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LONG-TERM OUTCOMES IN PATIENTS WITH ACUTE AND CHRONIC MYOCARDIAL INJURY

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LONG-TERM OUTCOMES IN PATIENTS WITH ACUTE AND CHRONIC MYOCARDIAL INJURY

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be defended in public at Birkeaulan, Karolinska University Hospital, Huddinge, 1 April at 09:00.

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To Martin Holzmann

POPULÄRVETENSKAPLIG SAMMANFATTNING

Högekänsliga troponin-analysmetoder (hs-cTn) har använts i Sverige sedan 2010 och har medfört att hjärtinfarkt kan diagnostiseras i ett tidigare skede, liksom att diagnosen kan uteslutas snabbare. Friska och unga människor har vanligtvis omätbara eller mycket låga nivåer av hs-cTn i blod, men när hjärtat blir belastat, direkt skadat eller utsätts för kronisk stress utsöndras troponiner från hjärtmuskelceller och detekteras med förhöjda nivåer i blod. Förhöjda nivåer av troponin definieras som myokardskada. Det finns fyra kategorier av myokardskada: i) typ 1 hjärtinfarkt, som orsakas av en plackruptur i ett kranskärl och ii) typ 2 hjärtinfarkt, som orsakas av syrebrist i hjärtmuskeln till följd av ökat behov av eller minskad tillförsel av syre till hjärtmuskeln, med symptom och/eller EKG-förändringar som vid typ 1 hjärtinfarkt, men utan trombos. Därtill finns ytterligare två entiteter av myokardskada som utgörs av så kallad icke-ischemisk myokardskada som definieras som cTn-nivåer ovan beslutsgränsen för hjärtinfarkt utan tecken på syrebrist i hjärtmuskeln: iii) akut myokardskada som karakteriseras av stigande och/eller sjunkande cTn-nivåer, men utan symptom eller EKG-tecken förenliga med syrebrist i hjärtmuskeln och iv) kronisk myokardskada som karakteriseras av kroniskt stegrade cTn-nivåer, som kan vara ett tecken till ständigt pågående nedbrytning av hjärtmuskelceller. Icke-ischemisk myokardskada och typ 2 hjärtinfarkt har visat sig vara associerat med en dålig prognos, både på kort och lång sikt. I och med införandet av högekänsligt troponin har en större proportion av patienter med icke-ischemisk myokardskada kunnat identifieras. Studier har visat att patienter med myokardskada utreds bristfälligt och att mer än hälften av patienterna med icke-ischemisk myokardskada och typ 2 hjärtinfarkt avlider inom 5 år. Detta projekt syftar till att skapa ny kunskap kring akut och kronisk myokardskada. I fyra delstudier undersöks klinisk karakteristika, betydelsen av läkemedelsbehandling samt prognos hos patienter med olika typer av myokardskada.

I **studie I** inkluderades 3 853 patienter med myokardskada från en kohort med bröstsmärta som sökt Karolinska Universitetssjukhusets akutmottagning under åren 2011 till 2014. Patienter kategoriserades i 4 grupper: i) typ 1 hjärtinfarkt, ii) typ 2 hjärtinfarkt, iii) akut icke-ischemisk myokardskada och iv) kronisk myokardskada. Vi fann att riskerna för död var mycket höga hos patienter med typ 2 hjärtinfarkt, akut icke-ischemisk myokardskada samt kronisk myokardskada, där nära hälften av patienterna avled inom 4 år jämfört med patienter med typ 1 hjärtinfarkt.

I **studie II** inkluderades alla patienter som dog och kategoriserades i studie I samt patienter som dog utan myokardskada under uppföljningstiden för att undersöka dödsorsaker samt risken för specifik dödsorsak jämfört med patienter utan myokardskada. Vi inkluderade 2 285 patienter i studien. Vi fann att patienter med typ 1 hjärtinfarkt och akut icke-ischemisk myokardskada hade högst risk för att dö av kardiovaskulära orsaker, men endast marginellt högre risk än patienter med typ 2 hjärtinfarkt samt kronisk myokardskada. Vi kunde också konstatera att patienter med akut icke-ischemisk myokardskada, kronisk myokardskada och

typ 2 hjärtinfarkt dog av kardiovaskulära orsaker i nästan lika hög frekvens som patienter med typ 1 hjärtinfarkt.

I **studie III** inkluderades alla patienter från studie I för att undersöka förskrivningen av vanliga kardiovaskulära läkemedel hos patienter med olika typer av myokardskada. Vi undersökte huruvida riskerna för död och kardiovaskulära händelser påverkades när patienter med olika grupper av myokardskada behandlas med flera läkemedel respektive få eller inga läkemedel. Vi fann att merparten av patienter med myokardskada utan typ 1 hjärtinfarkt var i lägre utsträckning behandlade med vanliga kardiovaskulära läkemedel än patienter med typ 1 hjärtinfarkt. Patienter med akut icke-iskemisk myokardskada, kroniskt myokardskada och typ 2 hjärtinfarkt med många läkemedel hade lägre risk för död även när man justerade för störfaktorer i den statistiska analysen.

I **studie IV** inkluderades alla patienter från studie I som förskrevs med en typ av blodfettssänkande läkemedel (statin). Vi undersökte hur högre doser av statiner påverkade risken för död hos grupper med myokardskada definierade i studie I. Vi fann att riskerna hos patienter behandlade med högre doser av statiner hade lägre risker för död, men att den reducerade risken inte kvarstod när vi justerade för störfaktorer.

ABSTRACT

Background: Myocardial injury is defined as any cardiac troponin (cTn) level above the upper reference limit, namely, the 99th percentile value, and is caused by either ischemic or nonischemic events. The presence of acute myocardial injury (i.e., myocardial injury with a dynamic change in cTn levels) with evidence of myocardial ischemia is required for the diagnosis of myocardial infarction (MI). Nonischemic myocardial injury, defined as myocardial injury without evidence of ischemia, and type 2 MI are linked to a substantial risk of death and a poor prognosis. The purpose of this thesis was to study the characteristics, risks of death, and cardiovascular events in patients with type 1 MI, type 2 MI, acute nonischemic myocardial injury and chronic myocardial injury. In addition, this thesis aimed to investigate the impact of common cardiovascular medications within each type of myocardial injury.

Methods: Patients with myocardial injury (i.e., high-sensitivity cardiac troponin T (hs-cTnT)>14 ng/L) identified from a cohort of patients from the emergency department with at least one visit for chest pain at the Karolinska University Hospital 2011 and 2014 were included in the studies. The cohort was obtained from the local administrative database that includes all patients seeking medical attention in the ED, while additional data were obtained from national registers. Study I was performed to investigate the long-term outcome in patients (n=3 853) with hs-cTnT levels>14 ng/L who were categorized as: type 1 MI, type 2 MI, acute nonischemic myocardial injury, and chronic myocardial injury. Study II was performed to investigate the causes of death in patients with myocardial injury compared with those without myocardial injury (hs-cTnT<14ng/L), who died during follow-up (n=2 285). Study III was performed to investigate how the number of commonly prescribed cardiovascular drugs (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, statins, and platelet inhibitors) impacts mortality and cardiovascular events in patients with different types of myocardial injury. Study IV was performed to investigate whether prescribed high-, medium-, and low-intensity statin therapy impacts risks and outcomes in patients with different types of myocardial injury.

Results: Patients with acute nonischemic myocardial injury and type 2 MI had a high risk of death, similar to patients with chronic myocardial injury, according to the findings of Study I. During a mean 4-year follow-up, nearly half of all patients in groups without type 1 MI died. Patients with nonischemic myocardial injury and patients with type 1 MI had similar high risk of cardiovascular death compared to patients with no myocardial injury. Patients with type 2 MI and chronic myocardial injury treated with 4 common cardiovascular drugs has a lower adjusted risk of death. Patients with nonischemic myocardial injury treated with two or three medications had a lower adjusted mortality risk compared to patients treated with zero or one medication. Patients with nonischemic myocardial injury and type 2 MI treated with high-intensity treatment had lower crude risks compared to patients treated with low-intensity treatment in corresponding groups, but estimates were not significant after adjusting for confounders.

Conclusions: Patients with nonischemic myocardial injury and type 2 MI have a high risk of all-cause mortality and share similar risks for cardiovascular death as patients with type 1 MI. Patients with nonischemic myocardial injury and type 2 MI may benefit from common cardiovascular medications. Currently no clinical recommendations are available for how patients with nonischemic myocardial injury or type 2 MI should be managed, and this warrants further attention.

LIST OF SCIENTIFIC PAPERS

The following studies are included in this thesis and are referred to as study I, II, III, and IV throughout the text. The studies are found at the end of this thesis.

I. Acute versus chronic myocardial injury and long-term outcomes.

Erik Kadesjö, Andreas Roos, Anwar J. Siddiqui, Liyew Desta, Magnus Lundbäck, Martin J. Holzmann.

Heart, 2019;105:1905–1912.

II. Causes of death in patients with acute and chronic myocardial injury.

Erik Kadesjö, Andreas Roos, Anwar J. Siddiqui, Ulrik Sartipy, Martin J. Holzmann.

The American Journal of Medicine, 2020;133:590–598.e2

III. Treatment with cardiovascular medications: Prognosis in patients with myocardial injury.

Erik Kadesjö, Andreas Roos, Anwar J. Siddiqui, Ulrik Sartipy, Martin J. Holzmann.

Journal of the American Heart Association, 2021;10:e017239

IV. Statin therapy and intensity: Prognosis in patients with myocardial injury.

Erik Kadesjö, Andreas Roos, Anwar J. Siddiqui, Ulrik Sartipy, Martin J. Holzmann.

The American Journal of Medicine, 2021;S0002-9343(21)00481-2

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LIST OF ABBREVIATIONS

ACEi/ARB	Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker
ACS	Acute coronary syndrome
AST	Aspartate transaminase
ATC	Anatomic Therapeutic Chemical classification system
CAD	Coronary artery disease
CCI	Charlson comorbidities index
CI	Confidence interval
CK	Creatinine kinase
CK-MB	Creatinine kinase-muscle/brain isoenzyme
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
cTn	Cardiac troponin
CV	Coefficient of variance
ED	Emergency department
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
Hs-cTn	High-sensitivity cardiac troponin
HR	Hazard ratio
ICD	International version of the disease classification
LoB	Limit of blank
LoD	Limit of detection
LoQ	Limit of quantification
MI	Myocardial infarction
NPR	National Patient Register

NSTEMI	Non-ST- Elevation Myocardial Infarction
NPV	Negative predictive value
OR	Odds ratio
PPV	Positive predictive value
STEMI	ST- Elevation Myocardial Infarction
SWEDHEART	The Swedish web-system for enhancement and development of evidence-based care in heart disease
UA	Unstable angina
URL	Upper reference limit
3UDMI	Third Universal Definition of Myocardial Infarction
4UDMI	Fourth Universal Definition of Myocardial Infarction

1 INTRODUCTION

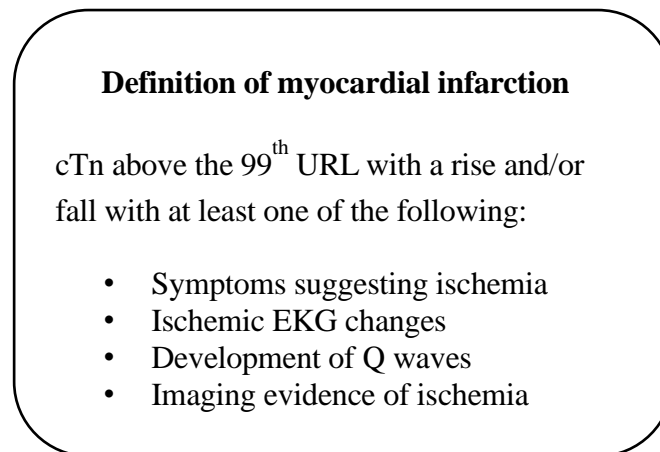


Figure 1 - definition of myocardial infarction according to the universal definition of myocardial infarction(1)

Myocardial injury is defined as any cardiac troponin (cTn) level above the upper reference limit (URL), i.e., the 99th percentile, induced by either ischemia or nonischemic events. The presence of acute myocardial injury (i.e., myocardial injury with a dynamic shift in cTn levels) along with evidence of myocardial ischemia is required for the diagnosis of myocardial infarction (MI) (FIGURE 1). Patients with MI experience myocardial ischemia as a result of a coronary plaque rupture (type 1 MI) or an insufficient supply or demand of oxygen to the heart (type 2 MI). The Fourth Universal Definition of Myocardial Infarction (4UDMI) (1) also acknowledges chronic myocardial injury as an own entity (1). A large proportion of patients in emergency departments(ED) are diagnosed with nonischemic myocardial injury (2), which has been associated with both short-term (3) and long-term adverse outcomes (4,5). Patients with type 2 MI and nonischemic injury die more often from cardiovascular causes than the general ED patient population (6). However, it is difficult to distinguish different myocardial injury from each other, and not rarely a type 1 MI may be misjudged as a type 2 MI (7). Only a few studies have investigated the prognosis and causes of death in patients with different types of myocardial injury according to the latest definition of myocardial infarction. Currently, there is no consensus or clinical guidelines on how to treat patients with type 2 MI or nonischemic myocardial injury. However, it is likely important to acknowledge and appreciate the opportunity to investigate these patients to exclude underlying cardiac disease. The evidence about treatment effects in patients with myocardial injury other than type 1 MI are scarce. Whether recommended cardiovascular drugs for type 1 MI reduce risks in patients with other types of myocardial injury is unknown.

The development of a cardio-specific troponin assay during the early 1990s was a breakthrough for the diagnosis of MI(8,9) and several assays with higher sensitivity were developed during the 1990s and 2000s. The fifth generation of high-sensitivity cardiac troponin (hs-cTn) assays substantially improved early diagnosis of MI (10,11). The hs-cTn assays not only improve early detection of MI but has also made it possible to safely and

effectively rule out a large proportion of patients with suspected non-ST-elevation MI(NSTEMI). Before the era of cTn assays, considerably less sensitive and specific biomarkers were used in clinical settings to diagnose MI.

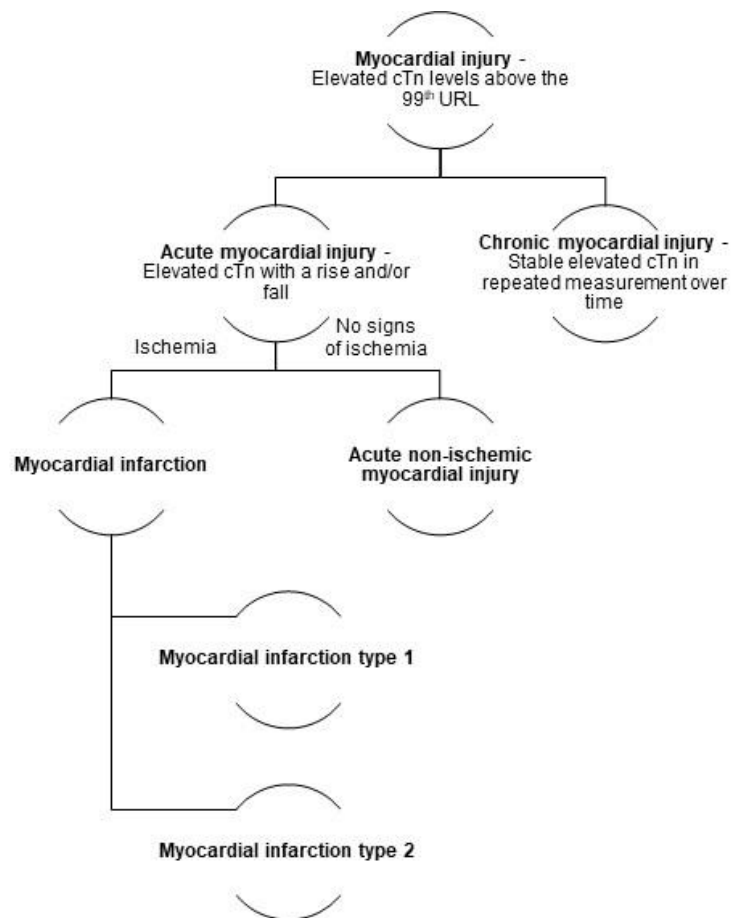


Figure 2 - nomenclature and definitions according to the 4UDMI(1)

At present, because of hs-cTn assays, systemic low levels of cTn have been found in several other conditions than MI. Patients with systemic high levels of cTn but no signs of MI have been diagnosed with myocardial injury (12). The vocabulary and concepts of myocardial injury have been refined in the latest expert documents of the universal definition of MI (1,12) (FIGURE 2).

2 LITERATURE REVIEW

2.1 BIOMARKERS IN MYOCARDIAL INFARCTION

The aspartate transaminase (AST) protein was identified in the 1960s and was used as a biomarker to diagnose MI. The biomarker was incorporated into the definition of MI and was routinely used during the 1960s (13). However, AST is not specific to cardiac muscle and the pursuit for more specific biomarkers continued. In the 1970s, lactate dehydrogenase and creatinine kinase (CK) were used as a biomarker, which are more specific for diagnosing MI compared to AST (14). Myoglobin, a protein found in muscle tissue that is elevated in patients with cardiac ischemia, also became a marker for MI. However, several conditions are associated with raised levels of myoglobin and therefore this biomarker deemed insufficient and nonspecific for MI diagnosis (15). Later, advancements in electrophoresis made it possible to detect more cardiac specific iso-enzymes for CK and lactate dehydrogenase. Implementation of the CK-muscle/brain isoenzyme (CK-MB), another biomarker added higher precision for MI diagnosis(16), as well as additional specificity, as CK-MB could be measured by the CK-MB mass assay that was introduced in 1985 (17).

The troponin protein was identified in striated muscle tissue in the 1960s (18). Several groups attempted to create a cTn assay in the 1980s. In 1989, the first cTn immunoassay was introduced (8), and several tests were validated during the 1990s, followed by several generations of troponin assays. Even though older generation cTn assays are still used and CK-MB assays may offer value in the diagnosis of early reinfarction (19), the hs-cTn assay is considered the recommended assay for the diagnosis of MI (20).

2.2 CARDIAC TROPONIN

The sarcomere is the functional intracellular unit of the cardiomyocyte that, together with billions of cardiomyocytes, builds a structured myocardium. The sarcomere consists of several proteins that regulate the contraction of striated muscle, but mainly consists of stacked proteins of thin actin and thicker myosin filament (FIGURE 3). The protein complex containing actin and myosin filaments, tropomyosin, and troponin (T, C, and I) (FIGURE 3) is the functional unit of the myocardium and are activated by action potentials. Troponin C acts as a signal carrier that is activated when calcium ions bind to it; Troponin T binds to the actin filament; and Troponin I inhibits contact with myosin heads when calcium ions are present in low concentrations (21).

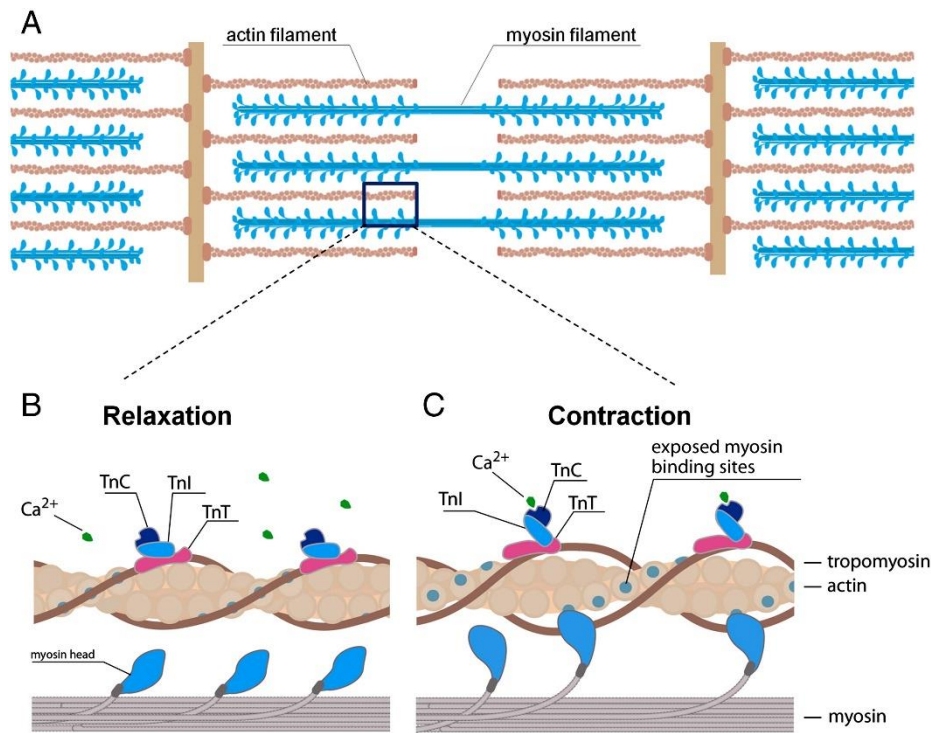


Figure 3- principal structure of the troponin protein complex. Image reproduced with permission from the publisher(22).

The cardiac isoforms of troponin I and troponin T are highly specific and are therefore excellent specific biomarkers for myocardial injury (23). More than 90% of all cTn is attached to the sarcomere while the rest is soluble in the myocyte cytoplasm (24).

