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CARDIOVASCULAR EVENTS IN HIP FRACTURE PATIENTS

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To Lauri and Edith

ABSTRACT

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Cardiovascular events in hip fracture patients

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Background: It was hypothesized that elevations in cardiac biomarkers indicating myocardial injury and strain are frequent in hip fracture patients, but do not always present any symptoms or changes in ECG.

Aims: To investigate the incidence and prognosis of cardiovascular events in an unselected population of hip fracture patients and to evaluate whether it is reasonable to perform routine cardiac biomarker testing in all hip fracture patients.

Material and methods: 200 consecutive hip fracture patients were enrolled in Turku University Hospital during 2009 – 2010. For study purposes only, routine measurement of troponin T (TnT) and ECG recordings were performed repeatedly pre- and postoperatively and N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) at least once perioperatively. The perioperative complications, 30-day, 2-year, 1000-day and 5-year all-cause mortalities were studied.

Results: Perioperative TnT elevation as a sign of myocardial injury was detected in a third of the participants, in half of them already preoperatively, and 70% of them had new ischemic ECG changes. Median [IQR] NT-proBNP level was 1415 [2932] ng/l. Participants with biomarker elevation seldom had symptoms suggestive of cardiac origin and the majority of cardiovascular events remained undiagnosed. TnT and NT-proBNP elevation were the only independent predictors of 30-day mortality and remained independent predictors of long-term mortality for the whole 5-year follow-up together with preoperative clinical characteristics.

Conclusions: TnT and NT-proBNP can detect those hip fracture patients who are suffering from a perioperative cardiovascular event and are at greater risk of death years after the fracture. Routine measurement of these biomarkers in all hip fracture patients could guide evidence-based treatment of perioperative cardiovascular complications.

Keywords: cardiac biomarker, cardiovascular event, hip fracture, mortality, myocardial infarction, myocardial injury, N-terminal fragment of pro-B-type natriuretic peptide, perioperative, prognosis, troponin T

TIIVISTELMÄ

LL Pauliina Nordling
Lonkkamurtumapotilaiden sydäntapahtumat

Turun yliopisto, Lääketieteellinen tiedekunta, Kardiologia ja kardiovaskulaarilääketiede, Turun kliininen tohtoriohjelma; Sydänkeskus, Turun Yliopistollinen keskussairaala, Turku, Suomi.

Tausta: Tutkimuksen hypoteesi on, että lonkkamurtumapotilailla esiintyy usein sydämen vauriota ja kuormitusta osoittavien merkkiainepitoisuuksien nousua, josta ei kuitenkaan aina aiheudu oireita tai EKG muutoksia.

Tavoitteet: Tutkia sydäntapahtumien yleisyyttä ja ennustetta valikoimattomassa lonkkamurtumapopulaatiossa, sekä arvioida onko kaikille lonkkamurtumapotilaille perusteltua tehdä sydänmerkkiainemääritykset.

Materiaali ja menetelmät: Tutkimukseen rekrytoitiin 200 peräkkäistä lonkkamurtumapotilasta Turun Yliopistollisesta keskussairaalasta vuosina 2009 – 2010. Tutkimuksen puitteissa troponiini T (TnT) määritys ja EKG rekisteröinti tehtiin toistetusti ennen leikkausta ja leikkauksen jälkeen sekä B-tyypin natriureettisen N-terminaalisen propeptidin (NT-proBNP) määritys ainakin kertaalleen. Tutkimuksessa seurattiin perioperatiivisien komplikaatioiden, 30-päivän, 2-vuoden, 1000-päivän ja 5-vuoden kuolleisuuksia.

Tulokset: Perioperatiivinen TnT nousu sydänlihasvaurion merkkinä havaittiin kolmanneksella tutkittavista, heistä puolella jo ennen leikkausta, ja uusia iskeemisiä EKG-muutoksia oli 70 %:lla näistä tutkittavista. Mediaani NT-proBNP taso oli 1415 [kvartaaliväli 2932] ng/l. Merkkiainenousun saaneilla tutkittavilla oli harvoin sydänperäiseksi tulkittavia oireita ja useimmat sydäntapahtumat jäivät diagnosoimatta. TnT ja NT-proBNP nousu olivat ainoat itsenäiset 30-päivän kuolleisuuden ennustajat ja säilyivät itsenäisinä pitkäaikaisen kuolleisuuden ennustajina koko 5 vuoden seurannan ajan yhdessä tutkittavien kliinisten ominaisuuksien kanssa.

