Critical evaluation of patients sent home from the emergency department with elevated troponin T levels

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Degree Project in Medicine

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Abstract

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Background

The diagnostics of acute myocardial infarction (AMI) is often based on symptoms such as chest pain and dyspnea in combination with an electrocardiogram (ECG) and blood samples. When the ECG is inconclusive, the diagnostics of AMI is often dependent on significant short time change in levels of high sensitive cardiac troponin T (hs-cTnT), indicating acute myocardial injury. But, if the event of the AMI occurred a few days before attendance to the emergency department (ED), the short time dynamic often required for the diagnosis would not be present, and the patient would have a stable troponin elevation above the cut off limit 14 ng/L. The hypothesis in this trial is that a follow up sample at least 10 days later might reveal a long time troponin dynamic, indicating that the patient did in fact have an AMI.

Aims

The aim is to get an overview on the medical history of the patients that are sent home from the ED with a stable troponin elevation. The aim is also to investigate whether there is a long time troponin dynamic that we are missing at the ED.

Methods

Patients were enrolled from the emergency departments at Sahlgrenska University Hospital in Gothenburg. In total, 32 patients were included. Follow up samples of hs-cTnT were collected and a review of the patients' medical records was done. A percental change in hs-cTnT more than +60% or -50% was considered pathological.

Results

The average age of these patients was 79 years. A percentage of 56.7% had a known ischemic cardiovascular disease, 28.1% had heart failure, 32.3% had an arrhythmia and 25.8% had chronic obstructive pulmonary disease (COPD). The patients had 2 or more severe diseases in 78.1% of the cases. The percental change in hs-cTnT in most of the patients were normal. Five patients had a pathological change, but they had other explanations for the acute troponin elevation at the ED, such as atrial flutter.

Conclusions

The results show that these patients are old and suffer from several co-morbidities. No long time troponin dynamic indicating a missed AMI was found. Even though this is a small study with few patients, it can still give the ED doctors a small insurance that they’re not missing myocardial infarctions at the ED with their current diagnostic routines.

Key words

Myocardial infarction, troponin T, stable troponin T elevation, troponin T change, aged

1. Introduction

When a patient presents with symptoms of acute coronary syndrome (ACS) and has an inconclusive electrocardiogram (ECG), the diagnosis of myocardial infarction (MI) is often based on the short time dynamic of high sensitive cardiac troponin T (hs-cTnT) (1). In the event of an acute MI the troponin level usually rises a few hours after myocyte necrosis and reaches a plateau after 10-15 hours, after which it slowly starts to decrease (2). Therefore, a significant short time rise and/or fall in hs-cTnT levels indicate that the patient is having an MI (1). However, if a patient was to attend the ED a few days after the infarction occurred, which several reports indicate happens quite often (3, 4), a significant short time dynamic may be absent. If a late presenting patient would also have an inconclusive ECG, the diagnosis of MI might be incorrectly dismissed, indicating a possibility to miss an MI if it's based solely on the short time dynamics of hs-cTnT.

This hypothesis is supported by a previous study which showed that in a clinical setting where a large hs-cTnT short time dynamic was not mandatory for the diagnosis, small change in hs-cTnT was common amongst non ST-elevation myocardial infarction (NSTEMI) patients (5). The long-term mortality rate in this group was at least as high as it was for patients with large short-term changes in hs-cTnT (5).There is also several other reports showing that several MI patients have relatively stable troponin elevations during the initial evaluation period (5-12).

For that reason, the aim of this trial is to evaluate the group of patients that has a stable elevation of hs-cTnT at the ED and are sent home, and investigate whether they have a long time troponin dynamic that we are missing at the ED, which would consequently suggest that we may be missing myocardial infarctions in these cases.

1.1. Acute myocardial infarction

Acute myocardial infarction (AMI) is a worldwide cause of great suffering and premature death. It is a common presentation of coronary artery disease (1). In 2010, ischemic heart disease

caused over 7 million deaths all over the world and was thus the biggest cause of death globally (13) and the global disability adjusted life years (DALY) for ischemic heart disease was 1884 (95% uncertainty interval: 1730-2004) per 100 000 inhabitant (14).

1.1.1. Statistics

Swedish statistics

M. Rosén et al studied the National AMI register in Sweden and found that between 1987 and 1995, 360 905 cases of AMI were diagnosed amongst 303 324 individuals. The men were 61% and 39% were women, and the attack rate was higher amongst men. The difference in attack rate between genders was bigger below the age of 60. They also saw a decrease in age-standardized AMI attack rate and mortality between 1987 and 1995. M. Rosén et al mention that lower smoking rates, better secondary prevention such as medication against high blood pressure and high cholesterol levels, more aggressive treatment against angina and bigger efforts to make lifestyle changes may all be contributing factors to this decrease. (15)

International statistics

The WHO MONICA project, a 10 year epidemiological study including 38 populations in 21 countries all over the world, studied coronary heart disease morbidity and mortality in men and women between the ages of 35 to 64 years. They found that the age-standardized annual event rates could show large variation from country to country. Tunstall-Pedoe H. et al mention that a possible explanation might be many missed events in countries with low event rates. (16)

1.1.2. Clinical features

Myocardial ischemia can have many different clinical presentations. In some cases, for example in some older patients, women, diabetics, or post-operative and critically ill patients, no symptoms are present at all. But typically, it presents with ischemic symptoms occurring during exercise or rest. Symptoms include diffuse pain or discomfort that is not affected by movement of the affected region. The pain/discomfort can be located to various regions, such as the chest,

the arms and the mandibular or epigastric region. Other symptoms are dyspnea and fatigue, and also non-specific symptoms such as sweating, nausea or syncope. (1)

In the article "The value of symptoms and signs in the emergent diagnosis of acute coronary syndromes" the authors investigated which specific symptoms that are more likely to be associated with AMI, which can be helpful in the diagnostic procedure. Their results indicate that central chest pain is more likely to be caused by an AMI in comparison to left-sided chest pain and that radiation to both arms has a stronger predictive value than radiation to the right arm, which in its turn has a stronger predictive value than radiation to the left arm. They also found that sweating was a significant predictive factor, even stronger when observed by the doctor than when self-reported by the patient. (17)

1.1.3. Classification of myocardial infarction

There are different types of myocardial infarctions.

Type 1: Spontaneous myocardial infarction

Rupture, fissuring, erosion or dissection of an atherosclerotic plaque in one or more of the coronary arteries leads to an intraluminal thrombus. This results in decreased circulation in the myocardial tissue distal to the thrombus which causes necrosis of myocytes in this region. (1) This episode may be a consequence of an underlying coronary artery disease, but in some cases no signs of this disease is found when a coronary angiography is performed, particularly in women. (18-20)

Type 2: Myocardial infarction secondary to imbalance in oxygen supply and demand

This type of myocardial infarction is not caused by a plaque-rupture in the coronary arteries. Instead it develops secondary to ischemia caused by either a decrease in blood flow to the myocardial tissue or by an increase in the myocardial demand of oxygen. (1)

A type 2 myocardial infarction can be caused by increased levels of catecholamine in the blood stream as a result of for example critical illness or undergoing of major (non-cardiac) surgery.

(1) Other examples of underlying causes is spasm of the coronary arteries or dysfunction of the endothelium. (21-23) Further conditions that can cause this type of infarction is anemia, tachyarrhythmia and respiratory failure. (24)

Type 3: Cardiac death due to myocardial infarction

When a patient suffers a sudden cardiac death that is believed to be caused by a myocardial infarction, it is called a type 3 infarction. Symptoms of acute myocardial infarction in combination with new changes on the electrocardiogram indicating a myocardial infarction often precede the event of death. In these cases biomarkers may perhaps not be obtained. Either the patient dies before his or her level of cardiac biomarkers elevate in the blood stream, or he or she dies before a blood sample is even taken. (1)

Type 4 and 5: Myocardial infarction related to procedures of revascularization

In some cases, it is necessary to perform a mechanical revascularization procedure: percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). (1) As a consequence to these procedures, various events can occur that may cause necrosis of myocardial tissue, consequently leading to elevated cardiac troponin levels. (25-28) However, its effect on the patient prognosis is not well known if it is an asymptomatic event. (29-31)

If the infarction is caused by a thrombosis on the stent that was put in, or by restenosis, they fall under a particular subcategory (type 4b). (1)

1.1.4. Electrocardiogram

The ECG is an important part in the diagnostic procedure of suspected acute myocardial infarction. It is recommended to be done and interpreted as soon as possible after onset of symptoms. If the first ECG is non-diagnostic and symptoms are still present, it is recommended to acquire a new ECG. (1)

The part of the ECG that is the most interesting in AMI diagnostics is the ST-segment and the T-waves. The J-point is used as a reference to value these. The presence of a new ST-elevation

≥ 0.1 mV in two contiguous leads is considered pathological in all leads except V_2 and V_3, where the change must be ≥ 0.2 mV in men ≥40 years, ≥0.25 in men <40 years and ≥ 0.15 mV in women. Reciprocal ST-segment depression is not unusual in these cases. If there is an ST-depression ≥ 0.05 mV in two contiguous leads and/or inversion of T-waves in two contiguous leads with a prominent R-wave, it is considered pathological and may be caused by an acute mycordial infarction. (1)

Table 1. Criteria for ST-T wave changes in ECG for the diagnosis of acute myocardial infarction. (1)

ST elevation	ST depression and T wave changes
New ST elevation at the J point in two contiguous leads with the cut point: ≥ 0.1 mV in all leads other than leads V_2-V_3 where the following cut points apply: ≥ 0.2 mV in men and ≥ 40 years. ≥ 0.25 mV in men < 40 years, or ≥ 0.15 in women.	New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads and/or T inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio >1.