2.2.1 Troponin assays – High-sensitivity cardiac troponin assay and the 99th percentile

Since the late 1980s, several generations of cTn assays have been developed (15). The use of the fifth generation troponin assays, the hs-cTn assay, dominates clinical practice whereas the first to third generation assays are commonly referred to as the conventional assay, and the fourth generation assays are commonly referred to as sensitive assay(25), may still be used in clinical settings. The hs-cTn assays can detect troponin at 10- to 100-fold lower concentrations than previous generations of assays, and they can identify cTn at very low levels at early phases of an ongoing MI (26).

The hs-cTnT assay is manufactured by Roche Diagnostics and is developed with the use of specific monoclonal antibodies against the central region of the cTnT-protein similar to the fourth-generation assay (27). However, hs-cTnT assay is not calibrated as is the fourth generation and levels of cTnT in prior assays do not correspond to the same levels as in the hs-cTnT assay (28).

Several high-sensitivity cardiac troponin I(hs-cTnI) assays are on the market, and the correlation of hs-cTnI between the different assays has improved. However, 100% consistency between the different commercial assays will be unlikely because they are all based on different antibody epitopes of the cTnI-molecule (27).

The first hs-cTn assay was approved in 2017 in the United States by the US Food and Drug Administration (29). In Sweden, hs-cTn assays have been used in clinical practice for almost a decade. Concerns have been raised about the implementation of hs-cTn assays in the US (30) because there is a low risk of MI when hs-cTn assays are not used with prior clinical assessments (31).

2.2.2 Nomenclature – Coefficient of Variation, Limits of Blank, Detection, and Quantification

A biomarker assay requires standards in order to obtain repeatable and trustworthy values, and guidelines for hs-cTn assays stress that the imprecision value (coefficient of variation [CV]) should be less than 10% at the 99th URL (20,32). The CV in practical terms is the analytical variability in repeated measurements at the 99th percentile. The limit of blank (LoB), limit of detection (LoD), and limit of quantification (LoQ) are all used to determine very low levels of cTn in hs-cTn assay, and all of these standards have been used successfully to effectively rule out patients with symptoms suggestive of MI (20) (FIGURE 4). The LoB is the highest expected cTn level found when repeating a sample without any analyte or the expected concentration of a repeated zero calibration. The LoD is the lowest reliable concentration of cTn that can be distinguished, while LoB is the background noise present in the assay. The LoQ usually represents the cTn value at which can be reliably reported as a value (33).

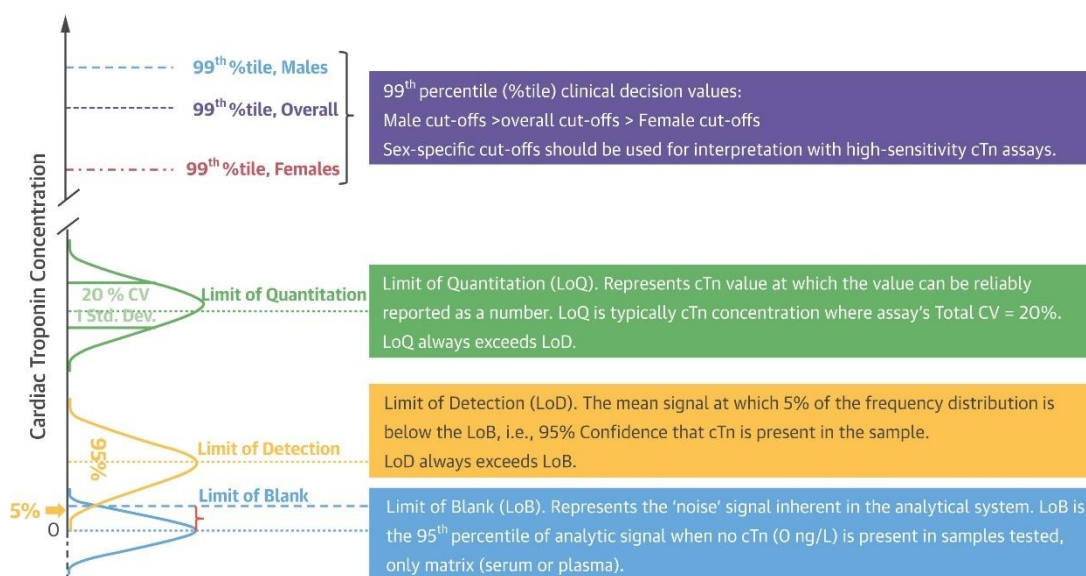


Figure 4 - terminology related to the hs-cTn assay. Image reproduced with permission from the publisher(34).

2.2.3 Upper reference limit: the 99th percentile

The first universal definition of MI (35) in 2000 suggested that 99th percentile of the healthy population was an appropriate cut-off for myocardial necrosis, during the period of contemporary assays. The assays are still used in clinical settings and are not able to detect very low levels of cTn; hence, they are more imprecise at the 99th percentile URL (32). The requirements of the fifth generation of cTn assays, the hs-cTn assays, in the guidelines have

sharpened. The guidelines stress that hs-cTn assays must be able to measure cTn in more than 50% of healthy subjects with a CV less than 10% at the 99th percentile URL (1).

Values above the URL are usually defined as abnormal. To explore and define the URL, a healthy reference population is required. There is currently no international standardization on how to choose subjects for this purpose, and there are several factors that influence the URL, such as sex, estimated glomerulation filtration (eGFR), and age (36). The need for standardization has been further highlighted by a study that revealed that 2 % of the general population in Dallas had hs-cTn levels above the 99th percentile (37). Furthermore, sex-specific cut-offs for several hs-cTn assays have been established (38) and are recommended by guidelines (1,39) (FIGURE 4).

Several studies emphasize the need for a universal approach when deciding URLs, and there are still considerations that might be incorporated in the future, such as age-specific cut-offs (25,36). However, this approach may cause reduced sensitivity for MI detection and diagnosis in healthy elderly people without comorbidities. The need for further diagnostic tools that are able to distinguish between types of myocardial injury is urgent, because a substantial proportion of patients visiting the ED have symptoms that might suggest evolving MI. Moreover, 50% of all patients with chest pain have myocardial injury, but only a small proportion will have acute MI as a final diagnosis (40).

2.2.4 Analytical concerns related to hs-cTn assays

Although clinically uncommon (41), there are several analytical interferences usually related to the hs-cTnT assay. Clearance of cTn is complicated, since cTn in its undifferentiated macro molecule e.g., from ischemic myocardium, is normally not cleared by glomeruli, although fragments of cTn may be. The hs-cTnT assays can detect small fragments of cTnT and in patients with renal failure, fragment accumulation of cTnT has been observed (42). Because hs-cTn is measured by an immunoassay in which antibodies detect epitopes in the cTn molecule (43), various complexes or fragments of cTn are detected with the assay, especially in the hs-cTnT assay. Therefore, it is often clinically challenging to interpret levels of cTnT in patients with severe renal dysfunction. In patients with skeletal myopathies such as Duchenne muscular dystrophy or Beckers muscle dystrophy, elevated hs-cTnT can be detected without signs of cardiac involvement, and if tested with a hs-cTnI assay, levels are normal (44). This might be due to chronic muscle damage, and to the reactivation of fetal isoforms of cTnT in skeletal muscle tissue (41). Nonetheless, hs-cTnT elevations in patients with skeletal myopathies are probably more likely to be caused by genuine myocardial injury and/or cross reactivity with skeletal muscle proteins such as CK (45). Furthermore, significant hemolysis, or a very high amount of vitamin B7 intake, could potentially cause false positive low hs-cTnT levels results, but this is rarely a concern in clinical practice (43). Lastly, the existence of auto-antibodies against cTnT and cTnI is well known, and these auto-antibodies are associated with false negative cTn levels, but the clinical relevance remains to be resolved (46).

2.3 DISCRIMINATION OF MYOCARDIAL INJURY

2.3.1 Cardiac troponin and mechanisms of troponin release

It is often a misconception among clinicians that all processes behind troponin levels are due to necrosis. Recent studies indicate that myocardial cells may regenerate to a limited extent (47). Therefore, cardiomyocytes may have “normal” cell turnover and regulated apoptosis (47). However, abnormal myocardial stress results in necrosis and irreversible injury, and is measured by elevated systemic cTn levels (48). Several cellular mechanisms leading to cTn release have been suggested: apoptosis, myocyte cell turnover, necrosis, the cellular release of proteolytic degradation products, and increased cell wall permeability (49). Furthermore, studies indicate that elevated cTn may be due to reversible injuries such as cell-wounds, membranous blebs or even microparticles (50,51). Whether these factors affect the interpretation of cTn levels in a clinical perspective is unknown; however, the factors indicate that there may be numerous mechanisms of cTn release. Future cTn assays may be able to differentiate between different types of cTn release and thereby facilitate interpretation of systemic levels of cTn in patients with different types of myocardial injury.

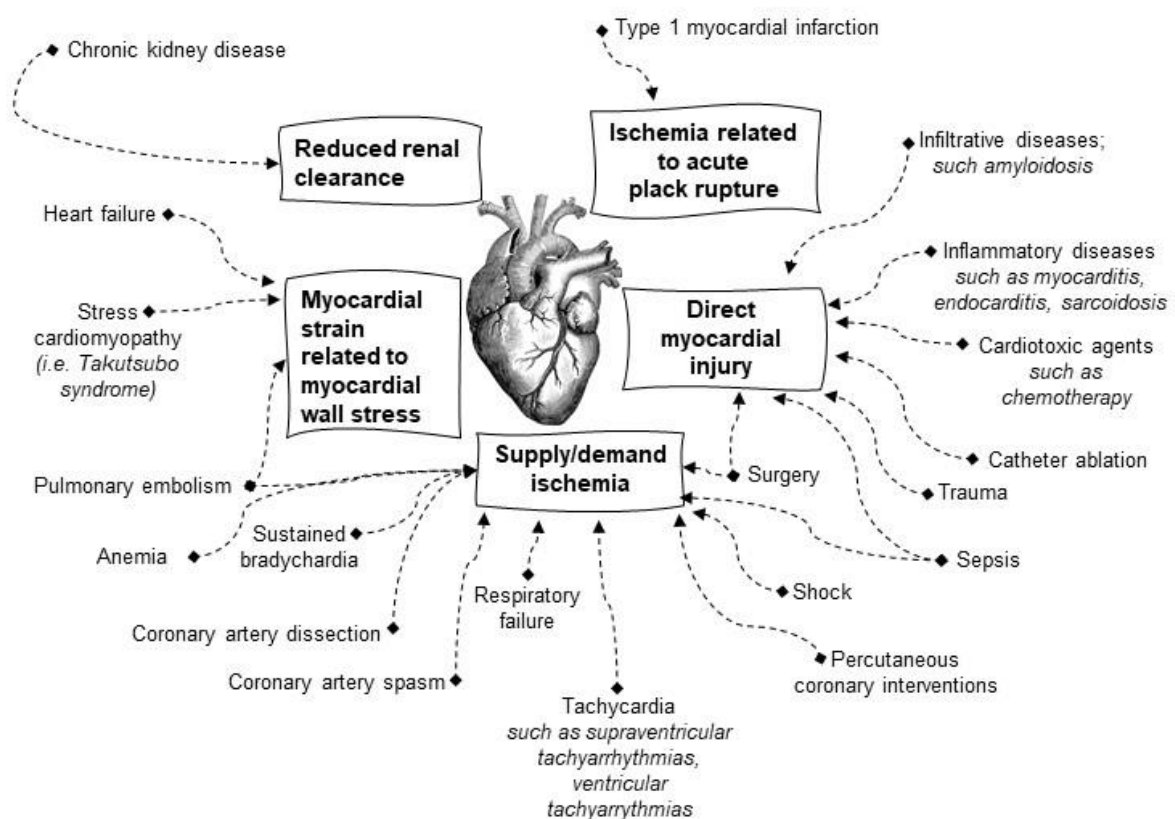


Figure 5 - medical conditions associated with myocardial injury

Numerous cardiovascular and non-cardiovascular conditions are associated with acute and chronic myocardial injury (FIGURE 5). Acute myocardial injury without acute coronary syndrome(ACS) is often associated with tachyarrhythmias, anemia, and respiratory failure (5,52–54). These are apparent causes of the mismatch in supply/demand of oxygen to the

myocardium. However, there is a lack of consensus as well as laboratory tools to determine the contribution of necrosis and/or apoptosis in myocardial injury (55). The clinical tools used today to understand nonischemic myocardial injury can only make plausible assumption about the cellular mechanisms that explain individual causes of high hs-cTn levels.

Elevated hs-cTnT concentrations in patients with chronic myocardial injury and low eGFR seem to be at least partly related to the accumulation of cTn degradation products (56). Parts of cTn are thought to be filtered through the glomerular membrane and partly cleared by the kidneys. However, clinicians should not attribute stable elevated hs-cTn levels only to lowered eGFR because it is not known to what extent lowered kidney function affects patients with a high-burden of cardiovascular co-morbidities and chronic kidney failure (57).

2.3.2 Clinical adjudication of myocardial injury

The overall indication for ordering hs-cTn testing is to first diagnose type 1 MI (1). The additional role of hs-cTn in the acute clinical setting at the ED is to effectively triage and risk stratify patients who are at low risk for a future cardiovascular ischemic event (58–61). The 4UDMI defines myocardial injury as acute if there is a rise and/or fall in cTn, with at least one level above the 99th percentile URL (1). Furthermore, the ESC 0h/1h algorithm (FIGURE 6) is a validated and effective strategy to rule out patients with suspected MI in hs-cTn levels below the 99th percentile URL (20).

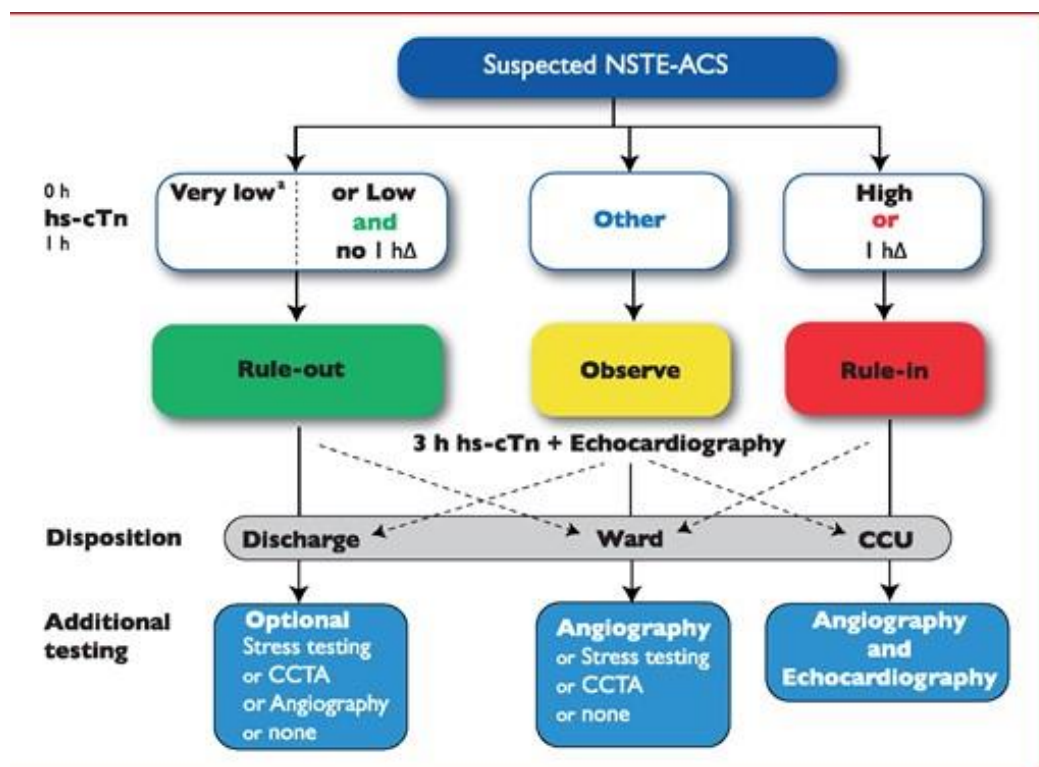


Figure 6- ESC 0h/1h rule-out and rule-in algorithm. Image reproduced with permission from the publisher(20).

However, despite effective algorithms that allow clinicians to safely discharge patients at low risk of MI, there are many patients with hs-cTn levels in the “observe zone” (FIGURE 6) or

above the 99th URL (i.e. myocardial injury) that might require further hs-cTn testing and investigations (62). There are several patients with hs-cTn levels in the “observe zone” or higher who present with symptoms such as chest and/or dyspnea with a plausible medical condition that may cause a supply and demand mismatch of oxygen to the heart, suggesting a type 2 MI or acute nonischemic myocardial injury (63). Diagnostic considerations may be further complicated in patients with chronic coronary artery disease (CAD) with acute conditions such as hypo- or hypertension, tachy- or brady arrhythmias, anemia, or respiratory insufficiency (64).

Lastly, the 4UDMI states that chronic myocardial injury is characterized by stable cTn levels with a variation of less than 20% in the appropriate clinical context (1). There are still knowledge gaps in how “stable cTn levels” should be defined. It is crucial to consider the time between blood samples collections when interpreting cTn levels. Some patients have stable elevated levels of cTn over hours, which are later normalized due to MI(65), for example; however, due to a short time between cTn analyses, these levels may be considered as “stable”.

2.3.3 The ambiguity of myocardial injury classification in clinical practice

The definition of different types of myocardial injury has differed in the past. This was, partially due to updated definitions of MI, and may have caused uncertainty between clinicians (1,12,66). Clinicians and guidelines have recognized elevated cTn in other medical conditions causing a mismatch of oxygen supply or demand in addition to MI. However, it was not until the introduction of the definitions for the different types of MI in 2007s definition of myocardial infarction (the Second Universal Definition of Myocardial Infarction) (FIGURE 7)(67) that the type 2 MI was formally acknowledged. Using the definition of MI from 2007, clinicians often gave diagnose of type 2 MI to patients with known coronary artery disease (68). The inclusion of cTn levels above the 99th percentile URL in the definition for MI was introduced only after the third universal definition of MI (3UDMI) in 2012 (12). Thus, studies exploring different types of myocardial injury and their associated prognose may differ considerably before the introduction of the 3UDMI. A large European prospective multicenter study that included patients presenting with symptoms suggestive of MI found a substantially higher incidence of type 2 MI when adjudicating using the 3UDMI compared with the Second Universal Definition of MI (68). This might explain the findings of a large real-life register study from the Swedish Health Care Register on Heart Disease (SWEDEHEART) in MI patients in 2011, in which the adjusted 1-year mortality risk for type 2 MI compared with type 1 MI was similar (69). The same group highlighted that there was poor inter-physician agreement between different types of myocardial injury in patients with MI obtained from the SWEDEHEART-register (70). Therefore, it may be inaccurate to determine MI type using earlier definitions of MI.

Definitions of Myocardial Infarction

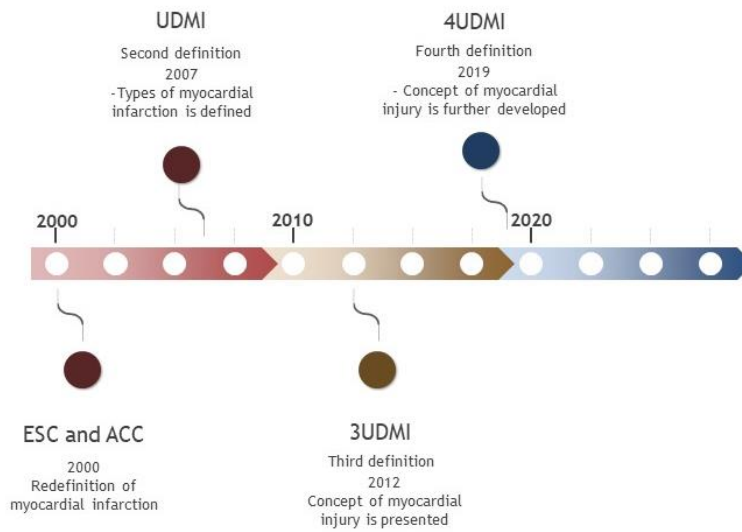


Figure 7 - definitions of myocardial infarction

Abbreviations: ESC= European Society of Cardiology, ACC = American College of Cardiology, UDMI = Universal definition of Myocardial Infarction, 3UDMI = Third Universal Definition of Myocardial Infarction, 4UDMI = Fourth Universal Definition of Myocardial Infarction.

There are several medical conditions associated with acute nonischemic myocardial injury, in which despite the absence of symptoms and clinical signs of ischemia, patients often share clinical characteristics with type 2 MI patients(63). Because the diagnosis of MI relies on clinical signs and/or symptoms of ischemia, it is often difficult to distinguish between acute nonischemic myocardial injury and MI (70,71). Clinicians must consider the clinical aspects of each patient, including comorbidities, and perhaps more importantly, age, in the clinical assessment (FIGURE 8).