Päätelmät: TnT ja NT-proBNP pitoisuusmäärityksillä voidaan tunnistaa ne lonkkamurtumapotilaat jotka sairastavat perioperatiivisen sydäntapahtuman ja ovat suuremmassa vaarassa kuolla vuosia murtuman jälkeen. Näiden merkkiaineiden rutiininomainen määritys lonkkamurtumapotilailta voisi mahdollistaa ajoissa aloitetun näyttöön perustuvan perioperatiivisten sydäntapahtumien hoidon.

Avainsanat: B-tyypin natriureettinen N-terminaalinen propeptidi, kuolleisuus, lonkkamurtuma, perioperatiivinen, prognoosi, sydäninfarkti, sydänlihasvaurio, sydänmerkkiaine, sydäntapahtuma, troponiini T

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ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ANOVA	Analysis of variance
AO/OTA	AO-Müller / Orthopaedic Trauma Association
ARB	Angiotensin-receptor blocker
ASA	American Society of Anesthesiologists
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass grafting
CI	Confidence interval
CK-MB	MB fraction of creatine kinase
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CT	Computed tomography
ECG	Electrocardiogram
ECLIA	Electrochemiluminescence immunoassay
ESA	The European Society of Anaesthesiology
ESC	The European Society of Cardiology
HR	Hazards ratio
IQR	Interquartile range
LBBB	Left bundle branch block
LMWH	Low molecular weight heparin
LVH	Left ventricular hypertrophy
NSTEMI	non-ST elevation myocardial infarction
NT-proBNP	N-terminal fragment of pro-b-type natriuretic peptide
PCI	Percutaneous coronary intervention
SD	Standard deviation
STEMI	ST elevation myocardial infarction
TIA	Transient ischemic attack
TnC	Troponin C
TnI	Troponin I
TnT	Troponin T

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications that will be referred to with the roman numerals I – IV throughout the text.

I Hietala P, Strandberg M, Strandberg N, Gullichsen E, Airaksinen KE. Perioperative myocardial infarctions are common and often unrecognized in patients undergoing hip fracture surgery. J Trauma Acute Care Surg 2013;74(4):1087-91.

II Hietala P, Strandberg M, Kiviniemi T, Strandberg N, Airaksinen KE. Usefulness of troponin T to predict short-term and long-term mortality in patients after hip fracture. Am J Cardiol 2014;114(2):193-7.

III Nordling P, Kiviniemi T, Strandberg M, Strandberg N, Airaksinen J. Predicting the outcome of hip fracture patients by using N-terminal fragment of pro-B-type natriuretic peptide. BMJ Open 2016;6:e009416.

IV Nordling P, Strandberg M, Strandberg N, Kiviniemi T, Mäkelä K, Airaksinen KE. Preoperative myocardial TnT elevation is associated with the fracture type in patients with proximal femoral fracture. Manuscript.

In addition, some previously unpublished data will be presented.

1 INTRODUCTION

Hip fracture patients are a fragile patient group, consisting mostly of seniors who often have pre-existing comorbidities (Panula et al., 2011), cardiovascular diseases being the most common of them (Roche et al., 2005). The treatment for a hip fracture is surgical. Frail hip fracture patients are prone to postoperative complications, pneumonia and congestive heart failure being the most typically diagnosed (Roche et al., 2005).

Perioperative myocardial infarction is a possible complication significantly affecting the outcome of operative patients (Devereaux et al., 2011, Smilowitz et al., 2017). Although clinical diagnosis of acute coronary syndromes in patients being treated for hip fracture is rare (Roche et al., 2005), the cause of death shortly after hip fracture operation is most commonly revealed to be acute myocardial infarction (Khan et al., 2013). It is plausible that many cardiovascular events in hip fracture patients remain undiagnosed in the perioperative setting.