1.1.5. Biomarkers

At the event of myocardial injury, necrosis of myocytes occurs. This leads to leakage of biomarkers that are almost exclusively present in the cardiac tissue. Therefore, these biomarkers are checked for example in the emergency department in the diagnostic procedure of acute myocardial infarction. (1)

Troponin is the most preferred biomarker due to its high specificity to myocardial tissue and high clinical sensitivity. There are two types of Troponin: Troponin T (TnT) and troponin I. (1) There are no reports that show that cardiac troponin I is expressed outside cardiac tissue. However, regarding TnT, fetal isoforms exist in skeletal muscle. These isoforms were detected with the older assays but the new generations of assay have antibodies that excludes these isoforms from being detected. Thus, today's TnT analysis are highly specific for myocardial tissue. (32) The newest high sensitive cardiac troponin T (hs-cTnT) assays have a significantly

improved analytical performance and has lowered the 99th percentile upper reference limit to 14 ng/L (33).

In Sahlgrenska University, where this trial is done, the biomarker used for diagnostics in acute myocardial infarction is hs-cTnT. Therefore, the biomarker that will be focused on in the following text will be troponin T.

Troponin T is one out of three protein subunits in the troponin complex of the contractile apparatus in the cardiac myocyte. (34) The troponin complex responds to calcium in the cytosol and phosphorylation of regulatory proteins and functions as a modulator of the sarcomere's contractile function. (32)

At the event of damage to the cardiac myocytes, the membrane leaks these proteins out to the bloodstream. Leakage of TnT to the bloodstream does not give us any information on the underlying mechanism causing the necrosis of myocytes. In order to distinguish which cases of TnT elevations that may be caused by an acute myocardial infarction (AMI) it is important to separate stable TnT elevations from acute elevations. (1)

Acute elevations may occur in acute events such as acute myocardial infarction, aortic dissection or an arrhythmia, whilst stable elevations are related to chronic conditions such as heart failure and renal failure. Therefore, it is of great value in the diagnostic procedure to differ these two types of elevations from each other in the emergency department. This can be done by using the fact that chronic elevations do not tend to change significantly over a short period of time, while acute elevations show a significant rise and/or fall in TnT levels over a short period of time. This requires a series of blood samples from the patient in order to discover an eventual rise and/or fall in troponin T levels, which would then distinguish the acute elevations from the chronic elevations. (1)

When suspecting an acute coronary syndrome, it is therefore recommended that blood samples are drawn on the first assessment and 3-6 hours after (1). If the timing of the initial symptoms are unclear, further samples may be required (1). At the event of an AMI, the levels of TnT start to increase a few hours after myocyte necrosis and reaches a plateau level after 10-15 hours, after which it slowly declines (2). Therefore, a change ≥ 20% in a patient with an elevated troponin level at baseline is suggested as indicative of an AMI (35).

Compared to previously used biomarkers for AMI such as CK and CK-MB, TnT levels in serum are elevated for a longer time period after onset of symptoms. In cases with late and/or high peak concentrations it can be elevated for up to 3 weeks. Therefore TnT is not only an early marker for AMI, but also helpful in late diagnosing of AMI in patients who comes to the emergency department several days after onset of symptoms. (34)

The normal variation of the long time changes in troponin T is not yet well defined. Some studies have been done but the results vary between different study populations. Vasile VC. et al. studied the between-day hs-cTnT change in 20 healthy subjects and found the mean changes to be between +103.4% and -87% (36). Frankenstein L. et al. studied the weekly hs-cTnT change in 17 healthy individuals and found a variation of +/- 86-87% (37). Bjurman C. et al. studied the hs-cTnT level in 94 NSTEMI patients six weeks after the infarction and found that most of the patients had >400% in hs-cTnT change (5). Thus, in this study, the interval of long-term troponin T change considered normal is between +60% and -50%, that is a rise in hs-cTnT >60% and a fall in hs-cTnT >50%.

1.2. Elevation of troponin levels in the absence of acute coronary syndrome

A troponin T level above the 99th percentile of the upper reference limit (URL) is considered to be pathological (1). The new high-sensitivity cardiac troponin assays have lowered the upper reference limit to 14 ng/l (38, 39). Consequently the number of patients with elevated troponin T has naturally increased (9, 40), particularly amongst patients >65 years in the emergency

department without myocardial infarction (41, 42). Therefore, it is of great importance to evaluate whether it is an acute or a chronic elevation, since, as mentioned earlier, there are different causes to these elevations respectively (32).

A stable elevation can be caused by a variety of diseases, such as renal failure, severe left ventricular hypertrophy and chronic heart failure. Table 2 below is from the article "Recommendations for the use of cardiac troponin measurement in acute cardiac care" by Thygesen K et al. It shows a list of other reasons for troponin elevation than acute myocardial infarction. (32)

Table 2. Cardiac troponin level elevations not related to acute coronary syndrome.

Damage related to secondary myocardial ischaemia (MI type 2)	Damage not related to myocardial ischaemia	Indeterminant or multifactorial group
Tachy- or bradyarrhythmias	Cardiac contusion	Apical ballooning syndrome
Aortic dissection and severe aortic valve disease	Cardiac incisions with surgery	Severe pulmonary embolism or pulmonary hypertension
Hypo- or hypertension, e.g. haemorrhagic shock, hypertensive emergency	Radiofrequency or cryoablation therapy	Peripartum cardiomyopathy
Acute and chronic heart failure without significant concomitant coronary artery disease (CAD)	Rhabdomyolysis with cardiac involvement	Renal failure
Hypertrophic cardiomyopathy	Myocarditis	Severe acute neurological diseases, e.g. stroke, trauma
Coronary vasculitis, e.g. systemic lupus erythematosus, Kawasaki syndrome	Cardiotoxic agents, e.g. anthracyclines, herceptin, carbon monoxide poisoning	Infiltrative diseases, e.g. amyloidosis, sarcoidosis
Coronary endothelial dysfunction without significant CAD, e.g. cocaine abuse	Severe burns affecting >30% of body surface	Extreme exertion
		Sepsis
		Acute respiratory failure
		Frequent defibrillator shocks

As the table shows, other causes of troponin elevation than AMI can be separated into three groups: Secondary myocardial ischemia, diseases not associated with myocardial ischemia and

conditions with uncertain or multifactorial mechanisms. They all cause myocardial damage but with different or unknown mechanisms. (32)

Studies have shown that the mortality amongst several of these group of patients is higher if the patient has an elevated troponin level. (32) A few studies are presented below that show the relation between elevated troponin levels and higher mortality rates in cases without acute myocardial infarction.

For instance, elevation of high sensitive troponin T in patients with chronic heart failure has shown a significantly higher risk of death. If combined with elevation of N-terminal pro-B type natriuretic peptide (NT-proBNP), it showed a further increase in risk of death. (43)

Khan NA. et al did a meta-analysis study on the association between troponin T and mortality in patients with end-stage renal disease who did not have suspected acute coronary syndrome. They found that an elevated troponin T amongst these patients was related to increased mortality and increased cardiac death. (44)

Another meta-analysis study investigated whether elevation of troponin level amongst patients with pulmonary embolism is related to higher risk of negative outcome. They showed that an elevated troponin level was associated with a higher short-term mortality and adverse outcome events. (45)

Blich M. et al studied hospitalized patients to see if there is a relation between troponin levels and negative outcome in hospitalized patients. They found that an increase of troponin levels is frequent among consecutive hospitalized patients in absence of an acute coronary syndrome and is related to poor short- and long-term outcomes. (46)

A study that was done to investigate the relation between chronic obstructive pulmonary disease (COPD) and high-sensitive cardiac troponin T levels found that a stable COPD was associated

with higher troponin levels in comparison to the general population. They also saw that patients with a greater severity of the disease had higher levels of troponin. (47)

The relation between troponin levels and sepsis, septic shock and systemic inflammatory response syndrome (SIRS) was investigated by Ammann P. et al. The patients included had no acute coronary syndromes. They saw that there was an elevation of troponin in 85% of the patients with sepsis, septic shock or SIRS (n=20) whilst none of the patients in the control group had an elevation of troponin. (48)

2. Aim

The aim is to get an overview on the medical history of the patients that are sent home from the ED with a stable troponin elevation. The aim is also to investigate whether there is a long time troponin dynamic that we are missing at the ED.

2.1. Specific objectives

How does the medical history look like in the group of patients that attend the ED with the chief complaint chest pain and/or dyspnea, and is sent home from the medical section of the ED with a stable troponin T elevation?

How many of the patients that attend the ED with the chief complaint chest pain and/or dyspnea, and are sent home from the medical section of the ED with a stable troponin T elevation have a long time dynamic change of troponin T?