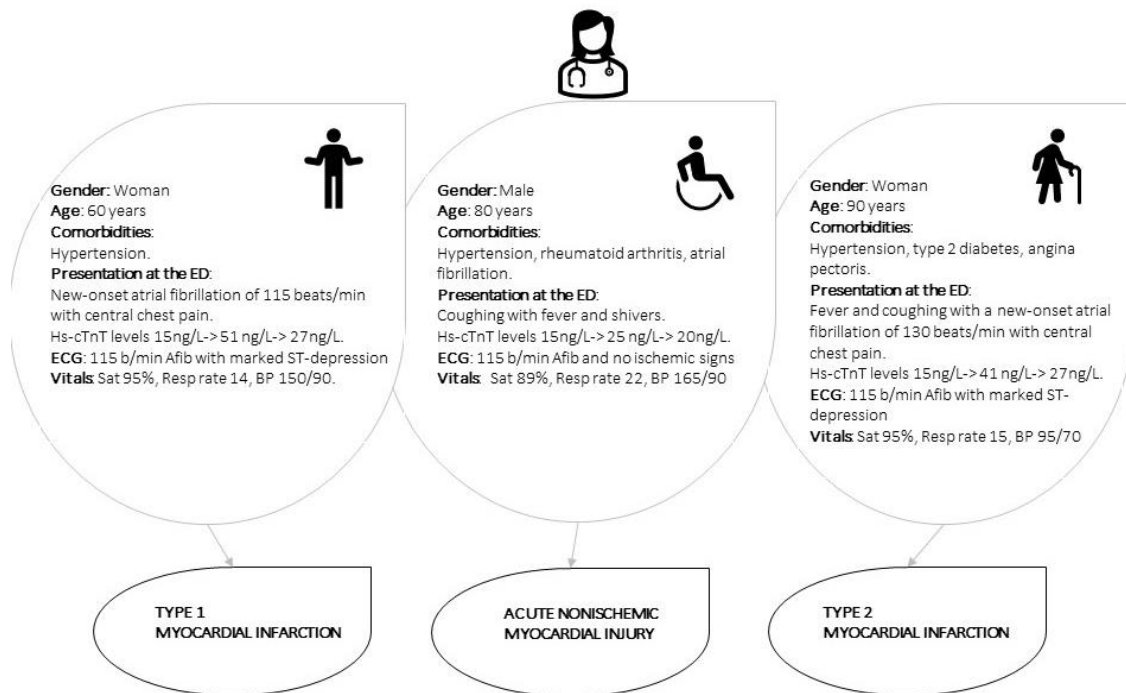


Figure 8- fictive clinical cases of myocardial injury, leaving the abundant information from investigations.

The latest universal definition of MI provides guidance for the classification of the different types of myocardial injury (1). This is important because the pathophysiological processes and management of myocardial injury differ between type 1 MI and other types of myocardial injury (1). Furthermore, hs-cTn assays have significantly improved the diagnosis of type 1 MI (8,9). Moreover, serial measurements, in conjunction with clinical signs, symptoms, and preexisting comorbidities, may provide more information for the differentiation of types of myocardial injury. However, the identification of type 2 MI and nonischemic myocardial injury is often based on symptoms and non-invasive investigations. Therefore, there may be difficulties in the diagnosis of coexisting acute and chronic medical conditions.

2.3.4 Acute coronary syndrome and hs-cTn-levels

Early troponin assays retain prognostic value for patients with ACS (72). The hs-cTn assay has not only streamlined the diagnosis of MI but also enabled detection of acute myocardial injury early in the event of an ongoing type 1 MI (11,26). The hs-cTn assay can detect small changes in cTn levels within 60 minutes of ongoing ischemia (73). However, cTn levels may not peak until 10–12 h in MI patients (74) and do not always cross the 99th percentile URL in very early stages. Therefore, the 99th percentile URL alone is not sufficient to rule out MI. However, at very low levels of hs-cTn (hs-cTnT <5) in patients with symptoms suggestive of MI or hs-cTnT small delta value (hs-cTnT >3ng/L) following a repeated measurement after 1 h with initial low level hs-cTn (hs-cTnT <12ng/L) (FIGURE 6) have been prospectively

validated and have very high negative predictive values (>99.5%) (75). Other similar approaches show similar negative predictive values (76).

Patients with suspected MI with higher levels of hs-cTn have higher positive predictive values (PPV). Moreover, patients with elevations five-fold higher than the 99th URL have a >90% PPV for type 1 MI, whereas elevations three-fold the 99th URL have a PPV around 60% (75). Therefore, patients with higher hs-cTn levels are more likely to be diagnosed with type 1 MI.

Unstable angina (UA), which is included in the ACS concept, can only be considered in the absence of myocardial necrosis (19) and the incidence of UA fell during the implementation of the hs-cTn assays (77). Older studies using less sensitive cTn assays were not able to detect acutely elevated cTn concentrations above the decision limit for MI. In retrospect, the cTn concentrations may have been considered to indicate MI if they have been measured with a hs-cTn assay (78). One study has shown that patients with UA but without myocardial injury have a lower risk of death than patients with myocardial injury (79). However, patients with UA appear to benefit less from early invasive strategies (80) and intensified antiplatelet therapy (81) compared with patients with NSTEMI. Nonetheless, patients with UA have substantially higher risks for adverse outcome than patients without coronary artery disease (82). Therefore, clinicians must consider the possibility that patients with chronic myocardial injury with symptoms suggestive of ischemia may suffer from UA, and should not exclude the possibility of a threatening acute coronary syndrome despite stable cTn measurements (77).

2.4 MYOCARDIAL INJURY IN THE EMERGENCY DEPARTMENT

The incidence of myocardial injury is highly dependent on the frequency of hs-cTn testing, which is highlighted in studies on unselected patients at the ED. Two studies classified 10%–17% of patients as having nonischemic myocardial injury (7,31). Chest pain is one of the most common complaints in ED patients (83), and MI is diagnosed in 10%–20% of these patients (84,85). Around 6%–11% of patients with symptoms suggestive of MI, including chest pain, in the ED have a final diagnosis of MI (52,61,71,86); however, this can vary considerably between different health care systems (31). Therefore, there might be substantial variation in the frequency of myocardial injury found in different health care settings. In a large prospective study in Scotland, 19% of all patients with suspected ACS had elevated hs-cTnI levels (TABLE 1) and 33 % of those were classified with nonischemic myocardial injury (18% and 14% with acute nonischemic myocardial injury and chronic myocardial injury, respectively). Among all patients with MI with hs-cTnI levels >URL, 12% were diagnosed with type 2 MI and 55% with type 1 MI (71). A recent prospective study showed that approximately 12% of patients in the ED who did not have symptoms of suspected ACS had nonischemic myocardial injury (87).

Table 1 - Incidence of myocardial injury in selected populations in the emergency department

Author	Setting	Population	Type 1 MI	Type 2 MI	ANIMI	CMI	Adjudication according	cTn-assay
Chapman (71) 2019	Consecutive patients with suspected ACS, Scotland.	47,037	10.6%	2.3%	3.6%	2.7%	4UDMI	Hs-cTnI
Bardají (6,86) 2018	Retrospective cohort study including all patients with serial testing with cTnI, Spain.	3,710	9.8%	3.8%	7.0%	2.9%	4UDMI	Sensitive cTnI
Author	Setting	Population	Type 1 MI	Type 2 MI	NIMI		Adjudication according	cTn-assay
Shah (31) 2017	Consecutive patients with a cTn requested from the clinician, Scotland.	5,815	14.5%	3.9%	5.9%		3UDMI	Hs-cTnI
Greenslade (52) 2017	Consecutive patients with chest pain and cTn, Australia.	2,349	6.3%	2.2%	4.2%		3UDMI	Sensitive cTnI-assay
Nestelberger (68) 2017	Consecutive patients with symptoms suggestive of MI. Multicenter in Europe.	4,015	17.0%	6.0%	4.3%		3UDMI	Sensitive cTn and hs-cTn
Lambrech (88) 2018	All hospitalized patients having cTnI measured on clinical indication, Denmark.	3,753	9.6%	3.2%	2.0%		Not reported	Hs-cTnI

Abbreviations. MI = myocardial infarction. ANIMI = acute nonischemic myocardial injury. CMI = chronic myocardial injury. cTn = cardiac troponin. hs-cTn = high-sensitivity cardiac troponin.

In patients with acute myocardial injury, the focus is to rule out ACS because of the potentially catastrophic consequences for patients with type 1 MI. Clinical judgement is required in the era of hs-cTn assays for patients with elevated cTn levels because individual preexisting comorbidities, age, and sex must be considered when interpreting the risks of an acute cardiovascular event. Moreover, patients with nonischemic myocardial injury and type 2 MI have an elevated risk of death compared to type 1 MI patients (3–7,71). Only a few prior studies have investigated patient prognosis in the ED with myocardial injury that has categorized types of myocardial injury according to 4UDMI (71,86). The prognosis in patients with myocardial injury is important to investigate further because a substantial number of patients presenting with symptoms suggestive of MI in the ED will not have an MI but may have elevated cTn and therefore other types of myocardial injury. Furthermore, the cause of elevated troponin in patients with chest pain is not always determined (89).

Finally, when acute myocardial injury occurs in the context of another acute illness, elevated cTn levels are more likely caused by type 2 MI or nonischemic myocardial injury than a type 1 MI. However, clinicians must be careful not to diagnose elevated cTn as type 2 MI or unspecified myocardial injury in situations where there is a moderate oxygen supply/demand mismatch. This is because such conservative approach may postpone or prevent the

appropriate treatment for type 1 MI patients because not seldom other illnesses may trigger a plaque rupture (90,91). The misdiagnosis of MI type may have been, in part, contributed variable reported incidences of type 2 MI that have been, previously reported (68,88,92).

2.4.1 Outcomes in myocardial infarction type 2 and nonischemic myocardial injury

Patients with nonischemic and type 2 MI have worse outcomes than patients with type 1 MI; this is often due to cardiovascular-related causes (3,5,71). A large prospective study (High-STEACS) in patients with suspected ACS in Scotland showed that over 23%, 33%, and 29% of patients with type 2 MI, acute nonischemic, and chronic myocardial injury, respectively, died after 1 year of follow-up compared to 14% of all patients with type 1 MI (71). A study, which included all hospitalized patients in a Danish tertiary hospital that had a fourth generation cTnI assay (sensitive cTn assay) measured on clinical indication, found that two-thirds of all patients with type 2 MI and nonischemic myocardial injury died after 3 years (88). An earlier study, also in Scotland on the consequences of the implementation of a sensitive cTn assay in patients with suspected ACS, found that 62.5%, 72.4% and 36.7% of patients with type 2 MI, nonischemic myocardial injury and type 1 MI died after a median follow-up of 5 years. The same study showed a two-fold higher adjusted risk of death in patients with type 2 MI and nonischemic myocardial injury compared with type 1 MI patients (5).

2.4.2 Chronic myocardial injury in the emergency department

The phenomenon of stable elevated cTn has been known for a long time (93–95). However, the definition of chronic myocardial injury was not presented until the latest definition of MI and may still be considered vague. The 4UDMI, highlights common conditions associated with chronic myocardial injury, such as chronic heart failure (96) and chronic kidney disease (CKD) (97), and chronic artery disease (37). Although, chronic myocardial injury is often associated with either chronic ischemic heart disease, heart failure, or chronic kidney failure, chronic myocardial injury is also linked to multiple other types of comorbidities, and/or older age (89). There are validated algorithms for patients in the ED that can effectively and safely exclude the presence of MI in patients with hs-cTn levels below the 99th percentile URL (20), but there are several patients tested and with hs-cTn levels in the observe-zone (62) or even with higher levels of hs-cTn but stable after repeated measurements over time (71,89). First, it is important to determine whether stable elevated cTn levels are of concern. A considerable proportion of patients with known cardiovascular diseases who seek medical attention in the ED because of symptoms suggestive of an MI have elevated historical hs-cTn levels. Many of these patients do not have any acute medical condition, such as MI, although they have high stable hs-cTn levels on repeated measurements (89). It is clinically important to appreciate the information that can be obtained from chronically elevated cTn levels because they are often a sign of vulnerability and high risk of adverse outcomes. Chronically elevated cTn levels do not usually imply acute measures in an ED setting, unlike acute myocardial injury that is usually associated with an acute medical condition or MI. Furthermore, it is

usually in the ED that patients with chronic myocardial injury are identified because the clinical focus is to exclude an MI diagnosis and therefore a series of measurements are taken. Patients with chronic myocardial injury need attention because they are often poorly investigated and discharged directly from the ED. A more effective referral strategy that can recommend medical treatment to patients from the ED may allow better treatment because patients benefit from closer and more continuous attention from one doctor (98).

2.5 CLINICAL UTILITY OF HS-CTN LEVELS IN SETTINGS OTHER THAN ACS

Extensive literature is available on the prognostic value of hs-cTn for a variety of acute and chronic conditions other than MI, but the practical and clinical use of hs-cTn levels remains limited (63).

The ESC guidelines for acute and chronic heart failure recommend cTn testing in patients presenting with acute heart failure caused by an ongoing ACS (99) because ischemic heart disease in addition to hypertension, is by far the most common cause to heart failure. One large meta-analysis showed that hs-cTn levels were independently associated with risk of heart failure after adjusting for common cardiovascular risk factors and natriuretic peptide levels (100).

Currently, no guidelines that support the use of hs-cTn as an acute diagnostic tool for cardiovascular diseases other than MI are available. Therefore, patients with elevated hs-cTn levels who do not meet the criteria of an MI, may be under-investigated (101), despite mounting evidence of poor long-term outcomes in these patients (4–6,86,102). In addition, no studies have presented evidence of new medical therapies in patients with type 2 MI, acute nonischemic or chronic myocardial injury. However, there are some examples of how the measurement of cTn levels in patients with medical conditions may aid in risk stratification, prognostication, and even clinical management. In pulmonary embolism, hs-cTn levels are used to risk-stratify patients and may inform on decisions for the management of acute pulmonary embolism (103). Furthermore, there is a growing body of evidence that indicates that hs-cTn testing is useful for the diagnosis and monitoring of patients with potential cardiotoxic reactions due to cancer treatment (104).

Guidelines recommend testing of cTn levels in patients presenting with symptoms suggestive of stroke to diagnose not uncommon coexisting ACS, and may also provide additional prognostic value for patients with diagnosed stroke (105).

Furthermore, raised cTnT levels are associated with neuromuscular disorders (44,106) and have shown promise as potential markers for disease progression in amyotrophic lateral sclerosis (107).

Lastly, several studies have investigated levels of hs-cTn in the general population. A large meta-analysis incorporated over 150 000 participants and detected measurable hs-cTn levels in 80% of the participants. The study found that higher levels of hs-cTn were associated with higher risk of cardiovascular disease even in levels below the 99th percentile URL (108). A

large project that accumulated data from population-based studies reported an increased risk for cardiovascular death at higher quintiles of hs-cTnI levels under the decision point of MI compared to lower quintiles of hs-cTnI levels (109). The clinical utility of hs-cTn in a general asymptomatic population remains immature. Nonetheless, although hs-cTn assays are highly specific markers for processes concerning the heart and may even predict cardiovascular events and mortality, there is still little evidence that a reduction in hs-cTn levels is associated with a lower cardiovascular risk or total risk of death. Furthermore, values of hs-cTn levels close to the LoD can vary in serial measurements and add uncertainty to individual risk stratification.

2.5.1 Treating patients with myocardial injury

Future studies will hopefully provide tools to aid the utilization of hs-cTn levels for individual risk stratification, specific diagnostics, and better patient management. In future, with the analysis of preexisting comorbidities and indirect signs of vulnerability of the heart, clinicians maybe able to identify patients with high levels of hs-cTn and to carry out the appropriate treatment based on this information. However, patients identified with chronic myocardial injury in the ED do not often undergo cardiovascular investigations (101). Furthermore, patients with type 2 MI and nonischemic myocardial injury are seldom treated with common cardiovascular medications, such as beta-blockers, ACEi/ARBs, or statins, despite patients exhibiting several known risk factors (71). Currently, no guidelines are available on how to manage patients with nonischemic myocardial injury or type 2 MI, except for the management of the inherent condition causing the supply and demand disequilibrium (1). However, guidelines are available that recommend that echocardiography is performed in patients with unexplained raised levels of hs-cTn (20) and some suggest that more attention should be given to patients with type 2 MI, with possible cases of CAD, and/or with structural heart disease that might be treatable (71). There are several studies on patients with type 2 MI in which the presence of underlying CAD has been found to be strongly associated with the risk of future cardiovascular events (5,68). Furthermore, limited data on the cause of death in patients with type 2 MI suggest that these patients often die of cardiovascular causes (59).

Few intervention studies examine patients with nonischemic myocardial injury or type 2 MI. However, some indicators suggest that hs-cTn levels may respond to interventions (110,111) and may also be followed by improved outcomes (111). One study showed that alirocumab, a proprotein convertase subtilisin/kexin type 9(PCSK9) inhibitor and potent cholesterol-lowering agent, may lower the risk of type 2 MI compared with placebo (112). Furthermore, data suggest that statin therapy may lower cTn concentrations and that the lowered mortality risk is independent of cholesterol levels in healthy middle-aged men (111). Moreover, one study showed that intensified rate control in patients with chronic atrial fibrillation and nonischemic myocardial injury lowered the cTnT levels (113). In summary, several studies indicate that it is important to optimize treatment in underlying cardiovascular diseases in

patients with nonischemic myocardial injury and type 2 MI to lower the risk of adverse outcome.

Patients who suffer from myocardial injury during non-cardiac surgery cannot be directly compared with patients in the ED, yet both groups face similar risks. Elevated hs-cTn levels are a separate prognostic factor for the risk of cardiovascular events and death. In a 30-day observational study in patients with peri-operative MI who were administered statins and aspirin were associated with reduced risk of death compared to patients who were not treated (114). In a retrospective case-control study of patients who had undergone major vascular surgery, those who received intensified treatment with cardiovascular medications (antiplatelet therapy, statins, beta-blockers, or ACEi), had a lower risk; however, the differences were not statistically significant (115). Lastly, despite a significant drop-out and a criticized of primary outcome, patients with MINS who were randomly assigned to receive dabigatran 110 mg had a better primary cardiovascular composite outcome than the placebo group in a large international randomized multicenter trial (MANAGE Trial) (116).

However, patients identified with nonischemic myocardial injury and type 2 MI have various comorbidities, and are often older in age (5,88) than type 1 MI patients, and are therefore not often subjected to further intensified cardiovascular risk elimination procedures in-hospital (71). Several patients are likely to be in these groups who require more attention and risk elimination in an out-patient setting. There are proven cardiovascular pharmacological interventions such as statins, anticoagulant, antiplatelet, and antihypertensive therapies that may potentially lower risks and ultimately improve the prognosis of these affected groups.

3 RESEARCH AIMS

The overall aim of this thesis was to investigate the characteristics, risks, and outcomes for different types of myocardial injury (i. type 1 MI, ii. type 2 MI, iii. acute nonischemic myocardial injury, iv. chronic myocardial injury).

The specific aims for each project within this thesis were the following.

Study I

To categorize and investigate different types of myocardial injury in patients in the ED. We aimed to evaluate the risks of death and cardiovascular outcomes in patients with acute nonischemic myocardial injury, type 1 MI and type 2 MI compared with patients with chronic myocardial injury.

Study II

To evaluate the cause of death in patients with type 1 MI, type 2 MI, acute nonischemic and chronic myocardial injury compared with patients without myocardial injury. In addition, we aimed to compare the risks of different causes of death, with special reference to cardiovascular and non-cardiovascular causes, in groups of patients with myocardial injury, compared with patients without myocardial injury.

Study III

To investigate whether the numbers of commonly prescribed cardiovascular medications (0–1, 2–3, or four types of medications; ACEi/ARBs, beta-blockers, statins, and platelet inhibitors) impacts mortality and cardiovascular events in patients with type 1 MI, type 2 MI, acute nonischemic, or chronic myocardial injury. Patients prescribed 2–3 and four types of medications will be compared with patients prescribed 0–1 drug with the corresponding type of myocardial injury.

Study IV

To investigate whether prescribed high- and medium-intensity statin therapy impacts risks and outcomes in patients with type 1 MI, acute myocardial injury (which consisted of patients with type 2 MI and acute nonischemic myocardial injury), and chronic myocardial injury compared with patients receiving low-intensity statin with the corresponding type of myocardial injury.

4 MATERIALS AND METHODS

4.1 METHODOLOGICAL BACKGROUND

4.1.1 Study design

The studies in this thesis are longitudinal cohort studies. The cohort is defined as a group of participants that share a defined characteristic. Participants of cohort studies of medical purposes share a characteristic of being at risk; that is, they are all at risk for a particular outcome of a certain event, or disease, but the outcome may or may not happen during the study. A priori, the researcher strictly defines the exposure to divide participants into exposed and non-exposed. Over time, the outcome is investigated according to exposure status.(117)

The studies included in this thesis are all observational cohort studies. Several factors impact the choice of study design, such as the nature of the research question, type of available data, or economic resources. Intervention studies, particularly randomized controlled trials, are often the best design to find causal relationships. A randomized controlled trial can minimize the influence of confounding or other systematic types of bias, while observational studies are able to make associative conclusions and may also generate hypotheses but cannot claim causality. However, observational studies may be the only and best alternative to make clinical assumptions for situations in which intervention studies are impossible, for instance because of feasibility or ethical considerations. Epidemiologists in Sweden have excellent opportunities to perform large observational studies. All national registers have excellent coverage, and all registers handled by the National Board of Health and Welfare cover the entire Swedish population with extremely few losses to follow-up (118–120).

A cohort study may be prospective or retrospective, which refers to how the data is collected. A prospective study allows the researcher to control the quality of information on the exposure and the outcome (117). The studies in this thesis are retrospective in design and the registers of which the data were extracted have excellent coverage and high validity. Furthermore, the cohort studies in this thesis are open cohorts, meaning that in contrast to a closed cohort, new participants may be included over the course of the study.