Hip fracture patients have a 3-fold mortality compared to the rest of the population in the years after treatment of the fracture (Panula et al., 2011). The risk of death is even greater for those with pre-existing comorbidities (Ercin et al., 2017), and hip fracture patients with pre-existing cardiac disease have a significantly worse prognosis compared to other hip fracture patients (Castronuovo et al., 2011, Khan et al., 2013). The most common cause of death years after the fracture is cardiovascular diseases (Panula et al., 2011). In addition to the excess risk of mortality, hip fracture patients also have a high risk of institutionalization after hospital discharge (Rapp et al., 2015), and the disability burden caused by hip fractures has been estimated to surpass that of liver cirrhosis and stomach cancer (Johnell and Kanis, 2004).

Until 20 years ago, the age-adjusted incidence of hip fractures in Finland was rising steadily (Kannus et al., 2006, Kannus et al., 1999). Even though the rise has now ceased, it has been suggested that the number of hip fractures, as well as the number of fall-induced deaths, could double from 2010 to 2030 due to the ageing of the population (Korhonen et al., 2013a, Korhonen et al., 2013b). This would inevitably increase the morbidity and mortality associated with these fractures.

Since little data exist on cardiac events in hip fractures, this study was performed to investigate the epidemiology and prognosis of cardiovascular events in an unselected population of hip fracture patients and to evaluate whether it is reasonable to perform routine cardiac biomarker testing in all hip fracture patients.

2 REVIEW OF LITERATURE

2.1 Hip fracture diagnosis and classification

Fractures of the upper part of the femoral bone are called hip fractures. According to the data retrieved from the National Institute for Health and Welfare, 10 508 new hip fractures were diagnosed in Finland in 2016. Of these hip fracture patients 65 % were women. The mean age of hip fracture patients is 79 - 82 years (Leavy et al., 2015, Panula et al., 2011). The fractures are most often caused by a simple fall while walking indoors (Leavy et al., 2015, Tsur et al., 2014). The diagnosis of a hip fracture is based on a clinical examination together with radiographic imaging indicating the fracture. The fractures can be classified according to their location into femoral neck fractures, intertrochanteric fractures, i.e. fractures that go through or in between the trochanters, and subtrochanteric fractures, i.e. fractures that are in an area from immediately below the lesser trochanter to 5 cm lower (Figure 1).

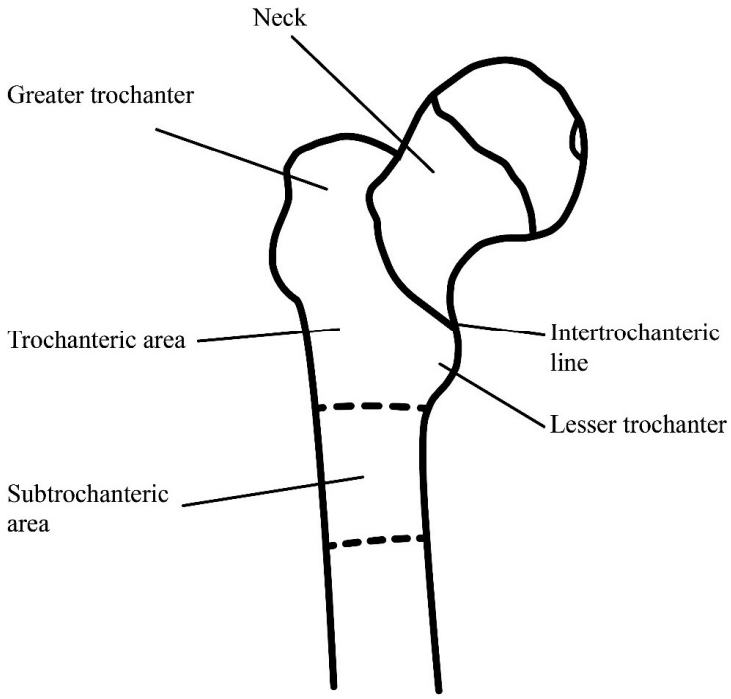

Figure 1. Anatomy of the proximal femur.