3. Material and Methods

This trial was conducted at Sahlgrenska University Hospital in Gothenburg, Sweden and included patients from the medical section of the emergency departments in Sahlgrenska hospital, Mölndal hospital and Östra hospital.

3.1 Study group

Patients included in the study were patients who had attended the emergency department (ED) with the chief complaints chest pain and/or dyspnea, had at least one high sensitive cardiac troponin T (hs-cTnT) value over 14 ng/L and was sent home.

3.1.1. Enrolling patients

In the EDs in Gothenburg, attending patients are registered in a program called ELVIS. This program was used for collecting patients. Patients who had attended the medical section of the ED between 25th of April 2016 and 7th of June 2016 with the chief complaint chest pain or dyspnea, and were sent home, were enrolled, since these are two symptoms strongly related to myocardial infarction (1).

The total amount of attendances with the mentioned chief complaints that resulted in the patient being sent home was 1372. Note that this is not the same as the amount of attending patients since some patients attended the ED more than one time during this time period. The patients included were the ones who during their ED visit had at least one hs-cTnT value >14 ng/L, which is the upper reference limit at Sahlgrenska University Hospital (38, 39). This landed in a total amount of 34 patients. When contacting the patients, two of them said they wanted to be excluded from the study. Therefore, the final number of patients was 32.

The patients' phone numbers were searched for in Melior, the system used at Sahlgrenska for medical records. The numbers that could not be found in Melior were attempted to be found at the webpages hitta.se and eniro.se. Then, all the patients whose numbers were managed to be found, were contacted. They got information on why they were contacted and were offered to book an appointment on which the patient would meet with Dr. Ola Hammarsten or medical

student Soza Zangana. Not all patients were reachable, and two of the patients who answered the call said they did not want to be included in the study. In total, 23 patients were managed to be booked for an appointment. Three of these patients were not able to get to the hospital, which is why a home visit was made in these cases. The patients the medical student met were always consulted with Dr. Hammarsten. During the consultations, an anamnesis was obtained based on a questionnaire that was made, see appendix 1.

The patients who were not reached by phone, a blood sample was managed to get a hold of in other ways. This was done by monitoring Flex-lab to see if recent samples had been taken on the patients, in which cases additional analysis were ordered on them including hs-cTnT. One patient did not want an appointment but agreed on leaving a blood sample at the nearest healthcare center. All blood samples were drawn at least 10 days after the patients' attendance to the ED.

3.1.2. Calculations and review of medical records

When the follow up samples were taken, the percental change in hs-cTnT was calculated according to the following equation: $\frac{hs{-}cTnT\ (follow\ up){-}hs{-}cTnT\ (ED)}{hs{-}cTnT\ (ED)}$. If the patient had more than one value >14 ng/L from the ED visit, a mean value was calculated and used in the equation. The patients who had booked an appointment with us were informed with the results by phone. The patients admitted to the hospital were not available on their phone and were thus not contacted.

A review of all the included patients' medical records in Melior was also done, so even though an appointment was not made with all the patients, information on their medical history was still collected. One exception was a patient who had his previous medical records in Halmstad, which is why this patient's medical record was not accessible.

3.2. Statistical analysis

Some of the data collected was statistically analyzed in Microsoft Excel 2016 by using t-test. P values <0.05 were considered significant.

4. Ethics

The integrity of the patients was exposed due to the full access of their medical journal and blood sample analysis. This ethical issue was taken into consideration as follows. Patients who attended for a follow up appointment were given thorough time to read the detailed information and fully comprehend the study before signing an informed consent form. Envelopes with information regarding the study along with a form for informed consent were sent home to the patients who did not attend to a follow up appointment. Even though none of the participants that received the form by post replied, the study had still received ethical permissions, according to the world medical association declaration of Helsinki:

1. Biobank med koppling till SWEDEHEART Dnr 803-12. Approved 2012-12-05.
2. Hur påverkas blodprovsanalyser av olika akuta sjukdomstillstånd? Dnr 755-09. Approved 2010-02-11.

5. Results

The total number of patients was 34. When contacting the patients, two of them said they wanted to be excluded from the study. Therefore, the final number of patients was 32. Since some information was not possible to obtain for some of the patients, the total number of patients is not 32 for all the presented variables.

5.1. Characteristics of the patients.

Table 3. Baseline characteristics of the patients.

Variable	Value	Total number of patients for which the value was known
Average age (years)	78.7	32
Women	53.1%	32
Smoking*	58.3%	24
Average body mass index (BMI)**	25.1	21
Ischemic cardiovascular disease	56.7%	31
Heart failure	28.1%	32
Arrythmia	32.3%	31
Chronic obstructive pulmonary disease	25.8%	31
Two or more severe diseases	78.1%	32
Antihypertensive drugs***	64.5%	31
Lipid-lowering drugs	35.5%	31
Average creatinine level (µmol/L)	95.9	32
Average troponine T level**** (ng/L)	27.9	32
ST-T abnormalities at ECG	21.9%	32

hs-cTnT = high sensitive cardiac troponin T.

* Current or former smoker; self-reported.

** Based on selfreported weight and length.

*** Thiazide diuretics, calcium antagonist, ACE-inhibitor, Angiotensine-antagonist.

**** At follow up sample.

The ages ranged between 50-95 years. The majority, 71.9% (23 patients), were between 70-89 years old. There was a significant age difference between men and women (p=0.01) (figure 1).

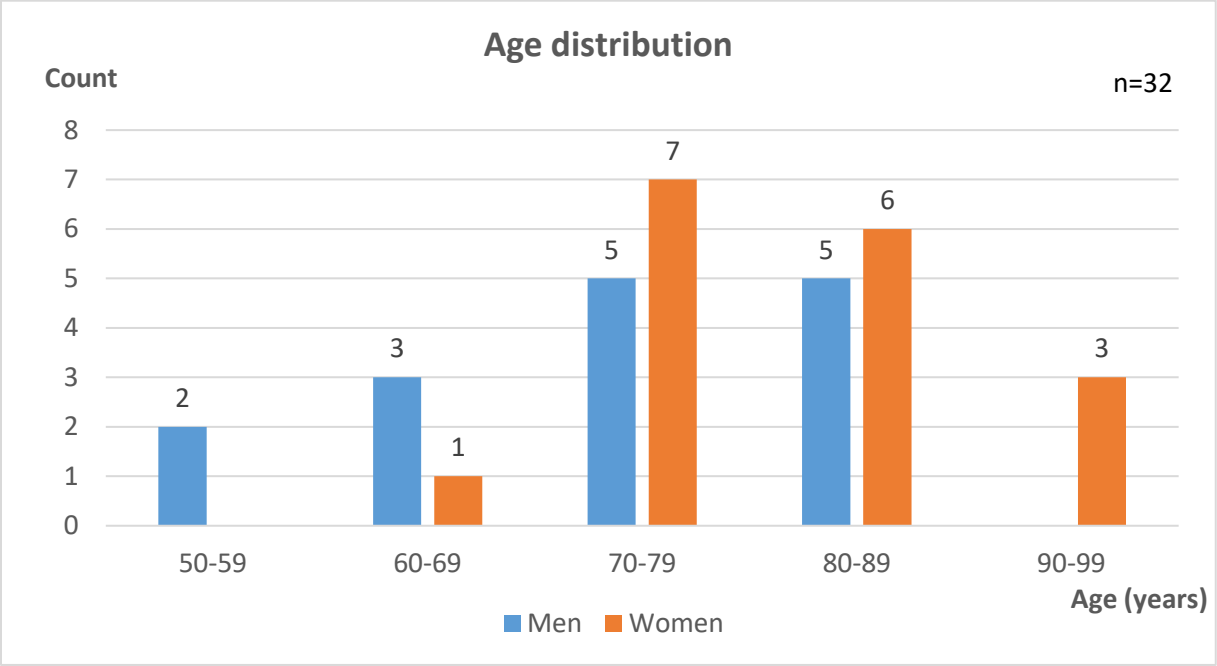

Figure 1. Patient distribution by age and gender. The total number of patients (n) is 32. The number written above the bars is the number of patients in each bar.

Figure 2 below shows how many severe diseases the patients have. Which diseases defined as severe were determined at the author's discretion and are listed in table 4.

Table 4. A list of diseases considered as severe.