Lastly, the reference or the non-exposed group may be internal or external. An internal reference group consists of unexposed patients of the same cohort. However, there are circumstances in which the entire cohort is exposed; for these cohorts, there is occasionally an appropriate external cohort that shares the same characteristics but not the examined exposure and this group or population may be used as a reference group. All studies conducted in this thesis used an internal reference group.

Overview of studies

TABLE 2. Study overview.

Study	I	II	III	IV
Aim	To evaluate the risks for death and cardiovascular outcomes in patients with acute nonischemic acute myocardial injury, type 1 MI and type 2 MI compared with chronic myocardial injury.	To evaluate the causes of death in patients with type 1 MI, type 2 MI, acute nonischemic and chronic myocardial injury, compared to patients no myocardial injury. In addition, we aimed to compare the risks of different causes of death, with special reference to cardiovascular and non-cardiovascular causes, in groups of myocardial injury, compared to patients with no myocardial injury.	To investigate whether numbers (grouped in to 0–1, 2–3, or four types of medications) of common prescribed cardiovascular drugs impacts mortality and cardiovascular events in patients with type 1 MI, type 2 MI, acute nonischemic acute, or chronic myocardial injury compared to 0–1 prescribed drug in the corresponding type of myocardial injury.	To investigate whether prescribed high- and medium-intensity statin therapy impacts risks and outcomes in patients with type 1 MI, acute myocardial injury (type 2 MI and acute nonischemic myocardial injury), and chronic myocardial injury compared to low-intensity statin therapy in the corresponding type of myocardial injury.
Hypothesis	Patients with chronic myocardial injury have similar long-term prognosis as patients with acute nonischemic myocardial injury and type 2 MI.	Patients with myocardial injury without type 1 MI have high risk of death due to cardiovascular causes compared to patients with no myocardial injury.	Patients who are prescribed a high number of common cardiovascular drugs have lower risks and incidence of death and cardiovascular events than patients treated with 0–1 drug.	Patients with all types of myocardial injury prescribed with high- or medium intensity statin have lower risks and better outcome than patients prescribed with low-intensity statin.
Study design	Observational cohort study			
Study population				
<i>Eligible patients</i>	All patients with at least one visit of chest pain in the ED and with at least one hs-cTnT level analyzed.	All patients with at least one visit of chest pain in the ED and with at least one hs-cTnT level analyzed who died during follow-up.	As study I.	All patients included in study I who had at least 1 dispensed statin prescription 30 to 180 days after the index date.
<i>Exclusion criteria</i>	Missed MI, STEMI, type 3–5 MI, age <25 years, eGFR <15, and/or renal replacement therapy, insufficient information on medical conditions to determine type of myocardial injury, early death (within 30 days)	As study I except early death (within 30 days)	As study I.	As study II.
Study setting	Karolinska University Hospital, Huddinge and Solna.			
Study period	January 1, 2011, to October 20, 2014	January 1, 2011, to October 20, 2014	January 1, 2011, to October 20, 2014	January 1, 2011, to October 20, 2014
Follow-up	All-cause mortality until December 31, 2017. All other outcomes until December 31, 2016.	All outcomes until December 31, 2016.	All outcomes until December 31, 2016.	All outcomes until December 31, 2016.

TABLE 2. Study overview (continued).

Exposure	Patients with myocardial injury (hs-cTnT >14ng/L) categorized into; type 1 MI, type 2 MI, and acute nonischemic myocardial injury.	Patients tested with hs-cTnT and categorized into; type 1 MI, type 2 MI, acute nonischemic myocardial injury, and chronic myocardial injury.	Patients with myocardial injury with categories of dispensed common cardiovascular drugs (ACEi/ARB, beta-blockers, statins, platelet inhibitors): 2-3 and 4 numbers of drugs	Patients with myocardial injury with categories of dispensed statin intensity: medium- and high-intensity statin treatment.
Referent	Patients with chronic myocardial injury.	Patients with no myocardial injury (hs-cTnT levels <14 ng/l).	Patient with dispensed 0-1 drugs in corresponding type of myocardial injury.	Patients dispensed low-intensity statin treatment in corresponding type of myocardial injury.
Statistical methods	Survival analysis (Cox regression). Complete case analysis Competing risk analysis (Fine-Gray proportional sub hazards model)	Logistic regression.	Survival analysis (Cox regression).	Survival analysis (Cox regression)
Outcomes	All-cause mortality Cardiovascular mortality Non-cardiovascular mortality Cardiovascular events	Cardiovascular mortality Non-cardiovascular mortality Cause specific mortality	All-cause mortality Composite of death, myocardial infarction, heart failure, stroke.	All-cause mortality Composite of death, myocardial infarction, heart failure, stroke.
Main findings	Patients with acute nonischemic myocardial injury and chronic myocardial injury had similar and very high risks of death, with almost half of patients being dead within 4 years of follow-up.	Patients with type 1 MI and acute nonischemic or chronic myocardial injury have high Risk of death from cardiovascular causes.	Patients with type 2 MI, acute nonischemic or chronic myocardial injury treated with several common cardiovascular medications are associated with reduced risks of death.	Patients with myocardial injury treated with high-intensity treatment had lower crude risks, but estimates were not significant association after adjusting for confounders.
Publication	<i>Heart</i> , 2019.	<i>American Journal of Medicine</i> , 2020.	<i>Journal of American Heart Association</i> , 2021.	<i>American Journal of Medicine</i> , 2021.

hs-cTnT = high-sensitivity cardiac troponin T, MI = myocardial infarction, N/A = not applicable, NSTEMI = non-ST-segment elevation myocardial infarction, STEMI = ST-segment elevation myocardial infarction

4.1.2 The dataset

FIGURE 9 illustrates the construction of the main dataset that was used in the investigations presented in this thesis.

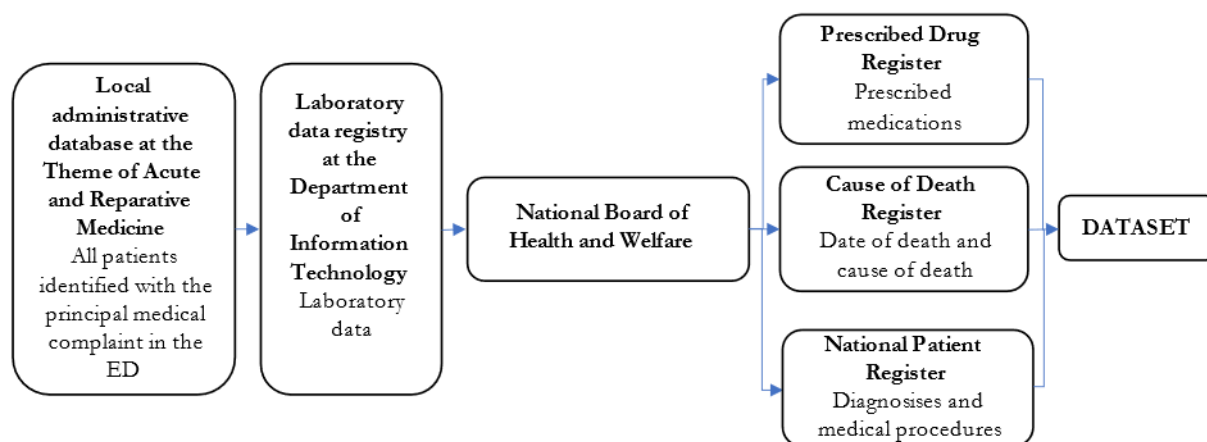


Figure 9 - the data assembly. ED = emergency department.

4.2 LOCAL DATA REGISTERS

4.2.1 Local administrative database

We identified the original cohort from the Karolinska University Hospital local administrative database. All patients visiting the ED are triaged by a nurse using a triage system (RETTs) and tagged with their principal complaint. The information such as date, time of visit, and duration of stay in the ED is registered and stored. The cohort identified in this thesis consisted of patients with chest pain as their principal complaint. Furthermore, for this thesis, we requested data from all other visits (including those with other principal complaints) from the patients who registered with chest pain during the inclusion period.

4.2.2 Laboratory data registry at the Department of Information Technology

The laboratory data for all patients visiting the Karolinska University Hospital are stored at the local laboratory data registry at the Department of Information Technology. After identifying all patients with chest pain as their principal complaint in the ED during the inclusion period we sent the information to the Department of Information Technology to collect the laboratory data of all the identified visits, including hs-cTnT levels. The Elecsys 2010 system (Roche Diagnostics, Mannheim, Germany) was used to analyze hs-cTnT levels in the identified patients in this thesis.

4.3 NATIONAL REGISTERS

4.3.1 The National Board of Health and Welfare

The Ministry of Health and Social Affairs oversees the Swedish National Board of Health and Welfare. The institution's responsibilities and activities include maintaining health data registries and official statistics, as well as developing standards based on legislation and acquired data. Every patient registered with a digital medical record is automatically updated in the Population Register. The register is maintained by the Swedish National Tax Agency, which has a long history in Sweden and contains almost 100% coverage of every individual in Sweden regarding identity, family status, migrations and marital status (120). All Swedish citizens are registered with a unique personal number (Personal Identification Number) which makes it possible to acquire specific data from public registers for e.g. research purposes (119). The data from the present cohort of patients was then sent to the Swedish National Board of Health and Welfare, where information on comorbidities and outcomes from the National Patient Register (NPR), medication use from the Prescribed Drug Register, and dates and causes of deaths from the Cause of Death Register were retrieved.

4.3.2 The National Patient Register

The NPR consists of information on all hospital admissions (the Swedish National Inpatient Register) since 2001, the NPR also holds information, including on patients treated in the outpatient setting. The register holds basic information, including about Personal Identification Number, sex, age, and place of residence, and holds detailed information about dates of hospital visits, diagnoses, and procedures. The register does not contain information on the primary care or visits where doctors were not been involved. Diagnoses, discharge, and surgical operations information are coded according to the international version of illness classification (ICD). At the time of discharge from hospital, the consulting physician in charge of the patient's care records the diagnosis. After that, the diagnostic data are sent to the NPR via electronically transmission. This approach is performed throughout Sweden, and it is believed that only 1% of inpatient data are underreported. The National Board of Health and Welfare register for in-patient diagnoses has been validated, and a meta-analysis showed that 85 to 95 percent of them were accurate (121). The ICD-10 was introduced in 1997 and has been used in all Swedish hospitals since 1998 (121). The PPV for several cardiovascular diagnoses is high; for MI, it is approximately 98–100% (121), for atrial fibrillation it is approximately 97% (121), and for stroke it is around 85% (122). The PPV for heart failure varies, but can reach 95% if only the primary diagnosis is considered (123).

4.3.3 The Prescribed Drug Register

The Prescribed Drug Register started in 2005 and contains all prescribed and dispensed drugs that have been collected from Swedish pharmacies. The register contains information about the patient such as sex, age, place of prescription and dispensation, and characteristics of the doctor who prescribed the drug (124).

4.3.4 The Cause of Death Register

Data retrieved from the local data registers concerning the cohort were sent to the National Board of Health, which is responsible for the Cause of Death Register, to collect information on all cases of death in the identified cohort. The Cause of Death Register has almost 100 % coverage. There are a few missing cases of causes of death every year due to citizens who die abroad. Deaths must be immediately reported to the Swedish Tax Agency by the responsible doctor and the cause of death is reported to the National Board of Health within 3 weeks of the individual's death. If there is an unnatural death, unclear identity, obscure case or suspicion of malpractice, the physician must report the death to the police authorities. These cases will often be the subject of subsequent forensic investigation. The cause of death is reported by the caring physician; the immediate contributing and underlying factors are also reported, as well as place, date of death, and other individual data (118). One study showed 77% agreement between the cause of death expected on case summaries and the cause of death from death certificates (125), but higher concordance was found between the Cause of Death Register and medical records for cardiovascular disease (87–88%) (125,126). Overall, malignant tumors have shown the highest accuracy (90%) regarding the agreement between the Cause of Death Register and case reports (125). Several factors make the cause of death certificate unreliable; death outside the hospital, the time between the last hospital visit and death, and discrepancy between the last main diagnosis and the cause of death can all influence the accuracy of the death certificate (127). The fall of the autopsy rate contributes to the uncertainty of the cause of death (128).

Finally, several aspects might influence the validity of the information in the Cause of Death Register, foremost in certain groups of diagnoses and/or more specific diagnosis codes, but overall, it withholds good accuracy. Furthermore, when correcting the underlying cause of death one study showed that, most diagnostic groups remained stable (125).

4.3.5 Origin of variables

The origins of the variables (both predictors and outcomes) are summarized in TABLE 3.

TABLE 3. Origin and description of variables used in studies I – IV.

Variable	Description/Definition	Used in study ^a			
		I	II	III	IV
Local administrative database					
Index date	The first date during the study period on which the patient seeks medical attention in the ED with at least one measurement of hs-cTnT (and for all patients with myocardial injury at least one above the URL).				
Local laboratory database					
Hs-cTnT levels					
Haemoglobin levels	Retrieved at the index visit.				
Creatinine levels ^b	Retrieved at the index visit.				
National Patient Register					
Age					
Sex					
Myocardial infarction ^{c, d}	ICD-10: I21, I22.1, I22.8				
Atrial fibrillation	ICD-10: I48				
Prior heart failure ^e	ICD-10: I50				
Prior revascularization ^f	ICD-10: FNG05, FNG02, FNA00, FNA10, FNC10, FNC20, FNC30, FNC40 or FNG00.				
Coronary angiography	ICD-10: AF037				
Prior stroke	ICD-10: I60-I64				
Chronic Obstructive Pulmonary Disease	ICD-10: J44.0, J44.1, J44.8, J44.9				
Hypertension	ICD-10: I10				
Active cancer ^g	ICD-10: C00-C97				
Cause-of-death register					
Date of death					
Cardiovascular death ^h	ICD-10: I-chapter (except I45.6, I45.8 and I54.4), M219, R001, R008, R012, R960 & R961				
Cardiovascular death ⁱ	ICD-10: I-chapter and R001, R008, R012, R960 & R961.				
Non-cardiovascular death	ICD-10: all other codes not specified above.				
Ischemic heart disease	ICD-10: I20-I25.				
Heart failure/cardiomyopathy	ICD-10: I50, I11.0, I42, I43, I25.5, I13.0, I13.2				
Other cardiovascular causes	ICD-10: All other diagnoses in the I-chapter not covered by ischemic heart disease, heart failure/cardiomyopathy including valvular heart disease I05-I08 and I33-I39, stroke I60-I64 and R960 and R961.				
Cancer death	ICD-10: C00-C97				
Non-cardiovascular noncancer death	ICD-10: All other chapters (except R960 & R961)				
Prescribed Drug Register					
<i>Dispensed medications ^j</i>					
Aspirin	ATC: B01AC06				
Clopidogrel	ATC: B01AC04				
Ticagrelor	ATC: B01AC24				
Prasugrel	ATC: B01AC22				
Beta-blockers	ATC: C07				
Statins	ATC: C10AA				
Hypoglycaemic medication ^k	ATC: A10				
ACEi/ARBs	ATC: C09				
Patient records					
<i>Investigations</i>					
ECG findings ^d					

^aVariables used in the studies are marked with **colour**.

^bEstimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:

CKD-EPI-formula = $141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209 \times \alpha} \times 0.993^{\text{Age}} \times 1.018$ [if female]. Where Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. All serum creatinine in the database is given in $\mu\text{mol/L}$ and must be divided by 88.7 to get mg/dL.

^cAll patients with an MI diagnosis associated with the index visit were identified by ICD-codes in any position, meaning that not only primary discharge diagnoses were used, but also MI diagnoses in secondary or any other positions. Prior MI was defined according to a discharge diagnosis in primary position before index date in the National Inpatient Register.

^dIn all studies, ECGs of all patients with acute MI associated with the visit were examined by at least one cardiologist, to exclude all patients with ST-segment elevation myocardial infarction (STEMI).

^eIn all studies, prior heart failure was defined according to ICD-codes only as primary diagnosis and only in the National Inpatient Register.

^fBoth prior Percutaneous Coronary Intervention (PCI) or prior coronary artery bypass graft (CABG).

^gAny ICD-code in a primary position within 2 years before the index date.

^hCardiovascular death was defined as death caused by atherosclerotic disease (I29).

ⁱCardiovascular death was defined as caused by atherosclerotic disease as previously and including I45.6, I45.8 and I54.4, except for M219 (acquired deformity of limb).

^jOngoing medication was defined as ≥ 2 dispensed medications during the year preceding the index date.

^kDiabetes was defined as ongoing medication with any hypoglycaemic agent under ATCA10.

ACEi/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, ECG = electrocardiogram, Hs-cTnT = high-sensitivity cardiac troponin t.

4.4 DATA COLLECTION AND STUDY POPULATION

The study populations of this thesis are presented in FIGURE 10. The index data were defined in all studies as the first occasion on which the patient sought medical assistance in the ED and with a measurement of hs-cTnT > 14 ng/L (TABLE 2). The hospital visit deemed as the index date was defined as the index visit.

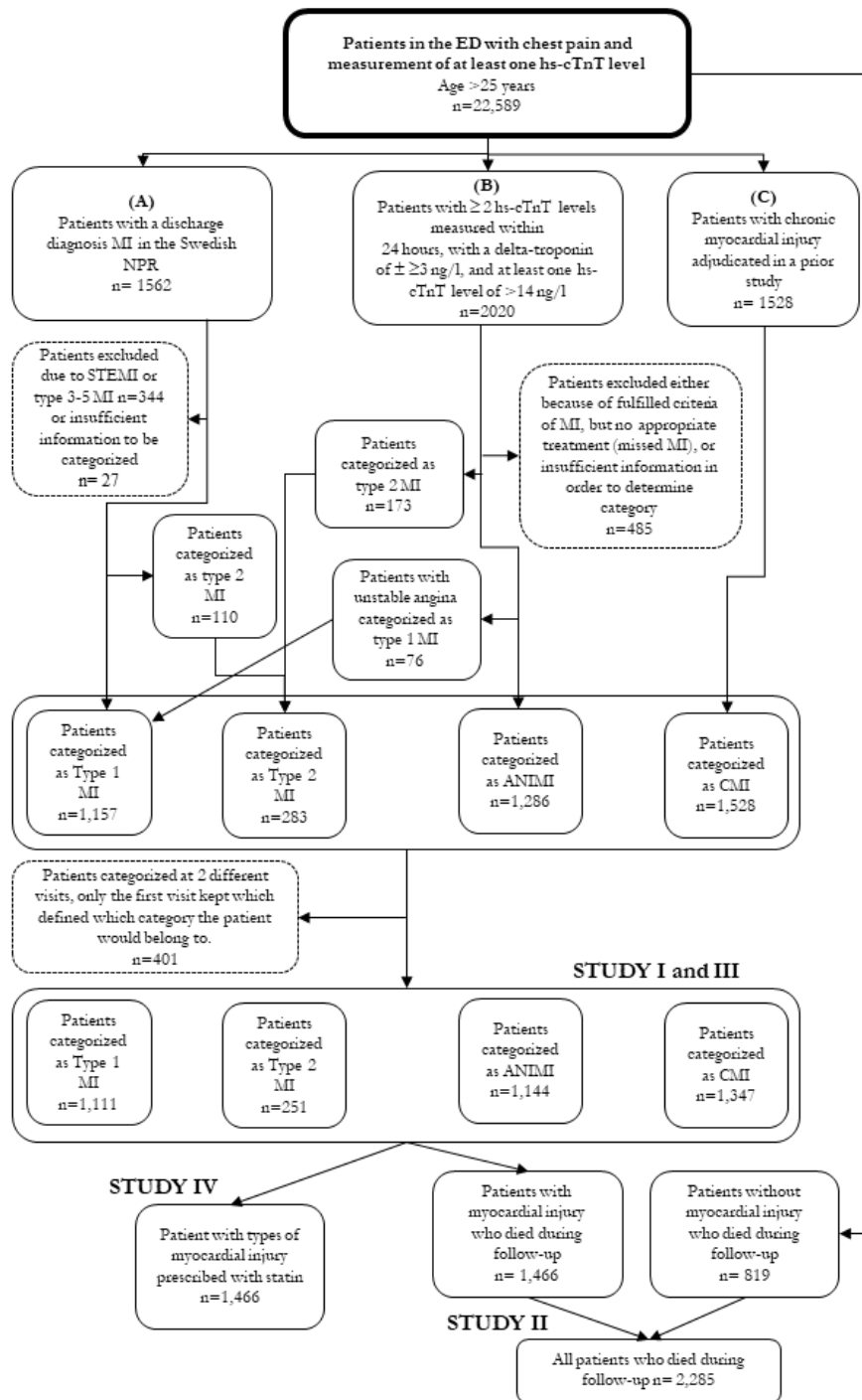


Figure 10 - the identification of the study populations. eGFR = estimated glomerular filtration rate, Hs-cTnT = high-sensitivity cardiac troponin T, MI = myocardial infarction, STEMI = ST-elevation myocardial infarction, NPR = National Patient Register, ANIMI = Acute nonischemic myocardial injury, CMI = chronic myocardial injury.

