h TnT + mHEART ≤3	124	511	297	0	100.0	100.0 (97.1–100.0)	19.5 (18.7–20.4)	36.8 (33.5–40.2)	31.9 (29–35)	45.2 (41.9–48.4)	0.88 (0.86–0.90)
ESC 0/3 h TnI + mHEART ≤3	124	510	298	0	100.0	100.0 (97.1–100.0)	19.6 (18.7–20.4)	36.9 (33.6–40.4)	32.0 (29–35)	45.3 (42.1–48.6)	0.93 (0.92–0.95)
High-STEACS TnT + mHEART ≤3	124	514	294	0	100.0	100.0 (97.1–100.0)	19.4 (18.6–20.3)	36.4 (33.1–39.8)	31.5 (29–35)	44.9 (41.6–48.1)	0.89 (0.86–0.91)
High-STEACS TnI + mHEART ≤3	124	514	294	0	100.0	100.0 (97.1–100.0)	19.4 (18.6–20.3)	36.4 (33.1–39.8)	31.5 (29–35)	44.9 (41.6–48.1)	0.93 (0.91–0.94)
Troponin-based algorithms combined with TIMI											
ESC 0/3 h TnT + TIMI ≤1	124	394	414	0	100.0	100.0 (97.1–100.0)	23.9 (22.7–25.3)	51.2 (47.7–54.7)	44.4 (41–48)	57.7 (54.5–60.9)	0.85 (0.83–0.88)
ESC 0/3 h TnI + TIMI ≤1	123	389	419	1	99.8 (98.3–100.0)	99.2 (95.6–100.0)	24.0 (22.7–25.4)	51.9 (48.4–55.4)	45.1 (42–48)	58.2 (54.9–61.4)	0.92 (0.90–0.94)

Continued

Table 5 *Continued*

	True pos	False pos	True neg	False neg	NPV (95% CI)	Sens (95% CI)	PPV (95% CI)	Spes (95% CI)	Rule-out/ low risk, %	Accuracy[a]	AUROC[b]
High-STEACS TnT + TIMI ≤1	124	404	404	0	100.0	100.0 (97.1–100.0)	23.5 (22.3–24.8)	50.0 (46.5–53.5)	43.3 (40–47)	56.7 (53.4–59.9)	0.85 (0.83–0.87)
High-STEACS TnI + TIMI ≤1	124	403	405	0	100.0	100.0 (97.1–100.0)	23.5 (22.3–24.8)	50.1 (46.6–53.6)	43.5 (40–47)	56.8 (53.5–60.0)	0.91 (0.89–0.93)
Troponin-based algorithms combined with T-MACS											
ESC 0/3 h TnT + T-MACS <0.02	124	445	363	0	100.0	100.0 (97.1–100.0)	21.8 (20.8–22.9)	44.9 (41.5–48.4)	38.9 (36–42)	52.3 (49.0–55.5)	0.93 (0.91–0.95)
ESC 0/3 h TnI + T-MACS <0.02	124	446	362	0	100.0	100.0 (97.1–100.0)	21.8 (20.7–22.8)	44.8 (41.3–48.3)	38.8 (36–42)	52.2 (48.9–55.4)	0.95 (0.93–0.96)
High-STEACS TnT + T-MACS <0.02	124	451	357	0	100.0	100.0 (97.1–100.0)	21.6 (20.6–22.6)	44.2 (40.7–47.7)	38.3 (35–41)	51.6 (48.4–54.9)	0.93 (0.91–0.95)
High-STEACS TnI + T-MACS <0.02	124	453	355	0	100.0	100.0 (97.1–100.0)	21.5 (20.5–22.5)	43.9 (40.5–47.4)	38.1 (35–41)	51.4 (48.1–54.7)	0.95 (0.93–0.96)
Troponin-based algorithms combined with EDACS											
ESC 0/3 h TnT + EDACS ≤15	123	439	369	1	99.7 (98.1–100.0)	99.2 (95.6–100.0)	21.9 (20.8–23.0)	45.7 (42.2–49.2)	39.7 (37–43)	52.8 (49.5–56.0)	0.87 (0.84–0.89)
ESC 0/3 h TnI + EDACS ≤15	121	417	391	3	99.3 (97.7–100.0)	97.6 (93.1–99.5)	22.5 (21.3–23.8)	48.4 (44.9–51.9)	42.3 (39–45)	54.9 (51.7–58.2)	0.92 (0.90–0.94)
High-STEACS TnT + EDACS ≤15	123	448	360	1	99.7 (98.1–100.0)	99.2 (95.6–100.0)	21.5 (20.5–22.6)	44.6 (41.1–48.1)	38.7 (36–42)	51.8 (48.6–55.1)	0.86 (0.84–0.89)
High-STEACS TnI + EDACS ≤15	122	430	378	2	99.5 (98.0–99.9)	98.4 (94.3–99.8)	22.1 (21.0–23.3)	46.8 (43.3–50.3)	40.8 (38–44)	53.7 (50.4–56.9)	0.91 (0.89–0.93)