Diseases
Chronic obstructive pulmonary disease (COPD)
Previous stroke/transient ischemic attack (TIA)
Coronary artery disease
Aortic aneurysm
Heart failure
Takutsobo cardiomyopathy
Atrial flutter
Sick sinus syndrome
Claudication
Kidney failure
Myeloma
Lymphoma
Prostate cancer
Breast cancer
Skin cancer
Rheumatoid arthritis
Parkinson's disease
Drug- or alcohol addiction

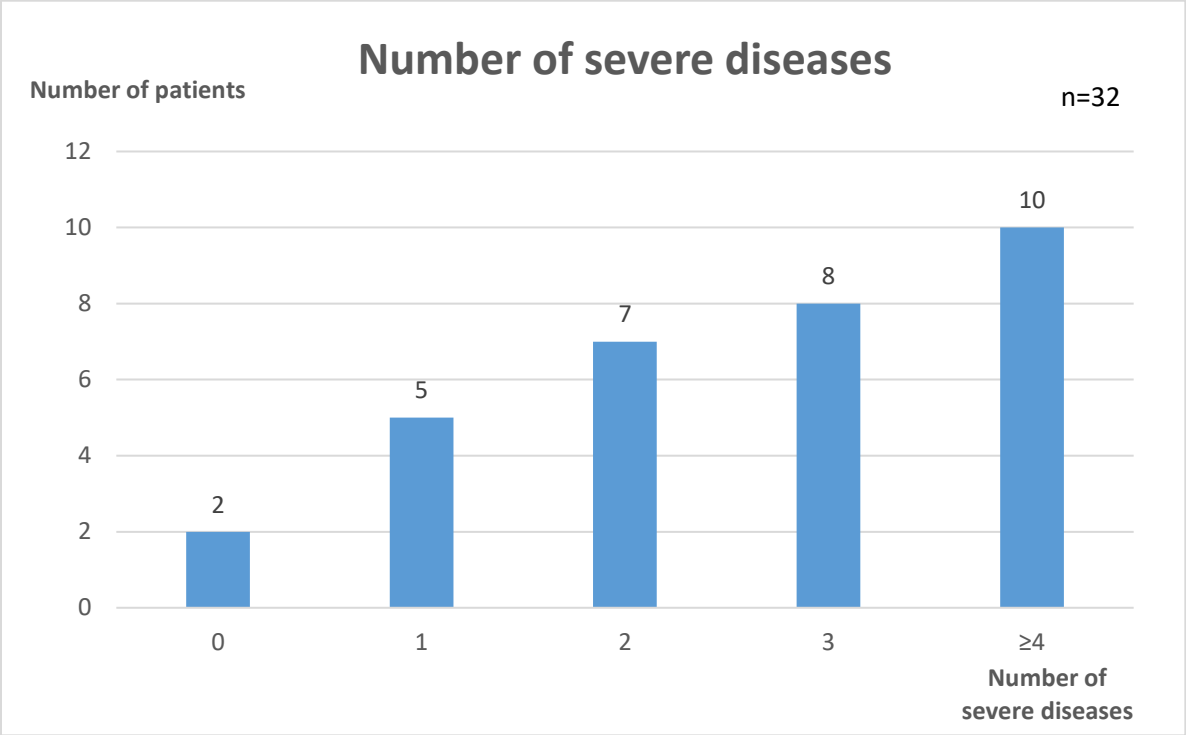

Figure 2. The patients distributed in different bars depending on number of severe diseases. For instance, the figure shows that 10 patients have 4 or more severe diseases. The total amount of patients (n) is 32. The number written above the bars is the number of patients in each bar.

The total amount of chief complaints is more according to the medical records in comparison to ELVIS (figure 3). This is because several chief complaints can be noted in the medical records, while in the registering system ELVIS only one symptom can be registered.

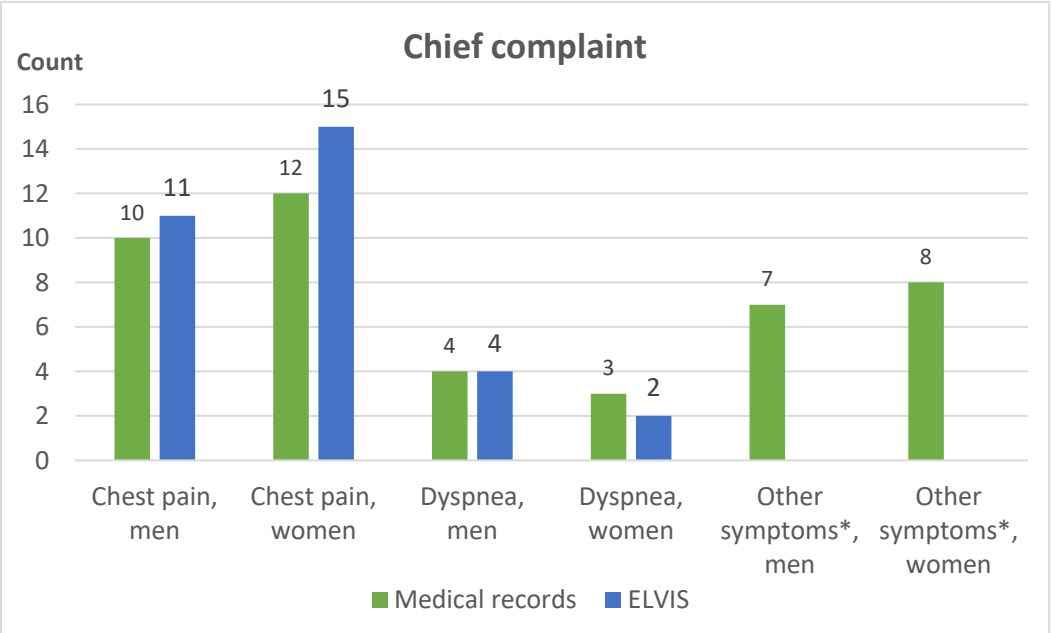

Figure 3. The chief complaint for men and women according to medical records (green bars) and ELVIS (blue bars) respectively. The number written above the bars is the number of patients in each bar.

*Other symptoms such as tachycardia and dizziness.

There was another possible cause aside from myocardial infarction for the troponin-elevation in 68.9% of the patients (22 patients) (figure 4). The alternative causes for these patients are listed in table 5. In the remaining cases, no other explanation for troponin-elevation was found.

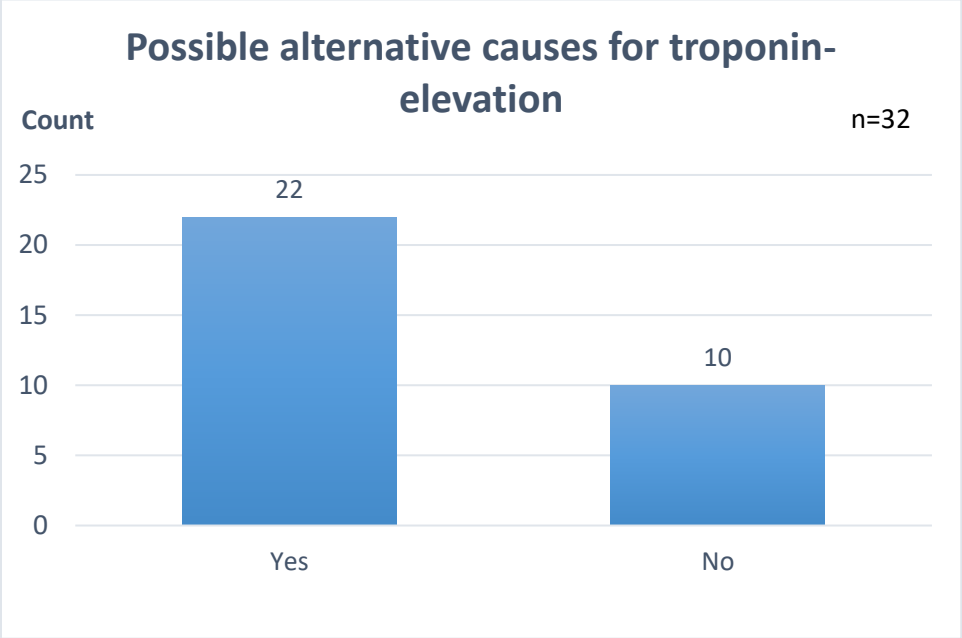

Figure 4. The chart shows how many patients who had a possible other cause for troponin elevation (32). The number written above the bars is the number of patients in each bar.

Table 5. Other possible causes for troponin elevation in this study group.

Other causes for troponin elevation
Heart failure
Atrial flutter
Respiratory failure due to chronic obstructive pulmonary disease (COPD)
Kidney failure
Sick sinus syndrome
Angina pectoris
Recent thorax operation (lung lobectomy)
Amfetamin abuse
Recent extreme workout
Sarcoidosis

There were pathological ECG-findings in 75.0% (24 patients) of the cases (figure 5) and 21.9% (7 patients) had ST-T abnormalities in their ECG (figure 6).

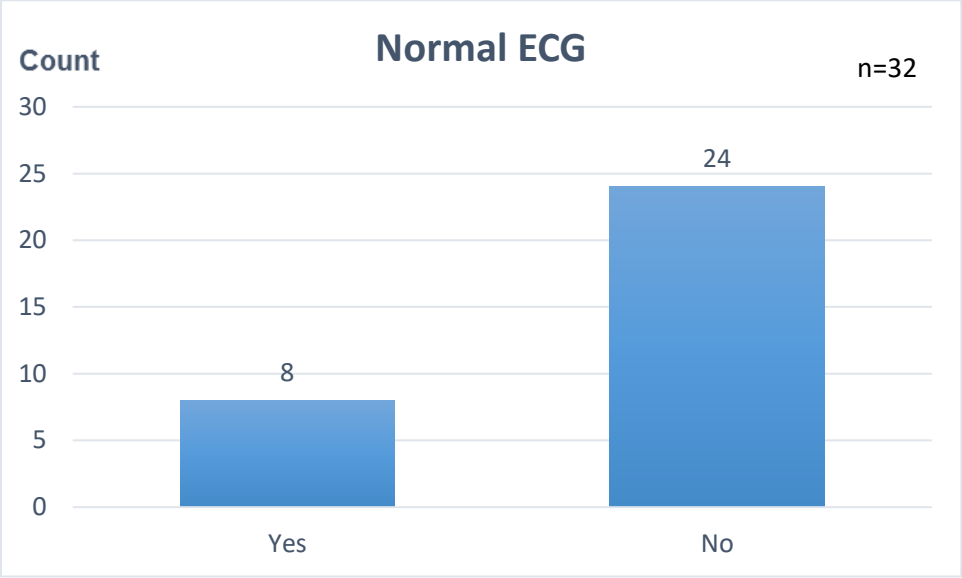

Figure 5. The number of normal and abnormal ECG's are demonstrated in this figure. The number written above the bars is the number of patients in each bar.