Study I – patient selection

The study population was retrieved from a cohort of 22 589 patients aged >25 years who all had at least one visit to the ED for chest pain at the Karolinska University Hospital in Stockholm, Sweden, between January 1, 2011, and October 20, 2014 (FIGURE 10). All additional visits over this period, including those for reasons other than chest pain, were also available. Therefore, we had information from every previous visit to the ED from January 1, 2011, onwards regardless of the principal cause of each visit; this information was also considered in the analysis. In addition, information on laboratory values that were measured during these visits was available. We identified all visits, regardless of primary complaint, with an available hs-cTnT measurement between January 1, 2011, and October 20, 2014. We identified all patients with a discharge diagnosis of MI in the Swedish National Register. Furthermore, all patients with delta-troponin $\pm \geq 3$ ng/L within 24 h from of the admission hs-cTnT level and at least one measurement >14 ng/L were identified; patients were then categorized patients into type 1 MI, type 2 MI, or acute nonischemic myocardial injury. Patients with chronic myocardial injury were identified and categorized in an earlier study (group C) (89).

We aimed to categorize patients into four categories: i. chronic myocardial injury, ii. acute myocardial injury, iii. type 1 MI, and iii. type 2 MI. To simplify the categorization of patients, we first identified all patients with a diagnosis of MI coded as I21 or I22 in any position in the NPR (group A). To find patients with acute myocardial injury, we restricted our search to patients who had at least two hs-cTnT measurements within 24 h, a delta-troponin level of $\pm \geq 3$ ng/L, and at least one hs-cTnT measurement indicating levels >14 ng/L (group B). The 2015 ESC guidelines for ACS recommend an exclusion criterion with low delta-troponin of hs-cTnT in patients with symptoms suggestive of NSTEMI (19), which constituted the rationale for the choice of delta-troponin value in our study. A modest delta-troponin value was chosen to achieve high sensitivity to ensure all patients with MI or acute nonischemic myocardial injury were detected. In total, 2020 patients were identified as potentially having acute myocardial injury. (FIGURE 10).

The adjudication of acute myocardial injury

All authors from Study I were involved in the adjudication process. Three of the authors were cardiologists (A.S., L.D., and M.J.H.), two were residents in internal medicine (E.K, and A.R.), and one in cardiology (M.L.). All identified cases were evaluated by two of the investigators of whom one always was a cardiologist. All cases in which the categorization was not consistent were debated in a group with at least three co-authors, one of whom was the senior author (M.J.H.). A consensual decision was sought, and if none could be reached, M.J.H. chose how to categorize the patient. All cases that were regarded as difficult to evaluate by any of the investigators were discussed within the group. This meant almost all type 2 MI cases were evaluated by at least three investigators. When there was insufficient

information on imaging, laboratory investigations, or other data to determine which type of myocardial injury was present, or if the patient met the criteria for type 1 MI but did not receive adequate treatment (missed MI) or insufficient information to determine category, the patient was excluded (n=485). To categorize patients, we examined all available information from the patient medical records, including comorbidities, vital signs, laboratory values, ECGs, imaging, coronary angiographies, echocardiographies, and cardiac magnetic resonance imaging. For the adjudication of type 1 MI and type 2 MI, we used the third and the fourth universal definitions of MI as an aid.(1,12) We used the criteria proposed by Saaby et al.(54) to determine "how much" is needed for a patient to develop a type 2 MI to distinguish acute nonischemic myocardial injury and type 2 MI, from type 1 MI. The following conditions with decreased oxygen supply to the heart were deemed to be associated with acute nonischemic myocardial injury, and type 2 MI: a hemoglobin concentration of <5.5mol/L for men and <5.0 mol/L for women; bradycardia requiring medical treatment or pacing; coronary embolism (endocarditis, venous thromboembolism); hypoxia with an arterial oxygen tension <8kPa and clinical signs of acute respiratory failure for longer than >20 min; and hypotension with a systolic pressure <90 mmHg concurrent with at least one of the following signs of hypoperfusion; i. metabolic acidosis, ii. arterial oxygen pressure <8kPa, iii. oliguria for longer than >3 h. The following conditions with increased oxygen demand were deemed to be associated with acute myocardial injury; ventricular tachycardia lasting >20 min; supraventricular tachycardia with a ventricular rate of > 150 beats/min; hypertensive pulmonary edema; and arterial systolic hypertension >160 mmHg with concomitant left ventricular hypertrophy.

We used the above-mentioned criteria as a guide, but we also analyzed each patient in a clinical context. The MI cohort (group A) (FIGURE 10) was adjudicated in accordance with to the criteria of the third universal definition of MI.(12) All patients with ST-segment elevation as well as type 3, 4, and 5 MI (n=344) were excluded from the study. All patients with an ICD-10 diagnosis of UA (n=76) were reclassified as type 1 MI based on the presence of cTn levels above the 99th percentile value, even if there were no substantial dynamic fluctuations in cTn levels, in accordance with the guidelines (1,12). Furthermore, we removed 27 patients with an MI diagnosis from group A who did not meet the MI criteria and had insufficient evidence to be classified into any other group. None of these patients had their MI diagnosis in the primary position. A total of 110 patients in group A met the criteria for type 2 MI. In group B (FIGURE 10), an additional 173 individuals met the criteria for type 2 MI. Patients who met the criteria for MI but did not receive adequate treatment (missed MI) and patients whom there was not enough information to identify an appropriate category (n=485) were excluded from the study.

Adjudication of patients with chronic myocardial injury

A previous study adjudicated cases with chronic myocardial injury (89). The patients in that study came from the same cohort of patients as the current studies in this thesis, although only those with a principal cause of chest pain were included in this study. The selection

process was described in detail in their paper (89). Briefly, all patients with at least one hs-cTnT level of >14 ng/L, or <12 ng/L and a delta-troponin of $\pm \geq 3$ ng/L proposed by the European Society of Cardiology guidelines (19) to identify patients at high risk for MI, during the index visit were identified and adjudicated to exclude patients with any concurrent acute medical conditions that could have resulted in elevated hs-cTnT levels. Only patients with at least two hs-cTnT measurements recorded during index visit were considered as having chronic myocardial injury. The research group evaluated cTn values obtained at various times over several months or years to determine whether each patient had chronic myocardial damage. The group used medical records and all relevant information in a similar way to the current investigation to determine the presence of persistent myocardial injury. To evaluate whether cTn levels changed, no precise criteria were used for determining the stability or elevation of cTn levels.

Final selection of the study population

Patients with i. chronic myocardial injury (n=1 528), ii. acute nonischemic myocardial injury (n=1 286), iii. type 1 MI (n=1 157), and iv. type 2 MI (n=283) were identified by the adjudication procedure (FIGURE 10). However, because there was some overlap between groups, we decided to only use the initial visit for the classification, which was regarded as the index visit, therefore, if a patient was originally classified into one group and then classified into another group based on a later visit to the ED, the initial visit (index visit) was used for classification. Based on this classification, the final study population consisted of n=1 347 patients with chronic myocardial injury, n=1 144 patients with acute nonischemic myocardial injury, n=1 111 patients with type 1 MI, and n=251 patients with type 2 MI.

Study II

All patients >25 years of age who had an index visit between January 1, 2011, and December 31, 2012, were eligible to participate in Study II (FIGURE 10). In this study we included all patients who died and were categorized in Study I during follow-up in the final analysis, including early death (0-30 days after index date) before December 31, 2017. Patients who died within the same period and who had hs-cTnT levels <14 ng/L were categorized as having no myocardial injury.

Study III

The study population in Study I was also used in Study III. The National Drug Register was used to obtain information on prescriptions that were dispensed to the patients (FIGURE 10).

Study IV

Using the same study population identified in Study I, we gathered information on all dispensed statin prescriptions from the National Drug Register after the index date. We included and defined the study population as all patients who had a dispensed prescription for any type of statin (30–180 days after the index date) (FIGURE 10).

4.5 EXPOSURE MEASURES

4.5.1 Study I

In Study I, the exposure variable was the level of hs-cTnT at the time of the index visit for all included patients. The exposure was categorized according to the following type of myocardial injury: type 1 MI, type 2 MI and acute nonischemic myocardial injury. Patients with chronic myocardial injury were used as reference group. We hypothesized that patients with chronic myocardial injury would have a similar long-term prognosis to patients with acute nonischemic myocardial injury and type 2 MI.

4.5.2 Study II

In Study II, the exposed group included all patients categorized with myocardial injury from Study I that had hs-cTnT levels <14ng/L and had visited the ED with the principal complaint of chest pain, who then died during follow-up. Patients with no myocardial injury were used as the reference group.

4.5.3 Study III

In Study III, included all patients in Study I. To identify patients who waited to initiate their medical therapy, medication at discharge was defined as at least one dispensed prescription between 0 and 180 days from the index date. In Sweden, the filling of one prescription do normally covers 3 months. The number of medications was determined by counting the number of prescriptions for cardiovascular medications, such as beta-blockers (Anatomic Therapeutic Chemical classification system (ATC) code C07A), ACE-i/ARBs (ATC C09A and C09C), statins (ATC C10AA), and platelet inhibitors (ACT B01AC). For example, if a patient had a dispensed prescription for different classes of cardiovascular drugs, every represented class would be counted, but, if a patient had several dispensed prescriptions for the same class of drugs, it would only be counted as one. Platelet inhibitors (acetyl salicylic acid and P2Y12 inhibitors) were defined as one group because P2Y12 is seldom used by patients with type 2 MI and only used by patients with nonischemic myocardial injury with prior revascularization, stroke, or type 1 MI. The number of medications was used to categorize patients into the following three groups: 0–1, 2–3, or 4 types of medications. Patients categorized into the 0–1 medication group were used as the referent group. All patients were stratified according to the type of myocardial injury.

4.5.4 Study IV

In Study IV, composed of all patients in Study I with at least one dispensed prescription of statins after the index date. However, because the number of patients with type 2 MI was much lower than the number of patients with other types of myocardial injury, we expected few outcomes within this group. As a result, we grouped all patients with type 2 MI and acute nonischemic myocardial injury together. A similar classification was previously proposed, which may make the definition of myocardial infarction easier to understand (130), and investigations show that they have similar prognoses (71). Treatment with statins was defined

as at least one dispensed prescription 30–180 days after the index date. Available information on all dispensed statins and their doses was retrieved from the National Prescribed Drug Register. The following statin types were included: simvastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin (TABLE 4). If patients had been prescribed different statin types or doses, only the first dispensed prescription and the corresponding dose were used as the exposure. The patients were categorized by the dose of the dispensed statin type into three statin intensity categories consistent with the American College of Cardiology/American Heart Association intensity chart (TABLE 4)(131). The exposed group was all patients with moderate- or high-intensity statin treatment. Patients with low-intensity statin treatment were used as the referent group. All patients were stratified according to the type of myocardial injury.

TABLE 4. Dispensed statin types identified in the study and presented in consistent with the American College of Cardiology/American Heart Association intensity chart

Type	ATC code	Low-intensity	Moderate-intensity	High-intensity
Pravastatin	C10AA03	10, 20 or 40 mg	-	-
Fluvastatin	C10AA05	20 or 40 mg	80 mg	-
Simvastatin	C10AA01	10 mg	20 or 40 mg	80 mg*
Atorvastatin	C10AA05	-	10 or 20 mg	40 or 80 mg
Rosuvastatin	C10AA07	-	5 mg	10, 20 or 40 mg

ATC = Anatomical Therapy Code; mg = milligram. Pitavastatin and lovastatin were not provided in Sweden during the study period.

*All dispensed prescriptions of simvastatin 80 mg were added to the high-intensity treatment category because such prescriptions are approved for use by the Swedish Medical Products Agency and European Medicines Agency and are, therefore, used occasionally in Sweden.

4.6 OUTCOME MEASURES AND FOLLOW-UP

4.6.1 Study I

All-cause death was the primary outcome in Study I. MI, heart failure, cardiovascular and non-cardiovascular death were all secondary outcomes. To get diagnoses for all outcomes, we used the Swedish NPR. Cardiovascular death was defined as death caused by atherosclerotic disease, as defined by the European Society of Cardiology (129). Follow-up for long-term outcomes began 31 days after the index date. For all-cause mortality, the end of follow-up was December 31, 2017, and for all other outcomes, it was December 31, 2016.

4.6.2 Study II

The outcome studied in Study II was cause of death because the study population consisted of patients who died during follow-up; the follow-up period ended on December 31, 2016. According to the underlying cause of death in the Cause of Death Register, cause-specific death was divided into two categories: 1) cardiovascular death and 2) non-cardiovascular

death. Any code in the I chapter, R960, or R961 in ICD-10 was considered a cardiovascular death, while all other deaths were considered non-cardiovascular. The following subgroups of cardiovascular death were identified: ischemic heart disease (codes I20–I25); heart failure/cardiomyopathy (codes I50, I11.0, I42, I43, and I13); all other cardiovascular causes of death (codes I05–I08 and I33–I39), ischemic stroke (codes I63–I64), hemorrhagic stroke (codes I60–I62), and all other code in the I chapter, including R960 and R961.

Noncardiovascular deaths were divided into two categories: 1) cancer deaths (codes C00–C97) and 2) non-cardiovascular non-cancer deaths (all other non-cardiovascular deaths).

4.6.3 Study III

The primary outcome for Study III was all-cause death. A composite of all-cause mortality, MI, heart failure, and stroke was used as a secondary outcome. Follow-up began 180 days following the index visit and ended on December 31, 2016.

4.6.4 Study IV

The primary outcome for Study IV was all-cause death. A composite of death, myocardial infarction, heart failure, and stroke was used as the secondary outcome. The follow-up period started when a statin prescription was first dispensed after the index date (at the earliest, 30 days after the index visit, and at the latest, 180 days after the index visit) and ended on December 31, 2016.

4.7 STATISTICAL ANALYSIS

Means and standard deviations, or medians, were employed to describe baseline characteristics in all studies in this thesis, while numbers and percentages were applied to describe categorical variables. In Study I, the World Programming System V.3.1 (World Programming Ltd, Romsey, Hampshire, UK) was used to handle data, and R V.3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) was used to perform statistical analyses. STATA and R software were used to manage data and perform statistical analyses in studies II–IV. Stata (v. 15.1; Stata Corp, College Station, Texas, USA) and R software were used in study II (v. 3.6.0; R Foundation for Statistical Computing, Vienna, Austria). Stata (v. 16.0; Stata Corp, College Station, TX, USA) and R software (v. 3.6.2; R Foundation for Statistical Computing, Vienna, Austria) were used in study III. Finally, Stata v. 17.0 (Stata Corp) and R software (v. 4.1.0 R Foundation for Statistical Computing, Vienna, Austria) were used in study IV.

4.7.1 Study I

In Study I, the cumulative incidence of all-cause mortality was calculated using the Kaplan-Meier method. We used patients with chronic myocardial injury as the reference group and Cox models were used to calculate hazard ratios (HRs) with 95 percent CIs for all-cause mortality, cardiovascular and non-cardiovascular mortality, hospitalization for heart failure, and MI in patients with acute nonischemic myocardial injury, type 1 MI, and type 2 MI, respectively. Age, sex, eGFR, prior MI, heart failure, stroke, chronic obstructive pulmonary

disease, atrial fibrillation, diabetes, and treatment with platelet inhibitors, beta-blockers, ACEi/ARBs, or statins were all used to determine the HRs. These covariates were chosen because they could all be associated to both the exposures and the outcomes. All covariates were complete except for three missing for eGFR. Complete case analysis was performed. Subgroup analyses were conducted to calculate unadjusted and multivariable adjusted HRs with % CIs for all-cause mortality in groups based on age, sex, and the presence or absence of chronic kidney disease, coronary artery disease, heart failure, and atrial fibrillation in groups based on age, sex, and the presence or absence of chronic kidney disease, coronary artery disease, heart failure, and atrial fibrillation. We investigated differences in outcomes by competing risk regression based on the Fine-Gray proportional sub hazards model (132) and calculated sub distribution HR and 95% CI. To investigate any impact of the change in sensitivity in the hs-cTnT assay after 24 April 2012, an additional subgroup analysis was conducted before and after this date. The proportional hazard assumption was tested by calculating the correlation between Schoenfeld residuals for the covariates and the ranking of the failure times. Test results implied that the assumption was met.

4.7.2 Study II

In Study II, logistic regression models were used to estimate the risk of death due to a certain cause. Unadjusted, age- and sex-adjusted, and multivariable-adjusted odds ratios (ORs) and 95 % confidence intervals (CIs) were presented. Patient age, sex, renal function, prior MI or revascularization, stroke, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, and medical treatment with aspirin, ACEi/ARB, beta-blockers, or statins were all included in the multivariable-adjusted logistic regression model. In these analyses, the exposure category no myocardial injury was used as the reference category. Finally, we calculated the age- and sex-adjusted incidence rate estimates using Poisson regression.

4.7.3 Study III

Unadjusted and multivariable-adjusted Cox regression models were used in study III to estimate HR for all-cause mortality and the composite outcome with 95% CI for the association between number of medications, using 0 to 1 medication as the referent, and stratified by type of myocardial injury. The following covariates were included in the adjusted analysis: age, sex, estimated glomerular filtration rates, prior MI, revascularization, stroke, cancer, diabetes mellitus, hypertension, atrial fibrillation, heart failure, and chronic obstructive pulmonary disease.

4.7.4 Study IV

In Study IV, to calculate cumulative survival, the Kaplan-Meier method was used. The association between low-, moderate-, and high-intensity statin categories and all-cause mortality and the composite outcome was estimated using unadjusted and multivariable-adjusted Cox regression models with 95% CI. The low-intensity statin intensity category was the reference category. The adjusted analysis included age, gender, and the Charlson

comorbidity index (CCI)(133,134) as variables. Using a Poisson model, we calculated age- and sex-adjusted incidence rates.

4.8 ETHICAL CONSIDERATIONS

The Regional Ethical Review Board in Stockholm gave its approval of the study protocols for all the studies included in this thesis. In thesis studies, no individual conflicts of interest have compromised the design or conduct or the data credibility. All study designs were generated after a thorough review, of relevant current literature to guarantee proper relevance of the research concerns and feasibility of the proposed studies. All the research in this thesis followed established protocols that laid out the study objective, data gathering methods, and data utility and security. All data were handled on hospital or KI computers and in line with the Patient Data Act and the supplemental laws to the EU Data Protection Regulation. The data were de-identified and stored on dedicated servers with high security for at least 10 years then destroyed, after which the data will be destroyed.

The cohort studies were all retrospective and consisted of a substantial number of patients, which made it impossible to obtain consent. However, the author believes that the participation in the current studies will not result in any disadvantages or danger of identification. The author also believes that the public interest of the studies surpasses any potential harm to the participants' integrity. The data used in the studies were identified data, that is, data that allowed the investigators to identify a specific individual because this was required during the assessment of medical records. After the assessment, all raw data were key coded to remove personally identifiable information. Data were not reported individually in any of the studies, but rather in aggregated and analyzed formats. As a result, there is very little danger that anyone involved in the studies will be offended in any way.

Lastly, the studies of this thesis adhere to the Declaration of Helsinki's standards (135). The act includes that medical research may only be conducted if the importance of the objective outweighs the risk and burdens to the research subjects. The author believes it is critical to identify high-risk patients and to describe relevant associations in greater detail. The author hopes that this thesis will generate new hypotheses for future investigations, which will influence clinical practice and enhance prognosis in patients with myocardial injury.

5 RESULTS AND DISCUSSIONS

5.1 STUDY I

Results

The study population

The study population consisted of 3,853 patients with myocardial injury, 35% had chronic myocardial injury, 30% had acute nonischemic myocardial injury, 29% had type 1 MI, and 6.5% had type 2 MI. Patients with chronic myocardial injury were older and had lower eGFR than the other groups (TABLE 5). Atrial fibrillation was the most common discharge diagnosis during the index visit in patients with acute nonischemic and type 2 MI according to the Swedish NPR (TABLE 6).

Mortality

In total, during a mean follow-up 3.9 (± 2) years, 41% (1 523) of patients died. The adjusted HR (aHR) for patients with acute nonischemic myocardial injury and type 2 MI were 21% and 46% higher, respectively, compared with chronic myocardial injury. Patients with type 1 MI had an aHR 0.86 (95% confidence interval [CI] 0.74–1.00) of death during follow-up. The aHR for non-cardiovascular death was higher in patients with acute nonischemic myocardial injury and type 2 MI and lower in patients with type 1 MI compared with the reference group (TABLE 7). The cumulative mortality in patients with acute nonischemic, chronic myocardial injury and type 2 MI, respectively, were substantially higher than type 1 MI patients (FIGURE 11).

Medication

Patients with type 1 MI were more often treated with cardiovascular medications compared with other groups of myocardial injury (TABLE 8).

Cardiovascular outcome

The aHR for MI was double in patients with type 1 MI, but similar in patients with acute nonischemic myocardial injury and type 2 MI compared with patients with chronic myocardial injury. In total 10% of patients suffered an MI during a mean duration of 3.1 (± 1.7) years of follow-up. In total 27% of patients were hospitalized for heart failure during a mean duration of 2.8 (± 1.8) years. Patients with type 2 MI and acute nonischemic myocardial injury had an aHR 1.30 (95% CI 1.00–1.69) and an aHR 1.24 (95% CI 1.07–1.43) for heart failure, respectively, compared with the reference group (TABLE 9). Few patients had acute nonischemic, chronic myocardial injury or type 2 MI that underwent revascularization (TABLE 7).