Femoral neck fractures are classified with the Garden classification according to completement and dislocation. A Garden I fracture is minimally dislocated and incomplete, a Garden II is nondislocated but complete, a Garden III is partially dislocated and complete fracture and a Garden IV completely dislocated. Intertrochanteric fractures are usually classified with AO-Müller / Orthopaedic Trauma Association (AO/OTA) long-bone fracture classification into simple, stable 2-fragment pertrochanteric fractures (A1.1-A1.3), unstable multifragmentary pertrochanteric fractures (A2.1-A2.3) and unstable intertrochanteric fractures (A3.1-A3.3). Subtrochanteric fractures are often classified similarly into stable and unstable fractures.

2.2 Treatment of hip fracture

The treatment for a hip fracture is operative. The surgery should be performed without unnecessary delay in order to reduce mortality, pain, and length of hospitalization (Bottle and Aylin, 2006, Moran et al., 2005, Orosz et al., 2004). In general, the treatment method for a femoral neck fracture is cemented or uncemented hemiarthroplasty, total arthroplasty or osteosynthesis (Hongisto et al., 2014, American, 2014). Osteosynthesis, such as with cannulated screws, is usually preferred for non-displaced femoral neck fractures. Intertrochanteric hip fractures are most often operated with trochanteric or long intramedullary nails or dynamic hip screws. Subtrochanteric fractures are preferably treated with intramedullary nails (American, 2014).

2.3 Myocardial injury

A myocardial injury means damage, for any reason, to the myocytes. It can be detected by an elevated level of cardiac biomarker troponin or MB fraction of creatine kinase (CK-MB) in the bloodstream (Thygesen et al., 2012b). Myocardial injury is frequent in critically ill intensive care unit patients, and has been found to independently predict short- and long-term mortality (Vasile et al., 2010).

2.3.1 Troponin

2.3.1.1 Background

Troponins I (TnI), T (TnT) and C (TnC) are regulatory proteins that together form the troponin complex that is, together with actin and tropomyocin they are responsible for the regulation of muscle contraction in the thin filaments of the striated muscle cells (Farah and Reinach, 1995, Cummins and Perry, 1978, Metzger and Westfall, 2004) Different isoforms of TnI and TnT are found in the skeletal muscles than in the cardiac muscle, which make them highly suitable for clinical diagnostics of cardiac conditions (Cummins and Perry, 1978).

Troponins are released from the cardiac myocytes when the cells are injured. The elevated level of troponin in the bloodstream indicates myocardial injury but does not explain the reason for the injury. Six different mechanisms for troponin release have been proposed, including myocyte necrosis, apoptosis, normal myocyte cell turnover, cellular release of proteolytic troponin degradation products, increased wall permeability and active secretion of vesicles, but even other, still unknown mechanisms, may exist (White, 2011). Troponins are released primarily in a complexed form, but also free troponins can be found in the bloodstream after myocardial injury (Wu et al., 1998).

2.3.1.2 Clinical use

It has been established that troponins are the most valuable biomarkers in the diagnosis of acute myocardial infarction. The conventional biomarkers CK-MB and myoglobin that were previously the primary choice for diagnosis of myocardial infarction do not bring valuable additional information to troponin (Eggers et al., 2004). The troponin level can already be seen to rise within 3 hours of the onset of ischemia in half of myocardial infarctions and can stay elevated for over 12 days (Katus et al., 1991). Troponin T increases gradually while Troponin I reaches its highest level quicker in 1-2 days and then decreases gradually (Metzler et al., 1997). In comparison, CK-MB is often elevated for only 24 hours limiting its clinical use in later diagnosis of myocardial injury (Metzler et al., 1997).

However, the clinical use of troponins is not limited to the diagnostics of myocardial infarction as other factors than myocardial infarction can cause myocardial injury leading to troponin elevation. These are presented in Table 1.

Table 1. Reasons for myocardial injury causing troponin elevation. Modified from (Thygesen et al., 2012b).