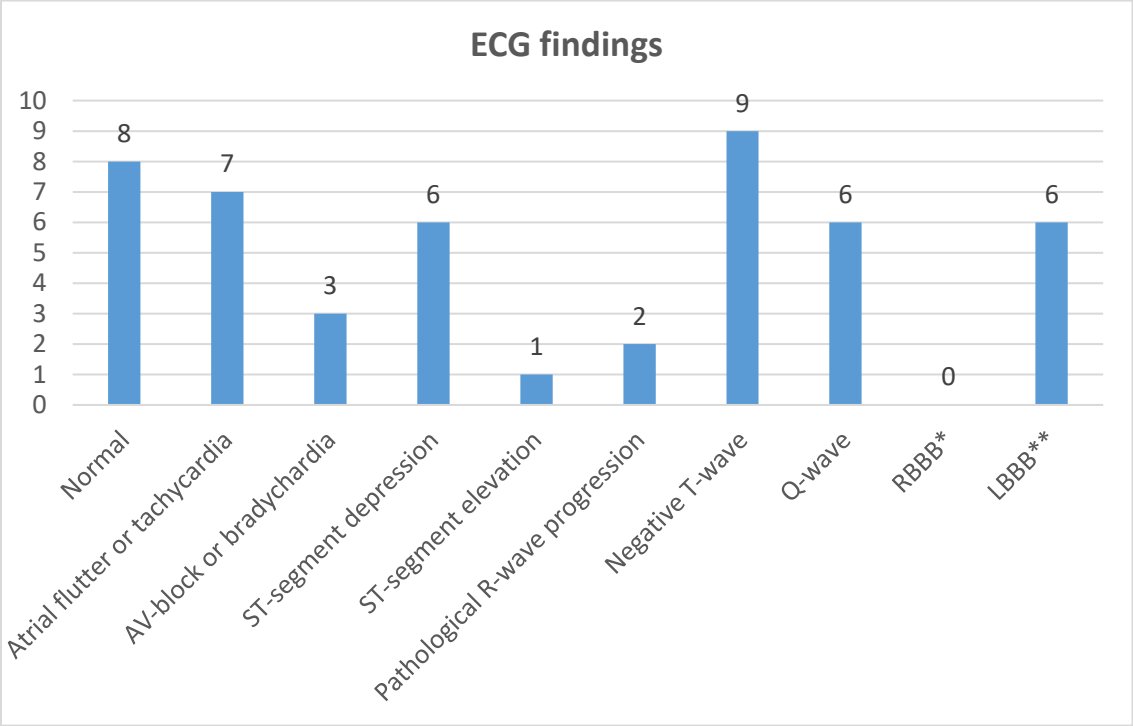

Figure 6. The number written above the bars is the number of patients with each finding. 8 ECG's were completely normal, the rest had pathological findings.
*RBBB = Right bundle branch block. **LBBB = Left bundle branch block.

An ultrasound cardiography (UCG) had been done in 18 (56.3%) of the cases and 16 (88.9%) of them had pathological findings.

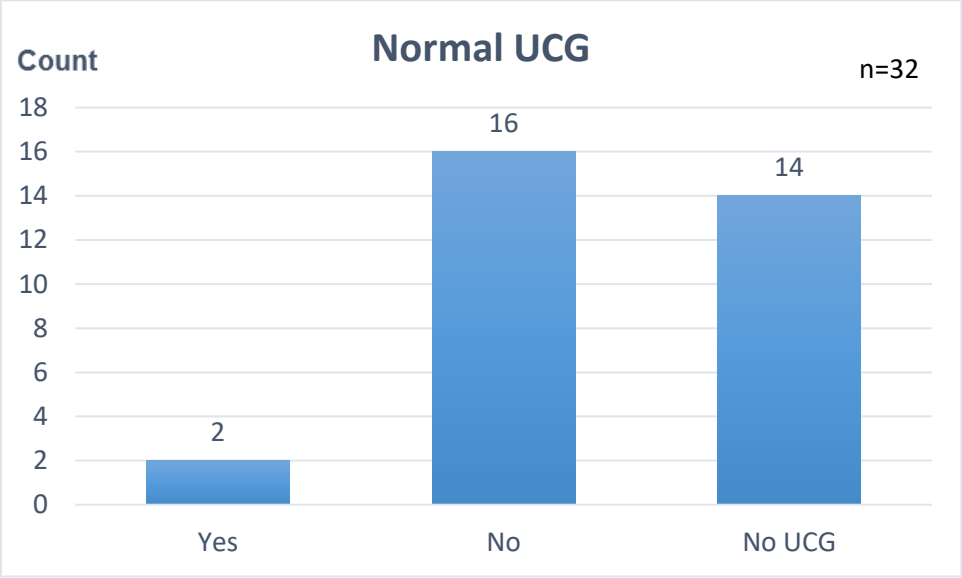

Figure 7. This chart shows the number of patients with pathological and normal UCG-findings. The patients who had not undergone a UCG-examination are included in the bar marked "No UCG". The number written above the bars is the amount of patients in each bar.

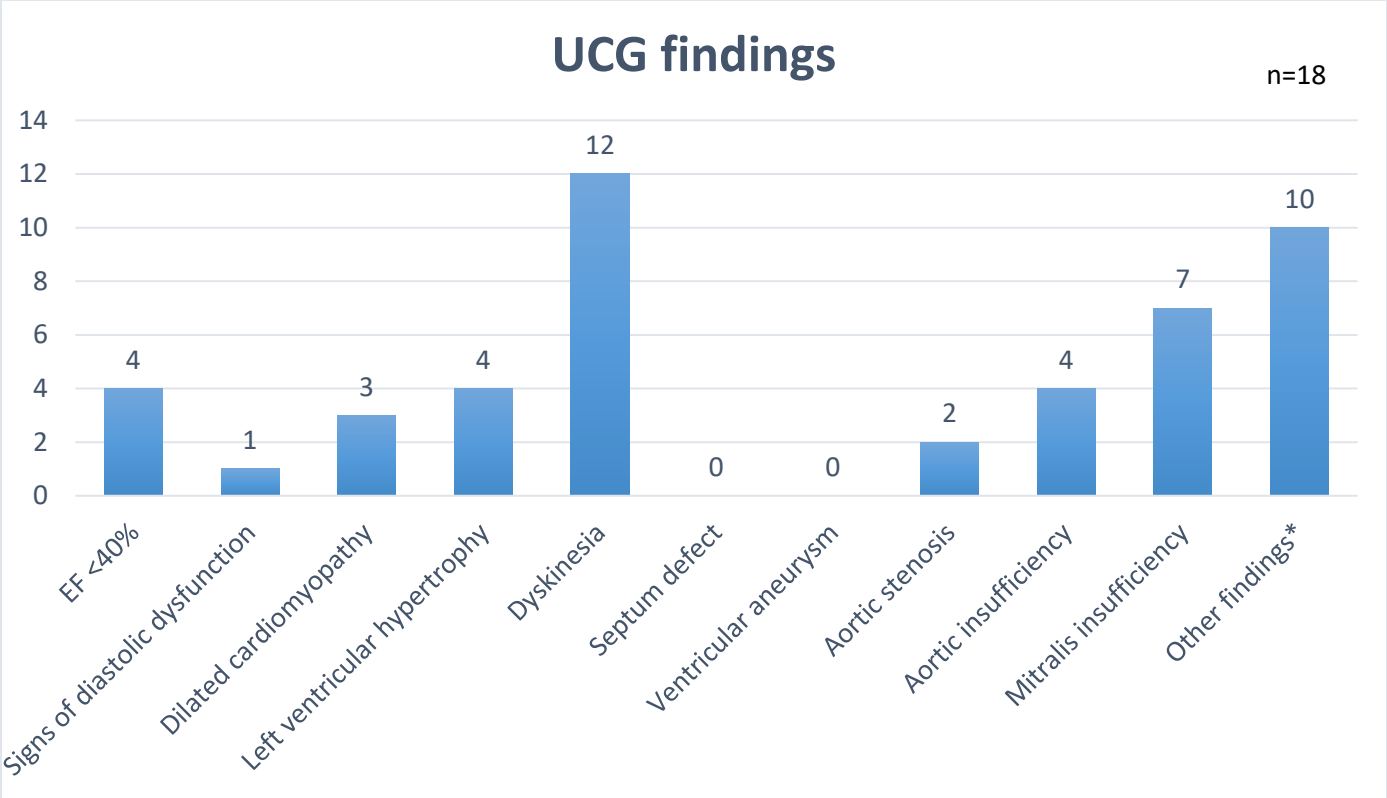

Figure 8. Frequency of different UCG-findings. Other findings include amongst others atrial enlargement and tricuspid insufficiency. The number written above the bars is the number of patients in each bar.