Table 5. Baseline characteristics in patients with acute myocardial injury (acute nonischemic myocardial injury), chronic myocardial injury and type 1 or type 2 myocardial infarction

Characteristic	All patients	Chronic myocardial injury	Acute myocardial injury	Type 1 myocardial infarction	Type 2 myocardial infarction
No. of patients (%)	3,853 (100)	1,347 (35)	1,144 (30)	1,111 (29)	251 (6.5)
Age, years (SD)	73 ± 13	79 ± 12	73 ± 14	69 ± 13	72 ± 13
eGFR, ml/min/1.73 m²					
Mean (SD)	65 (25)	61 (23)	63 (27)	74 (23)	67 (25)
Comorbidities					
MI, n (%)	730 (19)	273 (20)	217 (19)	48 (19)	48 (19)
Heart failure, n (%)	741 (19)	337 (25)	273 (24)	91 (8.2)	40 (16)
Stroke, n (%)	369 (9.6)	145 (11)	134 (12)	71 (6.4)	19 (7.6)
AF, n (%)	1,037 (27)	455 (34)	377 (33)	128 (12)	77 (31)
Diabetes, n (%)	833 (22)	317 (24)	247 (22)	213 (19)	56 (22.3)
Medication					
Aspirin, n (%)	1,614 (42)	618 (46)	468 (41)	427 (38)	101 (40)
P2Y12i, n (%)	158 (4.1)	55 (4.1)	48 (4.2)	48 (4.3)	7 (2.8)
Beta blockers, n (%)	1,950 (51)	758 (56)	593 (52)	458 (41)	141 (56)
ACEi/ARB, n (%)	1,920 (50)	737 (55)	584 (51)	468 (42)	131 (52)
Statins, n (%)	1,428 (37)	528 (39)	440 (38)	372 (33)	88 (35)

Abbreviations: SD, standard deviation; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; AF, atrial fibrillation; ACEi/ARB, angiotensin-converting-enzyme-inhibitor/angiotensinogen-receptor-blocker.

Table 6. The 5 most common diagnoses, or in the Swedish National Patient register in the study population during the index hospitalization

	Chronic myocardial injury	Acute myocardial injury	Type 1 myocardial infarction	Type 2 myocardial infarction
1	*Chest pain, 32%	Chest pain, 23%	MI, 83%	Atrial fibrillation, 21%
2	Heart failure, 12%	AF, 13%	*Unstable angina, 12%	MI, 19%
3	Angina pectoris, 11%	Heart failure, 8.9%	Chest pain, 2.5%	SVT, 9.6%
4	AF, 6.8%	PE, 6.3%	AF, 0.4%	Heart failure 3.8%
5	Obs. for MI, 3.9%	Dilated CMP, 3.1%	Hypertension, 0.2%	COPD, 3.2%

Abbreviations: AF, atrial fibrillation; MI, myocardial infarction; PE, pulmonary embolism; COPD, chronic obstructive pulmonary disease; SVT, supraventricular tachycardia; Obs., observation. These discharge diagnoses were collected from the National Swedish Patient Register.

Table 7. Proportions of patients with type 1 MI, type 2 MI, acute nonischemic, and chronic myocardial injury who underwent revascularizations and for what reason within 30 days and 1 year of follow-up

	T1MI	T2MI	Acute myocardial injury	Chronic myocardial injury
Revascularization				
30 days	51%	2.9%	1.2%	1.3%
31-365 days	3.4%	1.9%	2.2%	1.8%
Diagnoses associated with revascularization				
Myocardial infarction	83%	37%	44%	1.6%
Unstable angina	11%	0%	16%	7.7%
Angina pectoris	3.8%	13%	16%	50%

Abbreviations: MI, myocardial infarction

Table 8. Medication use within 90 and 365 days of discharge in patients with acute myocardial injury (acute nonischemic myocardial injury), type 1 myocardial infarction, and type 2 myocardial infarction, and patients with chronic myocardial injury

	Chronic myocardial injury	Acute myocardial injury	Type 1 myocardial infarction	Type 2 myocardial infarction
All patients, 90 days				
Number of patients	1,322 (36)	1,093 (30)	1,064 (29)	228 (6.1)
Diabetes medication, n (%)	273 (21)	199 (18)	193 (18)	39 (17)
Statins, n (%)	436 (33)	357 (33)	883 (83)	92 (40)
Aspirin, n (%)	543 (41)	414 (38)	918 (86)	101 (44)
Betablockers, n (%)	722 (55)	651 (60)	169 (74)	946 (89)
ACEi/ARB, n (%)	665 (50)	531 (49)	725 (68)	118 (52)
P2Y12i, n (%)	92 (7.0)	71 (6.5)	871 (82)	26 (11)
All patients, 365 days				
Number of patients	1069 (35)	861 (28)	967 (31)	181 (6)
Diabetes medication, n (%)	251 (23)	185 (21)	212 (22)	41 (23)
Statins, n (%)	469 (44)	362 (42)	800 (82)	73 (40)
Aspirin, n (%)	469 (44)	346 (40)	792 (82)	69 (38)
Betablockers, n (%)	666 (62)	542 (63)	813 (84)	134 (74)
ACEi/ARB, n (%)	625 (58)	501 (58)	672 (69)	114 (63)
P2Y12i, n (%)	68 (6)	56 (7)	199 (21)	13 (7)

ACEi/ARB means angiotensin-converting enzyme inhibitor/angiotensinogen-receptor-blocker; P2Y12i includes clopidogrel, ticagrelor, and prasugrel; medication use within 90 days is defined as at least one dispensed prescription of the abovementioned medications.

Table 9. Long-term risks for death, myocardial infarction, and heart failure in patients with acute myocardial injury (acute nonischemic myocardial injury), type 1 MI, and type 2 MI compared with patients with chronic myocardial injury

	All patients	Chronic myocardial injury	Acute myocardial injury	Type 1 myocardial infarction	Type 2 myocardial infarction
Number of patients	3,707 (100)	1,322 (36)	1,093 (30)	1,064 (29)	228 (6.1)
All-cause mortality[§]					
Number of deaths, n (%)	1,523 (41)	642 (49)	521 (48)	259 (24)	101 (44)
Rate per year	11%	13%	13%	5.4%	12%
Adjusted [‡] , HR (95% CI)	N/A	Reference	1.21 (1.08-1.36)	0.86 (0.74-1.00)	1.46 (1.18-1.80)
Myocardial infarction					
Number of MIs, n (%)	385 (10)	119 (9.0)	87 (8.0)	165 (16)	14 (6.1)
Rate per year (95% CI)	3.4%	3.0%	2.7%	4.6%	2.0%
Adjusted [‡] , HR (95% CI)	N/A	Reference	0.98 (0.74-1.30)	2.09 (1.62-2.68)	0.83 (0.47-1.44)
Heart failure					
Number of cases, n (%)	1,013 (27)	408 (31)	344 (31)	194 (18)	67 (29)
Rate per year (95% CI)	3.4%	12%	13%	5.4%	11%
Adjusted [‡] , HR (95% CI)	N/A	Reference	1.24 (1.07-1.43)	0.94 (0.78-1.13)	1.30 (1.00-1.69)

Follow-up started at day 31 after index-date. Therefore, 146 patients who died within 30 days were excluded from this analysis.

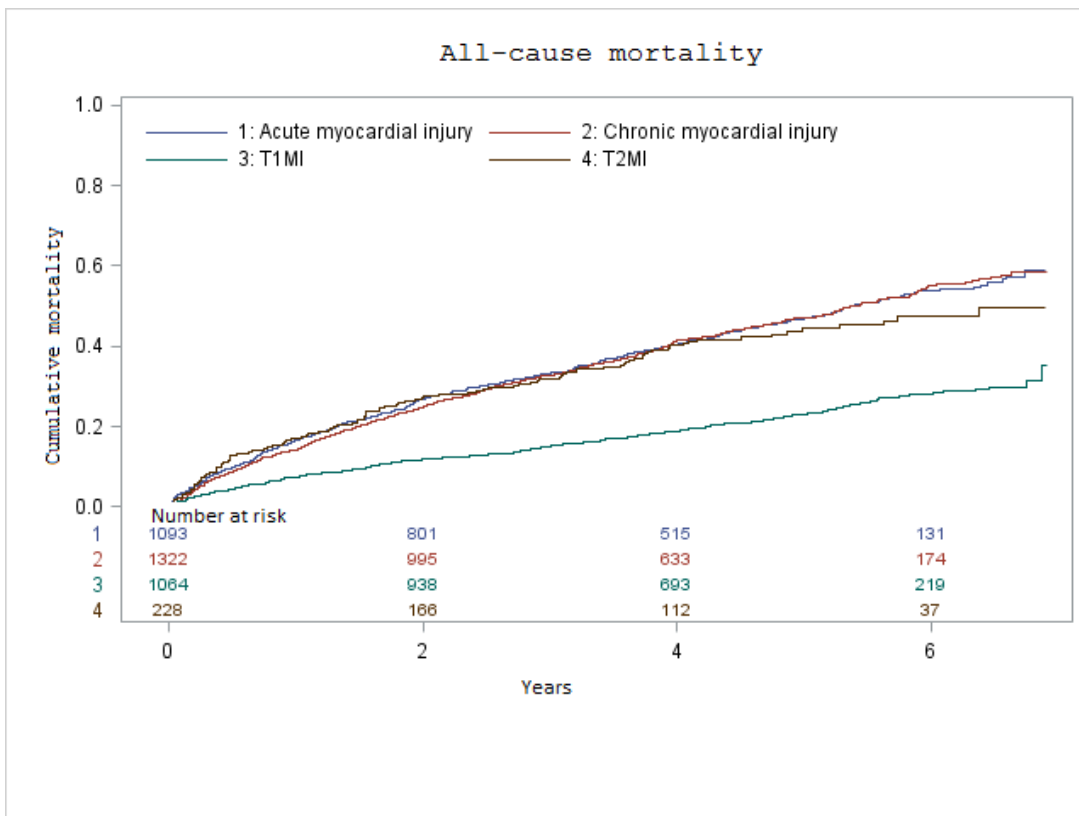


Figure 11 - This figure shows the cumulative mortality in acute myocardial injury (acute nonischemic myocardial injury), chronic myocardial injury, type 1 MI, and type 2 MI.

Discussion

Patients with acute nonischemic myocardial injury and type 2 MI had a similar and high risk of death compared with patients with chronic myocardial injury, according to the findings of Study I. During the 4 years follow-up, nearly half of patients without type 1 MI died. The results of this study add to previous research by differentiating between acute nonischemic and chronic myocardial injury. According to this study, these two entities have similarly high rates of all-cause mortality.

The main strength of this study was that historical hs-cTnT levels were available, which allowed us to classify patients into groups of chronic or acute myocardial injury. No patients were classified as having chronic myocardial injury unless stable hs-cTnT levels were available on several occasions. Furthermore, we tried to mimic clinical practice, using all available information from medical records and by discussing cases when we were uncertain, we believe these methods led to a high external validity. However, one limitation is that exposure may have been misclassified, particularly in the cases of acute nonischemic myocardial injury, type 1 MI, and type 2 MI, which have previously proven difficult to differentiate from one another. Apart from patients with type 1 MI, coronary angiographies were seldom performed seldom in the other types of myocardial injury.

5.2 STUDY II

Results

Study population

In this population 2 285 patients died during a mean follow-up duration of 4.0 (\pm 1.3) years; of these 819 did not have myocardial injury. Patients with myocardial injury who died were considerably older and more likely to have established cardiovascular disease, CKD, or chronic obstructive pulmonary disease (COPD) compared with patients without myocardial injury (TABLE 10).

Cardiovascular and non-cardiovascular mortality

The risk of cardiovascular death was higher in all groups of myocardial injury compared with patients without myocardial injury, and type 1 MI patients had a 77% (adjusted odds ratio [aOR] 1.77; 95% CI 1.29-2.41) higher risk of cardiovascular death compared with patients with no myocardial injury (FIGURE 12) (TABLE 11). Similar adjusted point estimates were observed for patients with acute nonischemic myocardial injury (aOR 1.40; 95% CI 1.07–1.84), chronic myocardial injury (aOR 1.36; 95% CI 1.05–1.76), and for type 2 MI patients (aOR 1.30; 95% CI 0.85–2.00) compared with the reference group. In subgroups of cardiovascular death, patients with type 1 MI and chronic myocardial injury had more than a 313% (aOR 3.13; 95% CI:2.16–4.55) and 68% (aOR 1.68; 95% CI 1.19–2.37) higher risk of death, respectively, due to ischemic heart disease, compared with patients without myocardial injury (TABLE 11) (FIGURE 13).

Table 10. Baseline characteristics

	Myocardial injury categories					
	Total	No myocardial injury	T1MI	T2MI	Acute myocardial injury	Chronic myocardial injury
Number of patients	2285	819 (36%)	266 (12%)	117 (5%)	498 (22%)	585 (26%)
Age, years, mean (SD)	76.5 (12.8)	69.9 (14.1)	79.7 (10.2)	78.9 (11.5)	78.9 (10.7)	81.9 (9.53)
eGFR (ml/min/1.73 m ²)						
>60	1254 (54.9)	649 (79.2)	128 (48.1)	48 (41.0)	199 (40.0)	230 (39.3)
≤60	1031 (45.1)	170 (20.8)	138 (51.9)	69 (59.0)	299 (60.0)	355 (60.7)
Prior MI	486 (21.3)	105 (12.8)	83 (31.2)	27 (23.1)	122 (24.5)	149 (25.5)
Heart failure	547 (23.9)	84 (10.3)	56 (21.1)	26 (22.2)	179 (35.9)	202 (34.5)
Prior stroke	298 (13.0)	76 (9.3)	40 (15.0)	14 (12.0)	82 (16.5)	86 (14.7)
Atrial fibrillation	763 (33.4)	178 (21.7)	72 (27.1)	34 (29.1)	219 (44.0)	260 (44.4)
COPD	267 (11.7)	66 (8.1)	25 (9.4)	14 (12.0)	92 (18.5)	70 (12.0)

Data are number of patients and percentages, unless otherwise noted. MI = myocardial infarction, SD = standard deviation, hs-cTnT = high-sensitivity cardiac troponin T, ACEi = angiotensin-converting-enzyme inhibitor, ARB = angiotensin II receptor antagonists, eGFR = estimated glomerular filtration rate, TIMI = type 1 MI, T2MI = type 2 MI, acute myocardial injury = acute nonischemic myocardial injury.

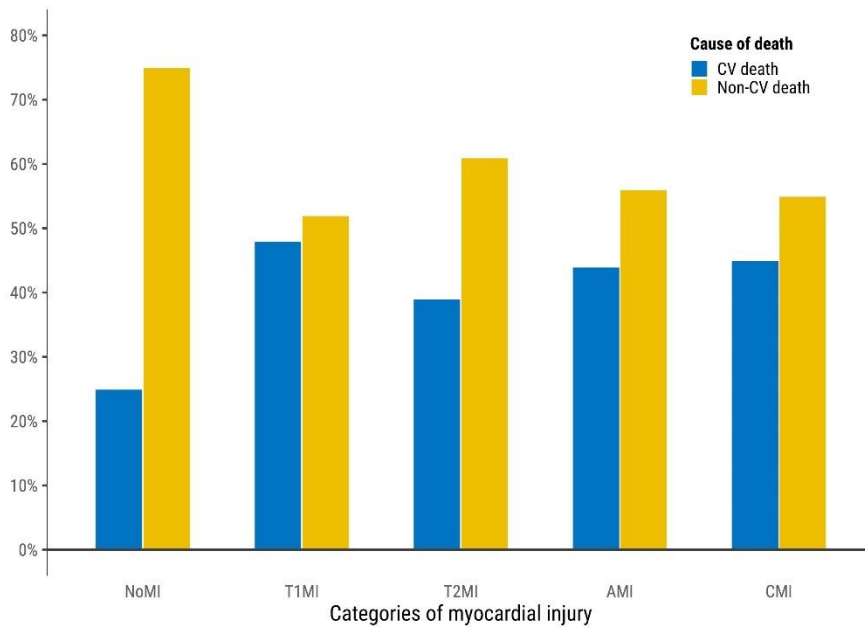


Figure 12- Causes of death according to myocardial injury, cardiovascular and non-cardiovascular death. Abbreviations: CV = cardiovascular, NoMI = no myocardial injury, T1MI = type 1 MI, T2MI = type 2 MI, AMI = acute nonischemic myocardial injury, CMI = chronic myocardial injury.

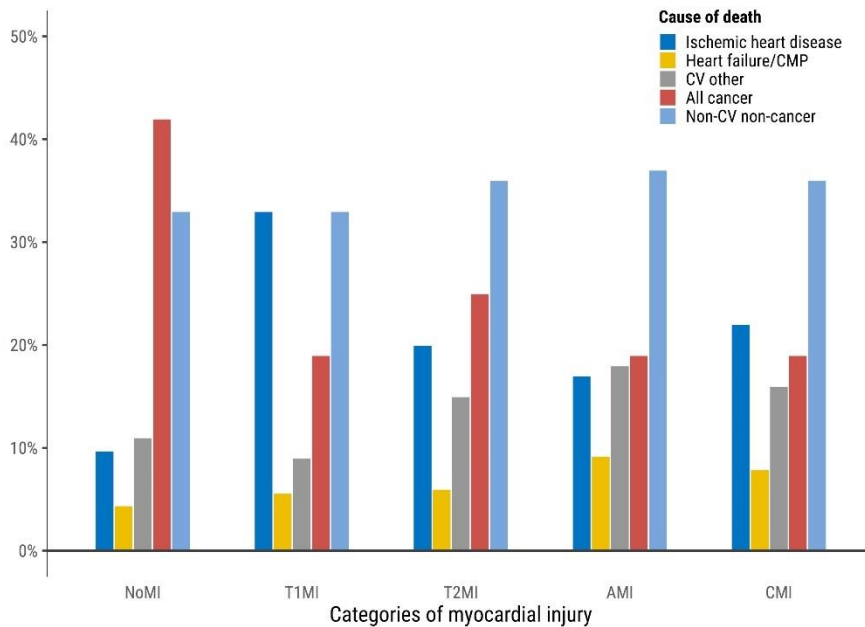


Figure 13 - Causes of death according to myocardial injury presented in subgroups of causes of death. Abbreviations: CV = cardiovascular, NoMI = no myocardial injury, T1MI = type 1 MI, T2MI = type 2 MI, AMI = acute nonischemic myocardial injury, CMI = chronic myocardial injury; CMP = cardiomyopathy.

Table 11. Risk for different causes of death according to myocardial injury categories.

	Myocardial injury categories				
	No myocardial injury	T1MI	T2MI	Acute myocardial injury	Chronic myocardial injury
CV death					
Number of deaths (%)	208 (25%)	128 (48%)	46 (39%)	219 (44%)	266 (45%)
*Multivariable adjusted OR (95% CI)	1 (ref)	1.77 (1.29–2.41)	1.30 (0.85–2.00)	1.40 (1.07–1.84)	1.36 (1.05–1.76)
Non-CV death					
Number of deaths (%)	611 (75%)	138 (52%)	71 (61%)	279 (56%)	319 (55%)
*Multivariable adjusted OR (95% CI)	1 (ref)	0.57 (0.41–0.77)	0.77 (0.50–1.18)	0.71 (0.54–0.93)	0.74 (0.57–0.95)
Subgroups of CV death					
IHD					
Number of deaths (%)	79 (9.7%)	89 (33%)	22 (20%)	83 (17%)	128 (22%)
Proportion of CV deaths, %	38%	70%	48%	38%	48%
*Multivariable adjusted OR (95% CI)	1 (ref)	3.13 (2.16–4.55)	1.51 (0.87–2.62)	1.20 (0.83–1.74)	1.68 (1.19–2.37)

OR = odds ratio, CI = confidence interval, CV = cardiovascular, MI = myocardial infarction, IHD = ischemic heart disease, T1MI = type 1 MI, T2MI = type 2 MI, acute myocardial injury = acute ischemic myocardial injury.

*Multivariable adjustment was made for: age, sex, renal function, prior MI or revascularization, stroke, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, and medical treatment with aspirin, ACE/ARB inhibitors, beta-blockers, or statins.

Discussion

The main finding of Study II was that patients with nonischemic myocardial injury had a similar high risk of cardiovascular death to those with type 1 MI. Although we did not perform head-to-head comparisons between type 1 MI and type 2 MI, or between type 1 MI and acute nonischemic myocardial injury, the associations when compared with patients without myocardial injury were similar although slightly higher for patients with type 1 MI. The adjusted incidence rate of death in ischemic heart disease was four times higher in patients with type 1 MI than in patients without myocardial injury, and almost twice as high as the rates within the other myocardial injury groups. However, for overall cardiovascular death, the incidence rates were similar in patients with type 1 MI, type 2 MI, and acute nonischemic myocardial injury, and slightly lower in patients with chronic myocardial injury. The strength of this study is the completeness of diagnoses and deaths in the

Swedish National Health Registers. The main limitation in study II is the validity of specific causes of death in the Cause of Death Register. Although, the validity is high for deaths from cardiovascular disease, the register has lower validity concerning exact underlying causes of death.

5.3 STUDY III

Results

The study population

In Study I, of 3,853 patients with myocardial injury, 25% (n=947) had been prescribed 0–1 medication, 45% (n=1 734) had been prescribed 2–3 medications and 30% (n=1 172) had been prescribed four medications of ACEi/ARBs, beta-blockers, platelet inhibitors or statins. In patients with 4 medications, 5% had type 2 MI, 17% had acute nonischemic myocardial injury, 20% had chronic myocardial injury and 59% had type 1 MI. The proportion of patients with type 1 MI compared with the other categories of myocardial injury gradually increased with the increasing number of medications. Proportions of patients with acute and chronic myocardial injury gradually decreased with the increasing number of medications, from 86% to 36% in patients treated with 0–1 and four medications, respectively (TABLE 12).