Diagnostic precision of troponin-based algorithms alone and in combination with clinical risk scores.
CARE, characteristics, age, risk factors, EGG; EDACS, Emergency Department Assessment of Chest Pain Score; GRACE, Global Registry of Acute Coronary Events; HEART, History, ECG, Age, Risk factors, Troponin; mHEART, modified HEART score with troponin points given if hs-Tn is measurable; MI, myocardial infarction; T-MACS, troponin-only Manchester Acute Coronary Syndromes; TIMI, thrombolysis in myocardial infarction.
[a]Sensitivity × Prevalence + Specificity × (1 - Prevalence).
[b]Calculations based on categorical data for troponin-based algorithms, continuous data for risk scores and continuous data for the combination of troponin-based algorithms and risk scores.
[c]Excluding five patients with unknown GRACE score.

The strength of this study is the broad inclusion criteria and no cut-off for the onset of symptoms before presentation, closely mimicking a real-life ED scenario with the object of identifying ACS as opposed to MI alone. Patients with non-ACS had a mean hospital stay of 40 h with several measurements of troponin concentrations, which makes coronary events unlikely to go undetected. Symptoms and clinical information collected from multiple sources allowed for evaluation of a variety of risk scores.

Study limitations

First, estimation of risk and gathering of clinical information was performed retrospectively. Even though the study cardiologist calculating HEART score was blinded for all further examinations and treatment, objective symptoms reported in medical journals may have been coloured by assumptions made by the ED physician and ambulance personnel. The retrospective gathering of information could also have affected EDACS, T-MACS, and Geleijnse–Sanchis, since some episodes of diaphoresis and vomiting may not have been reported. Other major characteristics, like location, character, and radiation of pain was described in detail in almost all patients.

The study contains few early presenters (<2 h) (10.4%), which makes the results less applicable for this category of patients. The long median time from symptom onset to presentation (8 h) also affects the applicability in patient groups who present to ED earlier.

Another limitation is that the adjudication of diagnoses was performed using cTnT as routine test, and the performance of the cTnT compared to the cTnI algorithms may potentially be overestimated. The use of a gender-neutral 99th percentile during the adjudication could have negatively biased the performance of the High-STEACS cTnI algorithm, that used gender-specific 99th percentiles.

Lastly, the study has a single-centre design and the inclusion period is long, which may raise questions about representativeness of the data. However, the rate of NSTEMI, UAP, and patient characteristics are similar to other cohorts, and the broad inclusion criteria should ensure a representative inclusion. The generalizability of the results would greatly benefit from being validated in a prospective validation cohort, preferably performed by another study groups.

Conclusion

Troponin-based algorithms intended to identify NSTEMI should preferable be combined with a clinical risk score rather than the ACS low-risk criteria recommended by ESC to improve sensitivity and NPV for identification of patients with high risk of MI, death, or need for invasive treatment. The number of patients eligible for rule-out were maintained. For clinicians who are reluctant to discharge chest pain patients from ED due to fear of malpractice and overlooking ACS, 2.2% risk of revascularization within 30 days might be acceptable. Future studies should compare the safety and efficiency of a strategy implying treatment of low-risk ACS patients during index hospitalization to a liberal practice using out-of-hospital follow-up of ACS patients eligible for rule-out.

Supplementary material

Supplementary material is available at *European Heart Journal: Acute Cardiovascular Care* online.

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Conflict of interest: K.M.A. has served on one advisory board for Roche Diagnostics and received lecturing fees from Siemens Healthineers. T.O. has served on advisory boards for Abbott Diagnostics, Roche Diagnostics, and Novartis, and has received research support from AstraZenica, Abbott Diagnostics, Roche Diagnostics, ThermoFisher, Singulex, and Biomedica via Akershus University Hospital, and speaker's honoraria from Roche Diagnostics and Novartis. Ø.S. has received lecture fees from Abbott Diagnostics.

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