Patients with relative estimated glomerular filtration rate (eGFR) above and below 60 ml/min/1.73 m^2 were dichotomized in two groups (figure 9). No significant difference was found when comparing the two groups' hs-cTnT levels (follow up sample) (p=0.67).

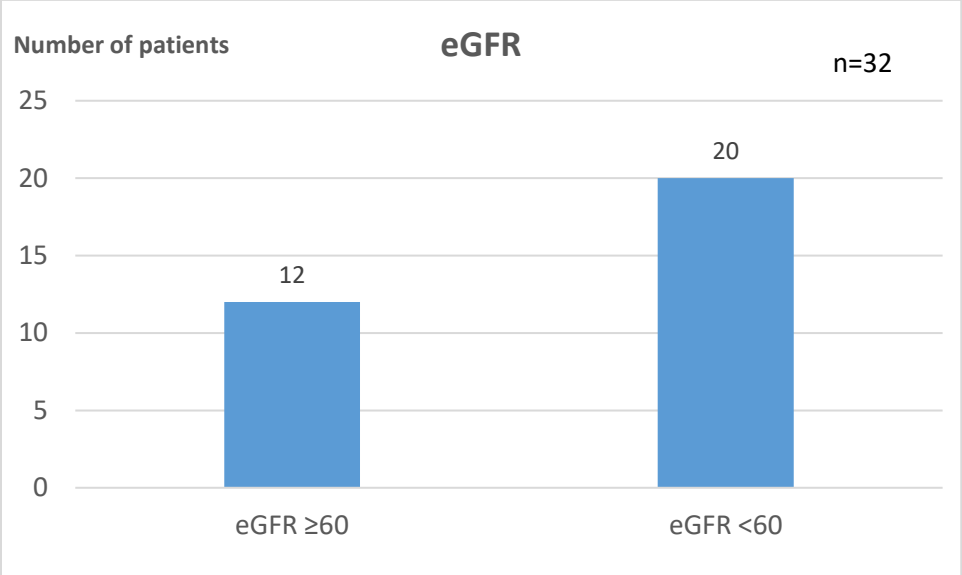

Figure 9. Patients dichotomized in groups with eGFR beneath and above 60 ml/min/1.73 m^2. eGFR = estimated glomerular filtration rate.

5.2. Troponin T

Some of the patients had several troponin T values from their attendance at the emergency department. In these cases, a mean value was calculated and used in the figures below.

The correlation between the patients' troponin levels and estimated glomerular filtration rate (eGFR) is presented in figure 10. The r-value is -0.23 and the p-value is 0.21.

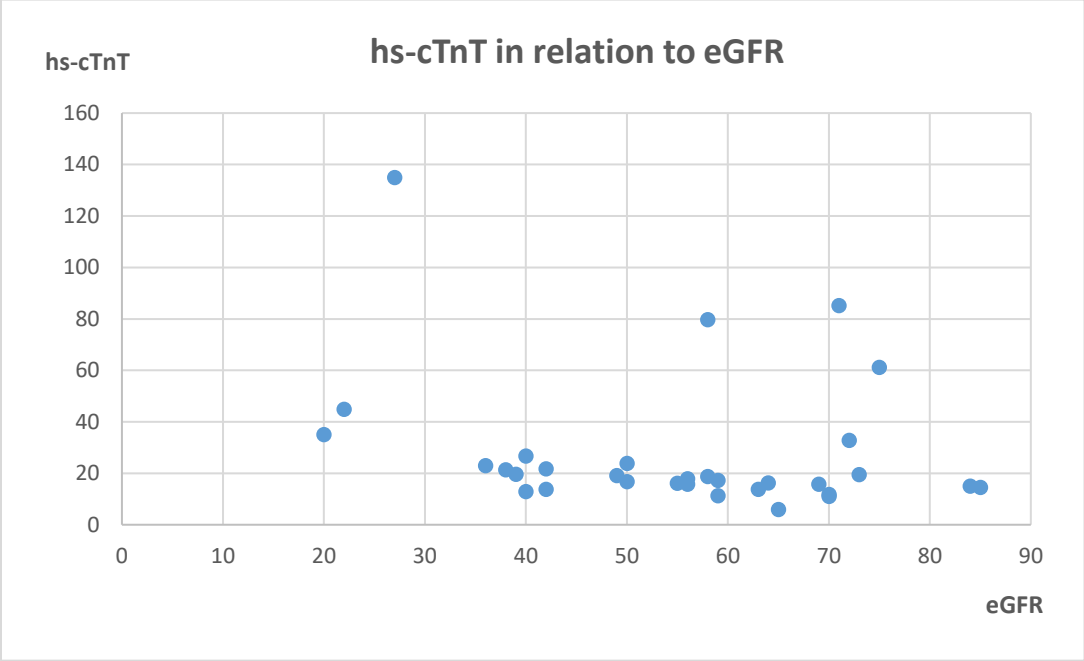

Figure 10. Troponin T levels from the follow up-sample scatterplotted against the patients' relative eGFR. hs-cTnT = high sensitive cardiac troponin T. eGFR = estimated glomerular filtration rate.

Percental change was calculated following this formula: $\frac{hs{-}cTnT\ (follow\ up){-}hs{-}cTnT\ (ED)}{hs{-}cTnT\ (ED)}$. The range of change considered normal in this study was between +60% and -50%. The range was chosen with a good safety margin, based on what previous studies have shown is a normal long-term percental hs-cTnT change (36, 37). The percental change in the majority of the patients were within this range, but six patients had changes outside these limits (table 6, figure 11). The mean value of the change is 14.0% (SD 69.1%; 95% confidence interval: -55.1%, +83.1%).

Table 6. Troponin T levels of each patient at the emergency department (ED) and at follow up sample. Patients with pathological changes are highlighted.

Patient	hs-cTnT ED	hs-cTnT follow up	Percental change
1	14,1	14,5	2,8%
2	14,2	26,7	88,0%
3	14,7	19,1	29,9%
4	14,8	15	1,4%
5	14,9	13,8	-7,4%
6	15,3	11	-28,1%
7	15,6	18,7	19,9%
8	15,9	16,2	2,2%
9	16,5	17,2	4,2%
10	17	21,7	27,6%
11	17	11,8	-30,6%
12	17,5	15,8	-9,7%
13	17,7	22,9	29,4%
14	18,2	16,1	-11,5%
15	20,5	13,8	-32,7%
16	18,7	23,8	27,3%
17	21,4	12,9	-39,7%
18	20,1	11,3	-43,8%
19	20,1	17,9	-10,9%
20	21,8	21,4	-1,8%
21	23,8	35	47,1%
22	22,1	19,5	-11,8%
23	23,7	85,2	259,5%
24	23,8	19,6	-17,6%
25	24,6	32,8	33,3%
26	24,7	79,7	222,7%
27	30,4	16,8	-44,7%
28	36,3	15,8	-56,5%
29	38	44,8	17,9%
30	44,8	5,96	-86,7%
31	45,1	61,2	35,7%
32	101,9	135	32,5%

hs-cTnT = high sensitive cardiac troponin T. ED = Emergency department.