Medical treatment

Less than half of all patients with type 2 MI, acute nonischemic or chronic myocardial injury were treated with statins (43%, 40%, and 40%, respectively) and half of the equivalent patient groups were treated with a platelet inhibitor (50%, 54%, and 48%, respectively). Corresponding proportions for treatment with statins and platelet inhibitors in patients with type 1 MI were 87% and 93%, respectively. In patients with acute nonischemic or chronic myocardial injury, 66% and 62% were treated with beta blockers, respectively. The proportion of patients treated with beta-blockers in patients with type 1 MI and type 2 MI were 91% and 75%, respectively (FIGURE 14).

Mortality

During a mean follow-up of 3.1 ± 1.5 years, 1 059 (27%) patients died. Yearly mortality rates decreased with increasing numbers of medications, from 0–1 medication to four medications, in all groups of myocardial injury; from 17% to 4% in patients with type 1 MI; 12% to 9% in patients with type 2 MI, 12% to 11% in patients with acute nonischemic myocardial injury; and 13% to 10% in patients with chronic myocardial injury (TABLE 13). Treatment with four drugs was associated with lower aHR of death in patients with type 2 MI (aHR 0.43; 95% CI 0.19–0.96), and chronic myocardial injury (aHR 0.63; 95% CI 0.46–0.87). A lower adjusted mortality risk was also found among patients with acute nonischemic and chronic myocardial injury treated with 2–3 medications, compared with the reference group (TABLE 14).

Table 12. Baseline characteristics

	Number of medications			
	All patients	0-1	2-3	4
N	3853	947	1734	1172
Age, years, mean (SD)	73.4 (13.5)	73.4 (16.3)	76.0 (12.3)	69.6 (11.7)
eGFR, mL/min/1.73m ²				
>60	2216 (58)	515 (54)	917 (53)	784 (70)
≤60	1637 (42)	432 (46)	817 (47)	388 (30)
CAD	1311 (34)	195 (21)	612 (35)	504 (43)
Hypertension	1738 (45)	311 (33)	871 (50)	556 (47)
Diabetes	833 (22)	127 (13)	359 (21)	347 (30)
Heart failure	741 (19)	146 (15)	416 (24)	179 (15)
Atrial fibrillation	1037 (27)	257 (27)	605 (35)	175 (15)
Stroke	369 (10)	77 (8)	204 (12)	88 (8)
Beta-blocker	2792 (73)	193 (20)	1427 (82)	1172 (100)
ACEi/ARB	2367 (61)	126 (13)	1069 (62)	1172 (100)
Platelet inhibitor	2391 (62)	126 (13)	1093 (63)	1172 (100)
Statin	2069 (53)	31 (3)	866 (50)	1172 (100)
Group				
Type 1 MI	1111 (29)	58 (6)	363 (21)	690 (59)
Type 2 MI	251 (7)	79 (8)	114 (7)	58 (5)
Acute nonischemic myocardial injury	1144 (30)	387 (41)	561 (32)	196 (17)
Chronic myocardial injury	1347 (35)	423 (45)	696 (40)	228 (20)

Numbers are n (%) unless otherwise stated. SD = standard deviation, CAD = coronary artery disease, AMI = prior acute myocardial infarction, eGFR = estimated glomerular filtration rate, COPD = chronic obstructive pulmonary disease, ACEi/ARB = angiotensin converting enzyme inhibitor/angiotensin II receptor blocker, Acute myocardial injury = acute nonischemic myocardial injury.

Table 13. Incidence rate in mortality among patients with type 1 and type 2 myocardial infarction, and acute and chronic myocardial injury in relation to the number of cardiovascular drugs dispensed at discharge.

	Number of medications		
	0-1	2-3	4
Incidence rate all-cause mortality			
Type 1 MI			
Incidence rate (95 % CI) *	17 (8.3–33)	7.5 (6.0–9.3)	3.8 (3.1–4.6)
Type 2 MI			
Incidence rate (95 % CI) *	12 (7.1–19)	12 (9.0–17)	9.1 (9.0–17)
Acute nonischemic myocardial injury			
Incidence rate (95 % CI) *	12 (9.7–14)	13 (11–15)	11 (8.7–14)
Chronic myocardial injury			
Incidence rate (95% CI) *	13 (11–16)	13 (12–15)	10 (8–13)

HR = hazard ratio, CI = confidence interval, MI = myocardial infarction.

*Incidence rate per 100 person-years.

Table 14. All-cause mortality among patients with type 1 and type 2 myocardial infarction, and acute nonischemic and chronic myocardial injury in relation to the number of cardiovascular drugs dispensed at discharge. Follow-up started at 180 days after index date.

	Number of medications		
	0-1	2-3	4
All-cause mortality			
Type 1 MI			
Number of events (%)	8 (44%)	78 (24%)	91 (13%)
Adjusted HR (95% CI) *	ref	0.82 (0.38–1.79)	0.54 (0.25–1.17)
Type 2 MI			
Number of events (%)	16 (34%)	39 (38%)	16 (29%)
Adjusted HR (95% CI) *	ref	0.50 (0.25–1.01)	0.43 (0.19–0.96)
Acute nonischemic myocardial injury			
Number of events (%)	99 (34%)	189 (37%)	63 (34%)
Adjusted HR (95% CI) *	Ref	0.76 (0.59–0.99)	0.71 (0.50–1.02)
Chronic myocardial injury			
Number of events (%)	133 (38%)	254 (39%)	73 (33%)
Adjusted HR (95% CI) *	Ref	0.73 (0.58–0.92)	0.63 (0.46–0.87)

HR = hazard ratio, CI = confidence interval.

*Adjusted for age, sex, eGFR, prior myocardial infarction, heart failure, stroke, revascularization, atrial fibrillation, COPD, diabetes, coronary artery disease, hypertension, and cancer.

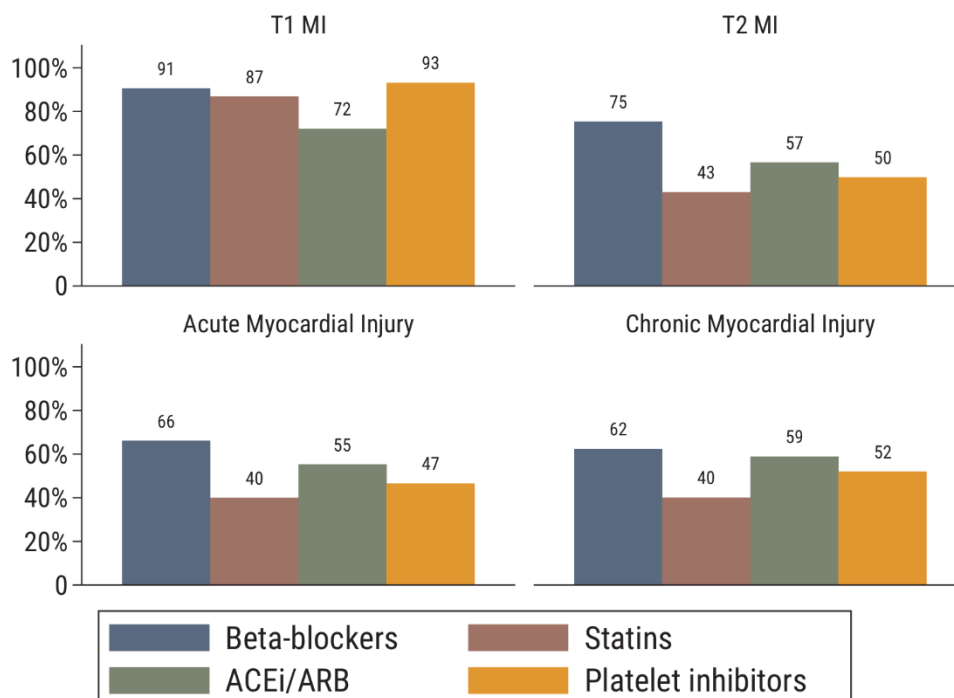


Figure 14- Proportions of treatments in patients with different myocardial injury. Abbreviations: T1 MI = type 1 MI, T2 MI = type 2 MI.

Discussion

In Study III, we investigated the association between the number of cardiovascular drugs used and mortality and cardiovascular outcomes. In comparison to patients with type 1 MI, patients with acute nonischemic or chronic myocardial injury and type 2 MI were prescribed ACEi/ARBs, beta-blockers, platelet inhibitors, or statins less frequently. In the adjusted analysis, we discovered that patients with type 2 MI and chronic myocardial injury who were given four different types of drugs had a reduced risk of death than those who were given one or none. Point estimates showed lower risk in patients with type 1 MI and acute nonischemic myocardial injury treated with four medications compared to the reference group, but this was not significant. The main strength of this study was that our categorization was robust and all the study data were retrieved from validated national healthcare registers. In addition, there was no loss to follow-up for any of the patients. A limitation was that medications were divided into three groups: 0–1 medication, 2–3 medications, and four medications, to avoid unstable estimations because cases were limited if categories of medications were separated into 0, 1, 2, 3, and 4 medications.

5.4 STUDY IV

Results

The study population

In study IV, 2 054 patients with myocardial injury (patients with acute nonischemic myocardial injury and type 2 MI were put into one category called acute myocardial injury) were prescribed statins, two-thirds of these were men. High-intensity statins were given to one out of every five patients, while moderate-intensity statins were given to three out of every four patients. At the time of inclusion, the average age of the patients was 71.2 ± 12 years, and older patients tended to receive lower-intensity statin therapy. At baseline, patients given low-intensity statins were more likely to have comorbidities than patients given higher-intensity statins (TABLE 15).

Mortality rate

The crude mortality rate gradually decreased as the intensity of statin treatment increased in all groups of myocardial injury. In patients with type 1 MI, the adjusted mortality rates indicated lower mortality among patients treated with higher intensity statins. Patients with acute and chronic myocardial injury had similar adjusted incidence rates in all statin intensity treatment groups for the primary outcome, but patients treated with higher-intensity statins had slightly higher estimates (TABLE 16). The cumulative mortality rate in groups of myocardial injury with low-, moderate-, and high-intensity statin treatment is presented in FIGURE 15.

Association between statin treatment intensity and outcomes

For all categories of myocardial injury, the unadjusted hazard ratios for death were reduced as statin treatment intensity increased compared with the reference group. In all categories of myocardial injury, increased statin therapy intensity was associated with a decreased unadjusted risk of the composite outcome. However, among patients with type 1 MI, the estimates were only statistically significant in the high-intensity category. No significant relationship was found between statin intensity and death or the composite outcome in the adjusted models (TABLE 17).

Table 15. Baseline characteristics, total population

	Overall	Statin treatment intensity		
		Low	Medium	High
Number of patients	2054	100	1532	422
Group				
Acute Myocardial Injury	558 (27.2)	38 (38.0)	449 (29.3)	71 (16.8)
Chronic Myocardial Injury	538 (26.2)	42 (42.0)	428 (27.9)	68 (16.1)
Type 1 MI	958 (46.6)	20 (20.0)	655 (42.8)	283 (67.1)
Age, years, mean (SD)	71.18 (12.05)	78.86 (11.66)	72.02 (11.82)	66.32 (11.30)
eGFR, mL/min/1.73 m ²				
>60	1308 (63.7)	42 (42.0)	952 (62.1)	314 (74.4)
≤60	746 (36.3)	58 (58.0)	580 (37.9)	108 (25.6)
Prior myocardial infarction	481 (23.4)	22 (22.0)	364 (23.8)	95 (22.5)
Diabetes	561 (27.3)	30 (30.0)	424 (27.7)	107 (25.4)
Hypertension	962 (46.8)	57 (57.0)	736 (48.0)	169 (40.0)
Coronary artery disease	841 (40.9)	49 (49.0)	631 (41.2)	161 (38.2)
Charlson Comorbidity Index				
0-2	1154 (56.2)	44 (44.0)	849 (55.4)	261 (61.8)
3-4	634 (30.9)	34 (34.0)	478 (31.2)	122 (28.9)
≥5	266 (13.0)	22 (22.0)	205 (13.4)	39 (9.2)

Data are n (%) unless otherwise specified. SD = standard deviation, eGFR = estimated glomerular filtration rate, COPD = chronic obstructive pulmonary disease.

Table 16. Number of events, person-years of follow-up, and unadjusted and age- and sex-adjusted incidence rates according to myocardial injury and statin treatment intensity

Outcome	Group	Statin treatment intensity	Events/Person-years	Adjusted incidence rate (95% CI) per 100 person-years
All-cause mortality				
Acute myocardial injury		Low	20/141.7	12.7 (6.7-18.6)
		Medium	205/1754.6	12.6 (10.8-14.3)
		High	22/257.5	11.7 (6.2-17.2)
Chronic myocardial injury		Low	20/150.8	10.8 (5.4-16.1)
		Medium	186/1698.5	11.5 (9.8-13.2)
		High	18/274.9	10.0 (4.5-15.5)
Type 1 MI		Low	9/82.1	6.7 (1.2-12.1)
		Medium	162/3197.6	5.7 (4.8-6.6)
		High	23/1167.6	3.2 (1.7-4.7)

Abbreviations: MI, myocardial infarction.

Table 17. Association between statin treatment intensity and outcomes according to myocardial injury

Group	Statin treatment intensity	Death Hazard ratio (95% CI)		Combined outcome* Hazard ratio (95% CI)	
		Crude	Model 2***	Crude	Model 2***
AMI	Low	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Medium	0.84 (0.53-1.32)	0.99 (0.62-1.59)	0.95 (0.62-1.45)	0.99 (0.65-1.53)
	High	0.63 (0.34-1.15)	0.73 (0.39-1.36)	0.84 (0.50-1.41)	0.87 (0.51-1.49)
CMI	Low	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Medium	0.81 (0.51-1.28)	1.10 (0.68-1.76)	0.82 (0.55-1.22)	0.87 (0.58-1.31)
	High	0.48 (0.26-0.92)	0.70 (0.36-1.35)	0.76 (0.46-1.25)	0.87 (0.52-1.45)
T1MI	Low	1 (ref)	1 (ref)	1 (ref)	1 (ref)
	Medium	0.46 (0.24-0.90)	1.23 (0.62-2.44)	0.62 (0.35-1.08)	1.23 (0.70-2.17)
	High	0.18 (0.08-0.39)	0.80 (0.36-1.77)	0.36 (0.20-0.66)	0.89 (0.48-1.64)

*Combined outcome is death, myocardial infarction, stroke, or heart failure.

***Model 2 was adjusted for age, sex, and Charlson comorbidity index

AMI = acute myocardial injury, CMI = chronic myocardial injury, T1MI = type 1 myocardial infarction, CI = confidence interval

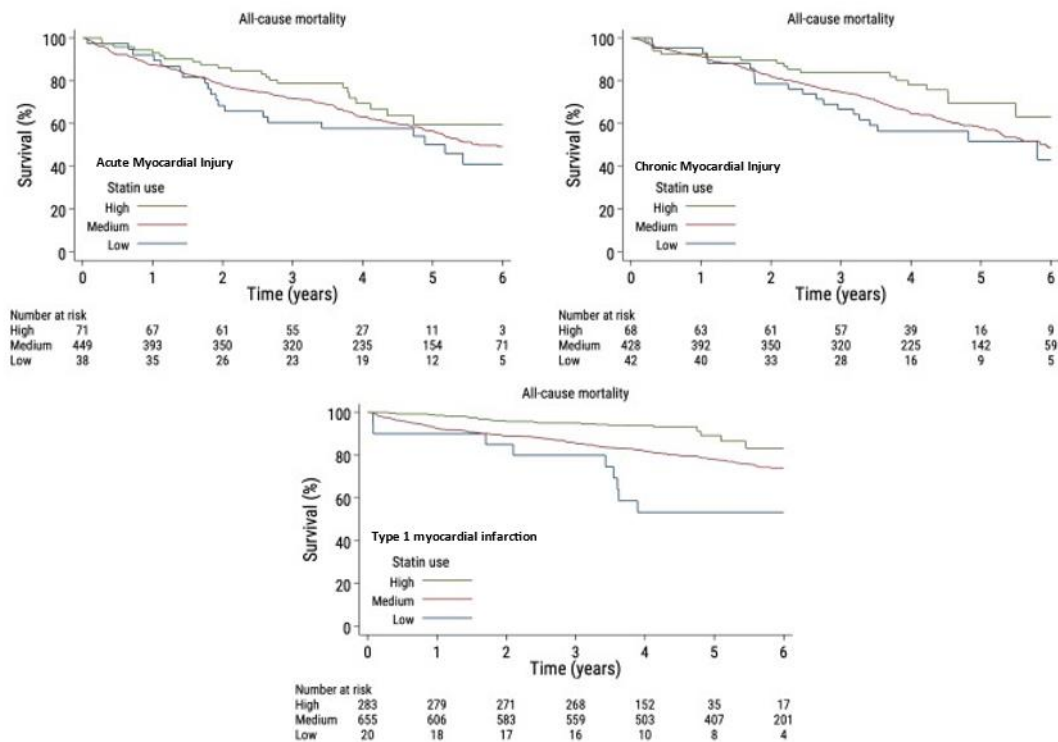


Figure 15 - KM plot all-cause mortality among patients with types of myocardial injury.

Discussion

In this study, we found that most patients with myocardial injury were treated with moderate-intensity statins. Only 30% of patients with type 1 MI were treated with high-intensity statins, and the corresponding proportions among patients with acute and chronic myocardial injury were only 12% and 13%, respectively. In our study, most patients with acute and chronic myocardial injury were treated with moderate- or low-intensity statin therapy. Patients in these treatment groups were older than those who received high-intensity therapy. The high burden of prior cardiovascular disease at baseline in our study may motivate clinicians to administer treatment with high-intensity statins in a large proportion of patients across all groups of myocardial injury. Although we found no significant risk reduction associated with high-intensity statin treatment compared with low-intensity treatment, point estimates indicated that there may be an association in all categories of myocardial injury. The main limitations in this study were the few numbers of deaths and cardiovascular events that may have contributed to widening of CIs.

6 INTERPRETATION AND OVERALL DISCUSSION

6.1 INTERPRETATION OF FINDINGS

Study I

The results from Study I indicate that patients with acute nonischemic myocardial injury, type 2 MI and chronic myocardial injury have a higher risk of mortality and almost 50% of patients died during an average follow-up of 4 years compared with 25% of patients with type 1 MI who died during follow-up. To our knowledge, this study was first to categorize patients according to the 4UDMI (1) into four groups of myocardial injury: type 1 MI, type 2 MI, acute nonischemic and chronic myocardial injury. This study found that despite different pathophysiological mechanisms underlying hs-cTn levels, acute nonischemic and chronic myocardial injury have similar risks of all-cause mortality.

Similar high-risk association were found for long-term death in patients with acute nonischemic myocardial injury and type 2 MI when sub-grouped by age, kidney function, and presence of cardiovascular comorbidities, compared with patients with chronic myocardial injury. However, patients with acute nonischemic myocardial injury and type 2 MI were associated with a slightly higher of risks of death in patients without cardiovascular comorbidities such as heart failure, CAD, or atrial fibrillation, compared with the reference group. Because risk was calculated in relation to chronic myocardial injury, this implies that the presence of these comorbidities may be more important for the risk of death in patients with chronic myocardial injury than in patients with acute nonischemic myocardial injury or type 2 MI. However, the findings may also indicate the magnitude of the acute medical condition causing acute nonischemic myocardial injury and type 2 MI in patients without cardiovascular comorbidities who suffer a higher risk of death. In this study, we also detected that a small proportion of patients with myocardial injury without type 1 MI underwent revascularization, some of these patients were treated with common cardiovascular medications (statins, aspirin, beta-blockers, ACEi/ARBs, or P2Y12i), even those with known previous CAD.

Although this study was not prospective, we found that among patients admitted to the ED with hs-cTnT levels above the 99th percentile URL, two-thirds were classified as having acute ischemic and chronic myocardial injury.

The association between patients with acute nonischemic injury, chronic myocardial injury, and type 2 MI regarding all-cause mortality should be given greater attention by clinicians. This will facilitate patient follow-up and aid in the identification of structural heart disease, as well as allow the treatment of traditional risk factors.

Study II

In this study, we investigated the deaths of patients with elevated hs-cTnT levels, which were categorized by type of myocardial injury. We analyzed deaths in patients who did not have

myocardial injury as a reference group. Previous studies have examined the causes of death in patients with nonischemic myocardial injury, in terms of cardiovascular and non-cardiovascular mortality (3,5,6,88); however, to our knowledge no other study has investigated the cause of death in patients with nonischemic myocardial injury divided into acute and chronic. Therefore, this study extends previously published literature to investigate the causes of death in more detail. Unsurprisingly, we found that the largest proportion of cardiovascular deaths was found in patients with type 1 MI, but similar proportions were found in patients with acute nonischemic myocardial injury and chronic myocardial injury. Patients with type 1 MI, acute nonischemic, and chronic myocardial injury identified from a cohort of patients visiting the ED had a higher risk of dying from cardiovascular causes compared with patients who visited the ED with chest pain who had hs-cTnT levels without myocardial injury.