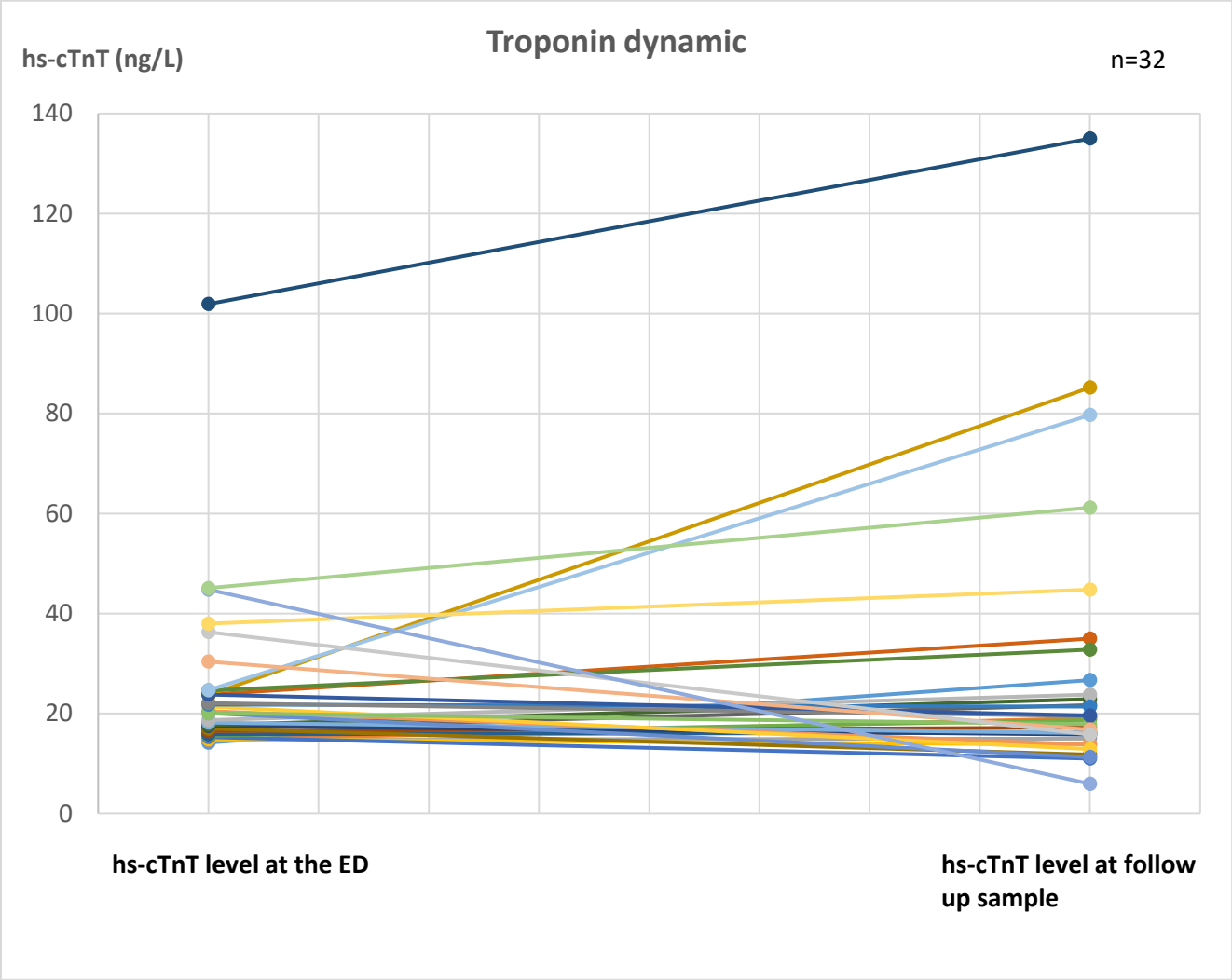

Figure 11. Troponin T levels at the emergency department (ED) and at the follow up sample are presented here with a line drawn between every patient's both samples.
hs-cTnT = high sensitive cardiac troponin T.

6. Discussion

This study had two aims: To get an overview on the group of patients that are sent home from the emergency department (ED) with a stable troponin elevation and to investigate whether there is a significant long time troponin dynamic that we are missing in the ED, which would consequently suggest that we may be missing myocardial infarctions in these cases. The obtained results show that these patients are old and suffer from several co-morbidities. No long-time troponin dynamic indicating a missed myocardial infarction was found.

6.1 Discussion of the results

The majority of the patients, 71.9% (23 patients), were between 70-89 years old (figure 1). This was not very surprising considering that older people have a higher burden of disease and thus have a greater risk of having a condition leading to a stable troponin elevation. This result is in line with the results in a study made by Cardinaels EP. et al which has shown that elderly people normally have higher troponin values (38).

The men were significantly younger than the women in the study group ($p=0.01$) (figure 1). This is consistent with the results shown by Cardinaels EP. et al showing that men in general have an elevated troponin value at a younger age than do women (38).

The co-morbidity of the study group was high (table 3, figure 2, 5-8). All patients but 2 had one or more severe diseases (coronary artery disease, previous stroke and more – see results). These results indicate that this is a group of patients with a high burden of disease. This is consistent with a number of studies which have shown that elevated troponin T levels are associated with several severe diseases such as heart failure and COPD (32, 43, 46, 47).

The chief complaint according to the medical records shows different information compared to ELVIS (figure 3). According to the medical records, some of the patients' chief complaint was nor chest pain or dyspnea. For instance, two of the patients had abdominal pain according to the medical records, but were registered in ELVIS as having chest pain. A possible explanation

could be that the patient was moved from the surgical section of the ED to the medical section of the ED to rule out an AMI, and thus was registered as a "chest pain" in ELVIS by the nurse, even if chest pain was not the patients' chief complaint.

There are two other possible sources of error concerning the chief complaint. First, the nurse could have simply typed in the wrong chief complaint in ELVIS. It is common that the patients attend with several symptoms, which sometimes can be diffuse, and can thus lead to misinterpretations in a stressed situation. Second, older patients with AMI commonly present with atypical symptoms (1), and are thus missed when chest pain or dyspnea are mandatory chief complaints for inclusion in the study.

The patients included in our study were in several cases difficult to communicate with, despite that we met them in a non-acute situation in comparison to the situation at the ED. Some of them had language difficulties, others focused a lot on irrelevant topics during the consultation. Both these factors may have contributed to difficulties with taking an anamnesis at the ED, which might have resulted in the clinician missing important information. This could possibly affect the handling of these types of patients. For instance, it may cause the clinician to miss information indicating an AMI and send the patient home incorrectly, or, in the opposite situation, it may lead to the patient being admitted to the hospital because of the uncertain anamnesis.

In our study group, 68.8% (22 patients) had another possible cause for troponin elevation (figure 4). The fact that there are numerous reasons for troponin elevation presents a challenging and possibly deceiving situation for the clinician. If a patient with another possible cause for elevated troponin attends the ED with symptoms of AMI, there is a risk that the clinician might incorrectly blame the elevated troponin on that other cause. In this group of patients, the

clinicians appear to have made a correct medical decision excluding an AMI, considering no patients had a missed AMI according to our results.

In figure 10, the patients estimated glomerular filtration rate (eGFR) was scatter plotted against their high sensitive cardiac troponin T (hs-cTnT) levels (follow up sample). No significant correlation between eGFR and hs-cTnT levels was found (p=0.21). There was also no significant difference in hs-cTnT levels (follow up sample) between patients with eGFR above and below 60 ml/min/1.73 m^2 (p=0.67). These findings are not consistent with previous findings indicating that patients with kidney dysfunction have an elevated troponin T level (49). Although, the number of patients in this study were few and not many of them had a severe kidney disease. This makes it difficult to draw conclusions regarding the relation between troponin T and kidney function from this data.

In this study, the range of hs-cTnT change considered normal was between +60% and -50%, that is a rise in hs-cTnT >60% and a fall in hs-cTnT >50%. The time between the patients' attendance to the ED and their follow up-sample was at least 10 days in order to study their long-time troponin-change. The mean value of the percental change in our patients was +14.0% (SD 69.1; 95% CI: -55.1%, +83.1%). The confidence interval for the long-time troponin dynamic in our study group is similar to that of the random population (36, 37).

The percental change in most of the patients was within the range considered as normal in this study, but five patients had a percental change outside these limits (figure 11, table 6). Three patients had a rise in hs-cTnT >60% and 2 patients had a fall in hs-cTnT >50%.

Patient #2 (table 6) had a percental change of +88%, which was probably due to the fact that she had a lung lobectomy done the time between the two samples were taken. Patient #23 and #26 (table 6) had an increased troponin value at the follow up sample with +260% and +223% respectively. Since these patients were not met with, there is no information on what could be

the cause of the elevation. Possible explanations are that they had an AMI after the ED visit, or that they were afflicted with another illness affecting their troponin levels. Either case, the elevation was probably not due to an AMI at the ED because in that case, troponin should have been decreased and not increased at follow up (2). But this doesn't eliminate the possibility that the patients had an AMI at the ED. There might have been a significant long-term decrease in these patients' troponin levels between the ED visit and the follow up sample, which is now disguised by a new elevation.

Patient #28 (table 6) had a percental change of -57%. This could be interpreted as a missed AMI, but according to the medical records, the patient had an atrial flutter at the ED, which was probably the cause of the troponin elevation at that time. Patient #30 (table 6) had a percental change of -87%. This patient was actually diagnosed with an AMI at the ED, since the patient had a significant short time-dynamic at the ED with a first hs-cTnT at 8 ng/L and second one at 40.5 ng/L. In this case, the patient chose to leave the ED against doctor's recommendations. The reason for leaving was that the patient was unsatisfied with the doctors' decision of not doing an acute PCI.

In future studies, it would be good to have a larger study group. It would also be interesting to study the following additional variables: the time elapsed between the onset of symptom to the first sample, how many troponin samples that were taken at the ED, at what time the samples were taken and how much time elapsed between the samples at the ED. The recommended time between samples are 3-6 hours (1) so it would be interesting to see if these recommendations were followed.

Considering that the interval for normal long-term troponin change is not yet well defined, bigger studies need to be done on healthy individuals' long-term troponin change.

6.2. Limitations

The study population was considerably small. Acute myocardial infarction is a relatively common illness which is why a bigger study population is needed for the results to be applicable to the general population. The problem in doing a similar but bigger study is that the method used in this study is time-consuming. It took a lot of time and a great amount of patience when trying to get a hold of all the patients to book an appointment. On top of that, each appointment took nearly 30 minutes and some patients even had to be visited at home. And after all consultations, the patients were contacted with the results by phone, which also took a lot of time since they did not always answer on the first call. To make a bigger study of this kind will probably demand a lot of resources.

It would be practical to send the patients a blood sample form with information and ask them to go to the nearest lab and leave a blood sample. The problem is that it would probably concern the patients if they are asked to take a blood sample. They might for example misinterpret the information and incorrectly believe that they have had a heart attack. Without a physical consultation, one can't take care of that concern or obviate eventual misunderstandings, which would be unethical. Possibly it could be solved by having phone contact with the patients both before and after taking the follow up sample. And of course, if making a similar study with a bigger study group, a strict plan must be in place on how to handle the situation if a missed myocardial infarction is found.

In this trial, there was no control group. This is due to the fact that a lot of people attend the emergency department with the symptoms chest pain and dyspnea without a troponin value above 14 ng/L. It would not be possible to meet with all these patients in the time frame of this study. Possibly this could be done in a future study.

Not all patients attended a physical follow up. Due to this, all the questions in the questionnaire was not answered for all patients, which lessens the strength of the results in some of the data

from the questionnaire. The questionnaire was mainly self-reported, which also decreases the strength of the results. Although, the self-reported information cannot be obtained in another way than from the patient.

Some of the patients were admitted to the hospital at the time of follow up. Therefore, they were unavailable for a follow up appointment, but a follow up-troponin level could still be obtained by ordering additional analysis to the samples that were drawn in the hospital. The cause of their admittance was not investigated since it was not part of the original aim, and is therefore unknown. It is possible that these patients had an illness that affected their hs-cTnT levels at the time for the follow up sample. Another bias regarding the follow up sample is that the time between the ED sample and the follow up sample is not the same for all patients. The only demand was that the follow up sample was taken at least 10 days after the ED visit. It would have been preferable to also have an upper limit on the number of days to the follow up sample. In our study, the time elapsed between the ED visit and the follow up sample varied a lot between the patients and could be up to 1,5 month.

As noted earlier in the discussion, the chief complaint of the patient was not always chest pain or dyspnea despite that ELVIS had registered it as one of these two symptoms. Consequently, the chief complaint as noted in ELVIS may not always be correct. Reproducing this study in the future should thus base the chief complaint on the information in the medical records rather than that in ELVIS.

7. Conclusions and implications

The results show that patients who attend the emergency department (ED) with chest pain and/or dyspnea, stable troponin elevations and are sent home are old and suffer from several co-morbidities. No long-time troponin dynamic indicating a missed acute myocardial infarction (AMI) was found in these patients. Even though this is a small study with few patients, it can still give the doctors at the ED a slight indication that they probably do not miss AMI's at the ED with their current diagnostic routines. Further studies with a bigger number of patients are needed to verify the results.

If further studies show opposite results compared to our study, that is, that we miss long time troponin changes, the situation of this patient group can be improved. The patient could be given the same treatment as patients with acute coronary syndrome, with the risk and benefit of the medication concordant with concomitant diseases taken into consideration.

8. Populärvetenskaplig sammanfattning på svenska

Långtidsdynamik i hjärtinfarktsmarkören Troponin T som tecken på genomgången hjärtinfarkt – missas hjärtinfarkter på akuten?

Hjärtinfarkt är en sjukdom som orsaker mycket lidande och är även en vanlig dödsorsak internationellt sett. Att fastställa diagnosen hjärtinfarkt är inte alltid så lätt. Diagnosen baseras dels på patientens symptom, dels på en undersökning av hjärtats elektriska aktivitet med ett elektrokardiogram (EKG) samt blodprov. Om EKG:t är diffust blir blodprovet ibland avgörande för diagnostiken. Blodprovet man tar heter troponin T. Detta är ett protein som läcker ut i blodbanan vid hjärtskada. Detta värde kan vara stabilt förhöjt hos en del individer med andra sjukdomar såsom hjärtsvikt eller kronisk obstruktiv lungsjukdom (KOL). För att diagnosen hjärtinfarkt ska ställas behöver man ha en signifikant dynamik i sitt troponinvärde, det vill säga troponinvärdet ska öka och/eller sjunka med ett visst antal procent under akutbesöket. Om en signifikant troponindynamik inte föreligger talar det emot diagnosen hjärtinfarkt, även om värdet är förhöjt.

I denna studie har man tittat på en grupp på 32 patienter som har en stabil troponinökning. Man har utvärderat vad det är för typ av patienter med avseende på till exempel ålder och samsjuklighet. Man har också tagit ett uppföljande troponinprov minst 10 dagar efter akutbesöket för att se om patienten har en signifikant långtidsdynamik, det vill säga att provet förändras mer än ett visst antal procent, vilket då skulle kunna tala för att patientens troponinökning på akuten var akut förhöjt och att man då felaktigt avfärdat diagnosen hjärtinfarkt.

Resultaten visade att detta är en patientgrupp som har hög ålder och stor sjukdomsbörda. Många hade sedan tidigare antingen en eller flera av sjukdomarna hjärtsvikt, KOL, hjärt- och kärlsjukdom med mera. Uppföljningen av troponinvärdet visade att det i de flesta fallen inte förelåg någon signifikant dynamik. Dock var det en liten del av patienterna som faktiskt hade

en signifikant långtidsdynamik, men i alla dessa fall fanns det andra förklaringar till dynamiken, som till exempel att patienten hade ett förmaksflimmer på akuten vilket också kan orsaka en akut stegring av troponinvärdet. Således fann man inget fall där diagnosen hjärtinfarkt felaktigt avfärdats.

Denna studie kan innebära en liten trygghet för akutläkarna. Den bekräftar att dagens diagnostiska rutiner kring hjärtinfarkt är fungerande och leder inte till några missar. Dock behandlar detta en relativt liten studiegrupp. Det skulle vara önskvärt att i framtiden göra en liknande studie i större omfattning för att styrka resultaten ytterligare.

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Appendices

Appendix 1.

Frågeformulär

Telefon: **Ring upp (datum):**

Namn: _____

Personnummer: _____

Vikt: _____ **Längd:** _____

Kroppsform (1-9)

Tar du några mediciner? Om ja, vilka?	**Ja** □	**Nej** □
Har du några tidigare sjukdomar?	**Ja** □	**Nej** □

Om nej, gå vidare till nästa sida.

Har du eller har du haft hjärtproblem?	**Ja** □	**Nej** □

Om ja, ange:

_____

Har du genomgått något ingrepp i hjärtat som insättning av pacemaker?	**Ja** □	**Nej** □
Har du eller har du haft njurproblem som njursvikt?	**Ja** □	**Nej** □
Har du eller har du haft lungproblem?	**Ja** □	**Nej** □

Om ja, ange:

_____

Har du någon gång drabbats av stroke eller hjärnblödning?	**Ja** □	**Nej** □
Har du diabetes?	**Ja** □	**Nej** □
Har du eller behandlas du för högt blodtryck?	**Ja** □	**Nej** □
Har du eller behandlas du för höga blodfetter?	**Ja** □	**Nej** □

Får du eller har du fått strålbehandling mot bröstet? **Ja** □ **Nej** □

Får du eller har du fått cellgiftsbehandling? **Ja** □ **Nej** □

Har du några andra sjukdomar? Om ja, ange vilka. **Ja** □ **Nej** □

Har du haft återkommande smärtor/obehag i bröstet? **Ja** □ **Nej** □

*Om nej, hoppa över alla frågor med * efter.*

Hur länge har du haft bröstsmärta/obehag?* _____

Hur ofta får du bröstsmärta/obehag?* _____

Hur länge håller det i när du väl får det?* _____

Får du bröstsmärtan/obehaget då du går i uppförsbacke, uppför trappor eller springer?* **Ja** □ **Nej** □

Jag anstränger mig aldrig på det sättet □

Får du bröstsmärtan/obehaget då du går normalt?* **Ja** □ **Nej** □

Vad gör du om du får smärtan/obehaget i bröstet medan du går?*

Stannar upp □ Fortsätter gå som vanligt □ Tar nitroglycerin □

Om du stannar upp, vad händer med bröstsmärtan/obehaget?*

Minskar/slutar helt □ Ingen skillnad □

Om det minskar – hur snabbt minskar det?*

Mindre än tio minuter □ Mer än tio minuter □

Bedömning: Typisk angina □ Oklart om angina □ Ej angina □

Har du någonsin haft svår smärta över bröstet som höll i mer än en halvtimme? **Ja □** **Nej □**

Du är här för att du tidigare sökt på akutmottagningen. Varför sökte du?

_____

Hade du något av följande symtom när du sökte:

Bröstsmärtor	**Ja □**	**Nej □**
Problem med andningen	**Ja □**	**Nej □**
Onormal trötthet	**Ja □**	**Nej □**
Svettningar	**Ja □**	**Nej □**
Kräkningar	**Ja □**	**Nej □**
Utstrålning i höger arm eller båda armarna	**Ja □**	**Nej □**
Annat		

_____

Sedan du sökte på akuten fram till idag – har du haft:

Bröstsmärtor?	**Ja □**	**Nej □**
Problem med andningen?	**Ja □**	**Nej □**
Onormal trötthet?	**Ja □**	**Nej**

Hur mycket alkohol dricker du i veckan?

_____

Röker du? **Ja □** **Nej □**

Om ja, hur många cigaretter per dag?

_____

Tränar du regelbundet? **Ja □** **Nej □**

Om ja, vad tränar du och hur många timmar i veckan?

_____

Har du haft problem med snarkning? **Ja □** **Nej □**

Upplever du mycket stress i din vardag **Ja □** **Nej □**

Har någon i din familj eller nära släkt haft hjärtinfarkt innan 65 års ålder? **Ja □** **Nej**