Our results indicate that patients with nonischemic myocardial injury have a similar high risk of cardiovascular death to patients with type 1 MI. Although we did not perform head-to-head comparisons between groups of myocardial injury, comparing patients without myocardial injury with patients with type 1 MI, the findings were comparable in other type of myocardial injury, although slightly higher risk of cardiovascular death in patients with type 1 MI. Furthermore, the adjusted incidence rates for all categories of myocardial injury were comparable. Our data suggest that cardiovascular disease is the leading cause of death in patients with nonischemic myocardial injury.

According to our findings, patients with type 2 MI and acute nonischemic myocardial injury had a higher mortality rate from lung disease compared to patients without myocardial injury. This is consistent with a previous report (88). Patients without myocardial injury in the ED, namely patients tested for hs-cTnT levels based on clinical suspicion and with hs-cTnT levels below the 99th percentile URL, died at a younger age and mainly from cancer. This was also seen in an earlier study in a similar healthcare setting (88). One can only speculate the reasons for this, but these findings might reflect that clinicians order hs-cTnT testing more generously in young patients with active cancer and/or that those with symptoms suggestive of MI are more likely to seek emergency care. The risks of cancer-related death were double compared with type 1 MI, acute nonischemic, and chronic myocardial injury, respectively, but they were not different for patients with type 2 MI. Interestingly, the incidence rate of cancer-related death was similar in patients with type 2 MI to that in patients without myocardial injury. The reason of this result is unknown; however, it could be that patients with active cancer are more susceptible to myocardial injury as a result of the cancer, as well as cancer treatment (136,137).

Currently, no clinical guidelines that aid in the diagnosis and treatment of patients with type 2 MI, acute nonischemic, or chronic myocardial injury are available. However, as demonstrated in this study, patients with type 2 MI, acute nonischemic, or chronic myocardial injury have a high risk of all-cause mortality and a similar risk of cardiovascular death as patients with type 1 MI.

Study III

In this study we investigated whether there was an association of increasing prescribed number, common, guideline-recommended cardiovascular medications with types of myocardial injury. The study showed that patients with type 2 MI and chronic myocardial injury who were treated with four types of medications compared with 0–1 types of medications had a lower mortality. Both patients with acute nonischemic and chronic myocardial injury who were treated with 2–3 medications had a lower mortality than patients treated with 0–1 drug. No association was found between number of drugs used and mortality in patients with type 1 MI. CIs were most likely wide and nonsignificant in patients with type 1 MI because there were very few deaths and death is a relatively uncommon event, although the point estimates indicated a lower mortality in those treated with 2–3 or four types of medications compared with 0–1 medication. The reason for the mortality reductions found in our study is most likely because of a combination of the cardiovascular drugs given.

To our knowledge, no studies have yet explored the combined effects of cardiovascular drugs on outcomes in patients with nonischemic myocardial injury or type 2 MI. Furthermore, few studies have explored patients with nonischemic myocardial injury or type 2 MI in an ED setting. In Canada, there is an ongoing controlled randomized trial in patients with type 2 MI in which patients are randomized to either rivaroxaban or placebo (ClinicalTrials.gov unique identifier: NCT04838808). In Scotland, there is an ongoing trial that aims to investigate the role of CAD in type 2 MI (ClinicalTrials.gov unique identifier: NCT03338504). Other studies have shown that the cholesterol-lowering medication, alirocumab, may lower the risk of type 2 MI (112) and that statin therapy may lower hs-cTn levels as an independent sign of reduced risk of all-cause mortality (111). Although our results are difficult to translate to all patients identified with myocardial injury, our findings may indicate that there are individual risk factors requiring intervention with pharmacological therapy. Furthermore, an earlier study that investigated patients with chronic myocardial injury, showed that they are a poorly investigated patient population for detection of structural heart disease (101). Lastly, a large study in patients identified with nonischemic myocardial injury and type 2 MI showed that a low proportion are treated with additional therapy of aspirin, statins, ACEi/ARBs or beta-blockers compared with patients with type 1 MI (71).

The population of patients with acute nonischemic myocardial injury, chronic myocardial injury and type 2 MI are typically identified at the ED because the indication of hs-cTn testing relates to the symptoms that suggest a potential acute MI. Hospitalized patients with nonischemic myocardial injury and type 2 MI are usually treated for underlying acute illnesses that may cause a disequilibrium of supply and demand of oxygen to the heart, but there might be a substantial group of patients who are treated sub-optimally regarding their cardiovascular risk that could be targeted in an outpatient setting. This study extends earlier studies by investigating the impact of the numbers of common cardiovascular medications rather than a single therapy. This study may motivate clinicians to oversee patients with

nonischemic myocardial injury and type 2 MI and search for undetected cardiovascular diseases and known risk factors.

Study IV

We found that most patients in this study were treated with moderate-intensity statins. Only 12% and 13% of patients with acute and chronic myocardial injury, respectively, were treated with high-intensity statins. Surprisingly, only one-third of patients with type 1 MI were treated with high-intensity statins. There might be several reasons for this. We included all patients in this study regardless of age which resulted in a high mean age in our study (71 years) and patients with higher age received lower intensity treatments compared with those at younger ages. Furthermore, in 2014, the regional drug committee in Stockholm, Sweden, had a restrictive recommendation for high-intensity statin therapy in patients with CAD, and this recommendation was debated at the time (138). Moreover, a study in a similar setting to the current study showed that patients with type 1 MI who did not undergo percutaneous coronary intervention received substantially lower guideline-recommended secondary preventive drugs such as ACEi/ARBs, statins, beta-blockers or platelet inhibitors (139). There are no recommended statin therapies for patients with myocardial injury without type 1 MI. One study indicated a positive association, regardless of age, between high statin intensity and mortality in patients with prior cardiovascular disease (140). Furthermore, a study in a general population of middle-aged men presented interesting findings that statin treatment may lower cTn levels and showed a lower risk of death in patients with lowered cTn levels, which was independent of the lowering of cholesterol levels (111).

We found no significant risk reduction associated with high-intensity statin treatment compared with low-intensity treatment, but point estimates suggested that there may be an association in all categories of myocardial injury. Overall, there were few deaths and cardiovascular events, and this may have contributed to widening of the CIs. The hospitalization of these patients is usually due to underlying acute illnesses and seldom to factors that may imply intensified statin therapy. Furthermore, care must be taken when considering the side effects of high-intensity statin therapy in patients with nonischemic myocardial injury or type 2 MI because they often have several comorbidities and are older in age (5,88). However, there may be subgroups of patients with nonischemic myocardial injury and type 2 MI who would benefit from and tolerate high-intensity statin therapy. The baseline characteristics showed a large proportion of the study population was treated with low- and moderate- intensity statin therapy, despite a high burden of CAD.

6.2 METHOLOGICAL CONSIDERATIONS

6.2.1 Internal validity

Internal validity relates to the extent that the effect of systematic errors can be minimized. Epidemiological studies are also under influence of random errors and together with systematic errors, they threaten the accuracy of the study results. Researchers often can reduce the effect of random errors by using a large cohort.

6.2.2 Systematic errors

Biases or systematic errors are inevitable in some studies. All epidemiological studies bear some influence of bias. In summary, there are three broad categories of biases: confounding, information bias, and selection bias (117).

6.2.2.1 Confounding

Systematic errors relating to factors that are both linked with the outcome and the exposure are known as confounding factors. A confounding factor is not of the causal pathway from exposure to outcome, and therefore should not be considered an effect of exposure. Consider the fact that COPD is linked to an increased risk of lung cancer. However, when adjusting for smoking, the link between COPD and the risk of lung cancer is lowered. Because smoking is not in the causal pathway between COPD and lung cancer, smoking is seen as a confounder. A directed acyclic graph (DAG) can often be used as a visual representation of this (FIGURE 16).

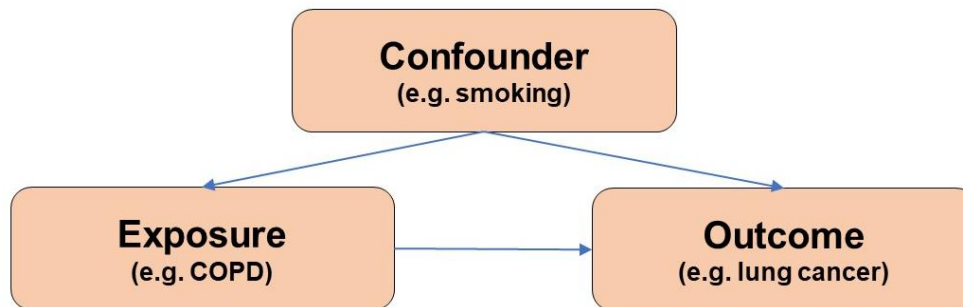


Figure 16 - DAG illustrating confounding.

All studies in this thesis were analyzed using multivariate models to minimize the effect of confounders. The models allow adjusting for confounders, such as age, comorbidities, and sex when calculating the risk estimates for the outcomes. However, residual confounders or factors that may have influenced the results may exist in all observational cohort studies. We did not account for socioeconomic confounders in any of the studies in this thesis, which could have influenced the results. Furthermore, because we lacked information on smoking habits, COPD was partly used as a surrogate for patients who had been exposed to smoking.

Confounding by indication usually refers to pharmacoepidemiologic studies of an intended drug effect. Studies of this character aim to investigate the outcome of patients who have taken versus those who have not taken the drug. Confounding by indication may arise when characteristics of patients differ between the treatment group and the non-treated group even if confounders are adjusted, such as comorbidities or age, there might be differences between the groups in disease severity or risk factors that are not known. In Study III and IV, we studied the effect of groups of medications and statin-intensity therapy, respectively. There may have been biases in these studies that could have influenced the results.

6.2.2.2 *Information bias*

Systematic errors may occur when collecting information about the study objects. This type of bias can lead to misclassification of data. Misclassification is distinguished as differential or non-differential. If misclassification of exposure is not equal between subjects who have or do not have the outcome, or when misclassification of the outcome is not equal across exposed and unexposed subjects, differential misclassification occurs. Misclassification that is unrelated to the other study variables is known as non-differential misclassification. Differential misclassification may threaten the study results while non-differential misclassification may dilute the actual true effect. In this study, we categorized the exposure into categories of myocardial injury using all the available data in the medical records. Despite comprehensive reviews and discussions, there may have been patients that were misclassified into incorrect type of myocardial injury based on comorbidities and age. This aspect may be identified as a differential misclassification error. However, we do not think the influence of misclassification is greater than other studies in the same setting, because the problem of categorization was found to be difficult to differentiate in previous studies (70). Furthermore, we used the NPR, which holds diagnoses according to the ICD-10 coding system and which has high validity (121), but NPR does not hold information on other diagnoses in the primary care setting; therefore, these data were unavailable. In Study I and II, we used the Cause of Death Register to identify the cause of death. We retrieved data concerning cardiovascular and non-cardiovascular death, as well as more specific causes of death in study II. Death outside of the hospital, the interval between the last hospital visit and death, and discrepancy between the last main diagnosis and the cause of death are all variables that make the cause of the death listed on the certificate uncertain (127).

In Study III and IV we estimated the exposure of secondary guideline-directed preventive medications and the dosage and types of therapy from dispensed prescriptions from the pharmacy, which do not represent actual use. Therefore, we used the dispensed prescriptions as a proxy for actual use. We did not explore indications in Study IV for statin use, nor did we investigate whether other cholesterol-lowering therapies were prescribed and dispensed with a combination of statins.

Immortal time bias is another type of misclassification bias that could have occurred during the process of these investigations. We identified patients from a cohort of patients with a principal complaint of chest pain, but also had information about all other visits of these patients. We identified all other visits in which hs-cTnT levels were found to be >99th percentile URL and categorized them in the appropriate category of myocardial injury; based on these criteria, if patients were differently categorized at two different visits, only the first visit was used to define which category the patient would be classified into. This might have created immortal time bias. However, we speculate that any potential immortal time bias would only have led to a vague underestimation of adverse outcome in patients with acute nonischemic myocardial injury or type 2 MI.

6.2.2.3 *Selection bias*

In cohort studies, selection bias occurs when both the exposure and the outcome influence whether a patient is included in the study population. Selection bias may occur in cohort studies if the cohort is established based on inadequate data, or if patients with missing data are omitted before the start of follow-up. In this thesis, we identified patients with myocardial injury from a cohort with a principal complaint of chest pain, but we also retrieved information from all other visits to the ED with other complaints and hs-cTnT > 14ng/L levels. This resulted in a study population of patients with myocardial injury and at least one visit with chest pain to the ED and therefore, several patients visiting the ED with other complaints and myocardial injury would have been missed. Patients triaged with chest pain will naturally undergo more frequent hs-cTnT testing and examination by doctors to determine the type of myocardial injury. Not including other types of principal complaints in the initial patient selection may have underestimated the prevalence of nonischemic myocardial injury, but we speculate that the adverse outcomes in patients with nonischemic myocardial injury and type 2 are unlikely to differ substantially. Furthermore, we used patients identified from an earlier study that included patients with chronic myocardial injury. The study population was evaluated of two external investigators that indicated a small proportion may have been incorrectly selected. We believe, however, that this selection bias would have had only a minimal impact on the risk estimations.

6.2.2.4 *Random errors*

Random errors, which are unexplained variations in study data that might impair the precision of risk estimations, can impact all studies. Precision refers to the capacity to replicate a study result under similar circumstances. As previously mentioned, a larger study size can reduce the impact of random error. When delivering a point estimate, precision is expressed using CIs. In Study IV, the numbers of patients in the low- and high-intensity statin therapy groups were small, and this would have contributed to imprecise estimates.

6.2.2.5 *External validity*

The degree of generalizability of a study's findings is referred to as external validity. All the studies in this thesis involved patients who were identified in the ED of Karolinska University Hospital, which has two locations in Stockholm County. We believe that the findings of our studies could be used in other health-care settings in nations with similar standards and using a hs-cTn assay. The study population was chosen of a cohort of patients with chest pain for whom we had information from all other ED visits during the study period. This allowed us to examine all visits for symptoms other than chest pain in which hs-cTnT levels were measured and to determine if myocardial injury was present. Therefore, we believe that proportions in Study I between different types of myocardial injury should be interpreted with caution. However, the proportions between groups of myocardial injury were similar to those found in other studies.

7 CONCLUSION

The overall aims of the studies included in this thesis were to investigate the characteristics, outcomes, and potential benefits of pharmacological therapy in patients admitted to the ED with different types of myocardial injury according to the 4UDMI. The conclusions in each study were as follows.

Study I

Patients with acute nonischemic myocardial injury and type 2 MI compared with patients with chronic myocardial injury have similar absolute long-term risks of death. Patients with type 1 MI had the lowest risk of long-term mortality. Patients with type 2 MI, acute nonischemic and chronic myocardial injury were all associated with very-high risks of adverse outcomes.

Study II

Patients with type 1 MI, acute nonischemic, and chronic myocardial injury have similar proportions and high risks of cardiovascular death. The incidence of cardiovascular death in all groups of myocardial injury was similar and higher than in patients without myocardial injury.

Study III

Patients with type 2 MI and acute nonischemic or chronic myocardial injury were infrequently treated with common cardiovascular medications (beta-blockers, ACEi/ARBs, statins, or platelet inhibitors). In these patients, treatment with guideline-recommended cardiovascular drugs were associated with lower risks of death and a lower combined risk of death, heart failure, MI, and stroke.

Study IV

Patients treated with low-intensity statin therapy who have myocardial injury, but no signs of type 1 MI, develop many comorbidities and have high mortality rate. High-intensity statin therapy was used in a small percentage of patients with myocardial injury without type 1 MI. Estimates indicate a benefit of high-intensity treatment in patients with all types of myocardial injury but, after attempting to control for confounders, we found no significant association between high- and moderate-intensity statin therapy compared with low-intensity statin therapy in patients with myocardial injury.

8 POINT OF PERSPECTIVE

Patients who are identified with myocardial injury and no type 1 MI have increased risks of adverse outcomes (3–7,71). There is a lack of evidence and guidelines for treating patients identified with acute nonischemic, chronic myocardial injury and type 2 MI. However, several patients with underlying cardiovascular diseases and risk factors that may be associated with myocardial injury may be targets for future interventions.

8.1 IDENTIFICATION OF MYOCARDIAL INJURY

Patients with nonischemic myocardial injury and type MI are commonly identified in the ED when hs-cTn testing is ordered, as usually suggest an ongoing MI. Although the risks of elevated hs-cTn levels in a variety of conditions are well understood, risk stratification generally intends to rule out a potential acute coronary syndrome. Patients with known or unknown underlying cardiovascular diseases who are affected by acute medical conditions that cause a supply and demand disequilibrium of oxygen to the myocardium may be diagnosed with nonischemic myocardial injury or type 2 MI and are associated with increased risks of adverse outcomes. Moreover, these patients frequently die due to cardiovascular causes. Patients with chronic myocardial injury may have different pathophysiological mechanisms causing increased hs-cTn levels compared with patients with acute myocardial injury but share similar risks of adverse outcomes. There are no guidelines to manage these groups of patients, but the evidence of adverse risk in patients with myocardial injury is considerable. There is a gap in our knowledge on how to risk-stratify patients with myocardial injury when type 1 MI is ruled out.

The studies in this thesis may motivate further studies that aim to risk stratify patients in the ED with nonischemic myocardial injury and type 2 MI. This may lead to intervention studies that ultimately lower the risk for adverse outcomes in these patients.

8.2 DISCRIMINATION AND RISK STRATIFICATION OF MYOCARDIAL INJURY

The tools used to differentiate between types of myocardial injury in an ED setting are mainly based on guidelines that aim to rule out a potential type 1 MI. However, guidelines suggest that unexplained elevated hs-cTn levels should be investigated to rule out underlying structural cardiovascular disease (20). Because a substantial proportion of patients have myocardial injury independent of plaque rupture, it is important to consider other cardiovascular diseases. The 4UDMI may work as a tool to categorize patients with elevated hs-cTn over the 99th percentile URL; however, guidelines do not offer any advice on how to manage patients with nonischemic myocardial injury or type 2 MI other than treating the underlying acute medical condition that causes supply and demand effects on oxygen delivery to the myocardium. We have, together with the high-STEACS-group, evaluated the GRACE 2.0 score in patients with type 2 MI compared with patients with type 1 MI. Similar studies, including this thesis raise questions as to whether patients with nonischemic myocardial injury and type 2 MI may be subjected to further risk stratification and examinations for CAD or structural heart disease. These diseases are treatable and

appropriate examination may improve prognosis in these patients. The hospitalization of these patients seldom offers a window for risk intervention; however, treatment may be optimized in an outpatient setting (FIGURE 17).

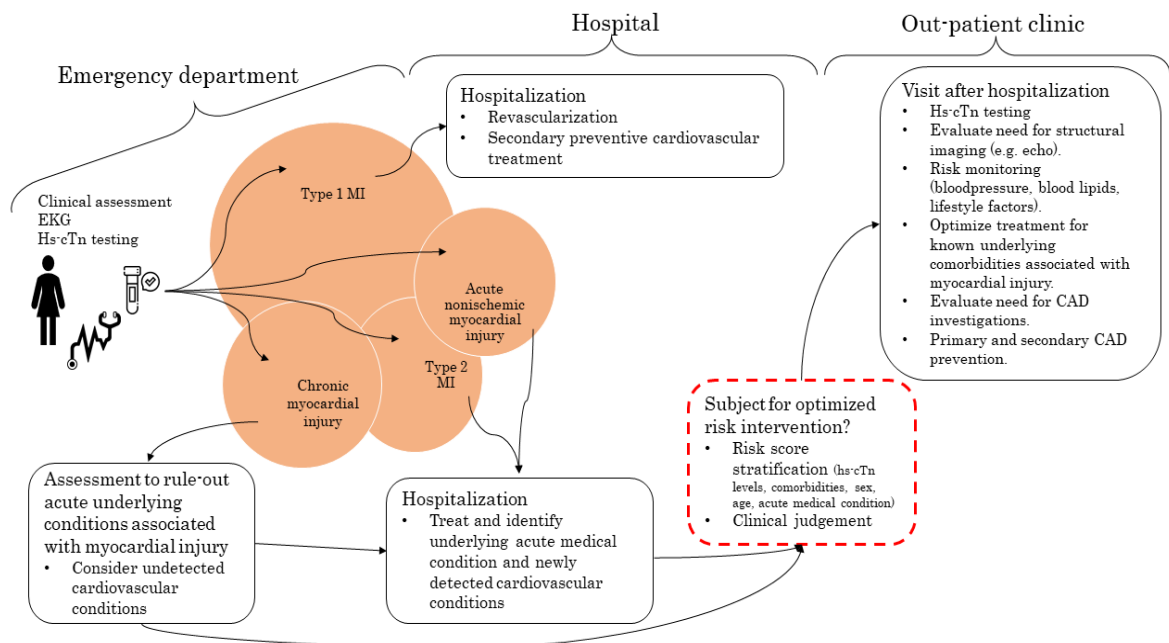


Figure 17- Potential strategies to optimize outcome in patients with myocardial injury

Using clinical information regarding disease presentation, comorbidities, and prior cardiovascular investigations in addition to the analysis of hs-cTn levels, may allow appropriate investigations that could ultimately lead to an applicable therapy in patients with nonischemic myocardial injury and type 2 MI. The creation of a risk-score that risk-stratifies these patients would potentially assist clinicians. Lastly, risk assessment always includes clinical judgement to avoid unnecessary investigations since they may have major financial implications for health systems.

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