Ischemia caused by imbalance in oxygen supply and demand	**Injury not related to ischemia**	**Indeterminate or multi-factorial**
Coronary embolism or vasculitis	Myocarditis	Heart failure
Coronary spasm or endothelial dysfunction without significant coronary artery disease	Cardiac contusion, surgery, ablation, pacing or defibrillator shocks	Severe pulmonary embolism or pulmonary hypertension
Hypertrophic cardiomyopathy	Cardiotoxic agents	Takotsubo cardiomyopathy
Aortic dissection or severe aortic valve disease	Rhabdomyolysis	Renal insufficiency
Tachy-brady-arrhythmias		Sepsis
Hypertension		Infiltrative diseases
Cardiogenic, hypovolemic or septic shock		Severe acute neurological diseases
Severe anemia		Strenuous exercise
Severe respiratory failure		

2.4 Myocardial infarction

2.4.1 Definition and diagnosis

The Universal Definition of Myocardial Infarction describes acute myocardial infarction as a clinical setting correlating with myocardial ischemia together with evidence of myocardial necrosis. Myocardial ischemia is the result of an imbalance between oxygen supply and demand. Prolonged ischemia ultimately leads to the death of myocardial cells (Thygesen et al., 2012b).

Criteria for acute myocardial infarction include any of the following (Thygesen et al., 2012b):

1. A rise or fall in the level of cardiac biomarker, preferably cardiac troponin, above the 99th percentile upper reference limit together with at least one of the following:

- Symptoms suggestive of ischemia
- New (or presumed new) significant ST-segment-T-wave changes or new left bundle branch block (LBBB)
- Development of pathological Q-waves
- Intracoronary thrombus in angiography or autopsy

2. In the case of a cardiac death that occurs before cardiac biomarker elevation or withdrawal, symptoms suggestive of ischemia together with new (or presumed new) significant ischemic ECG changes or LBBB
3. In the case of myocardial infarction related to percutaneous coronary intervention, elevation of cardiac troponin at least 5-fold above the 99th percentile upper reference limit in those with a normal baseline and at least 20% from the earlier level for those with an elevated baseline, together with any one of the following:
   - Symptoms suggestive of ischemia
   - New (or presumed new) ischemic ECG changes
   - Findings consistent with procedural complication in angiography
   - Detection of new loss of viable myocardium or new regional wall motion abnormality in imaging
4. In the case of stent thrombosis, an elevation or fall in the level of cardiac biomarker above the 99th percentile upper reference limit together with the setting suggestive of myocardial ischemia and findings in coronary angiograph or autopsy
5. In case of myocardial infarction related to coronary artery bypass grafting, elevation of cardiac troponin at least 10-fold above the 99th percentile upper reference limit in those with a normal baseline, together with any one of the following:
   - New pathological Q-waves or new LBBB
   - Findings consistent with new graft or new native coronary artery occlusion in angiography
   - Detection of new loss of viable myocardium or new regional wall motion abnormality in imaging

2.4.2 Ischemic ECG changes

When ischemia is suspected, the goal is to obtain the first ECG recording within 10 minutes after the onset of symptoms, but repeated ECG recordings are often needed due to the progressive ECG changes in ischemia. The possible signs of myocardial ischemia that may evolve into a myocardial infarction are new ST elevations of ≥0.1 mV at the J-point in two contiguous ECG leads, except in leads V2-V3 where the cutoff value is ≥0.15-0.2 depending on the gender and age of the patient, or new horizontal or down-sloping ST depression of ≥0.05 mV or T-wave inversion of ≥0.1 mV in two contiguous leads with prominent R wave or R/S ratio >1. Comparison to prior ECG recordings should be made if possible. LBBB and left ventricular hypertrophy (LVH) inhibit the evaluation of ischemic ECG changes (Thygesen et al., 2012b).

2.4.3 Clinical picture

The classic symptom of myocardial ischemia is extensive pain in the chest, possibly radiating to the jaws or upper limb. Symptoms may even include upper abdominal pain, dyspnea, nausea, syncope or fatigue. However, the symptoms may be atypical or absent, for example in post-operative or critically ill patients (Thygesen et al., 2012b).

2.4.4 Causes and classification

Myocardial infarctions can be classified based on the ECG findings into ST elevation myocardial infarction (STEMI) or non-ST elevation (NSTEMI) myocardial infarction. This classification is often used due to the differences in the treatment methods in these two. Another way of classifying myocardial infarctions is by their cause. Type 1 and 2 myocardial infarctions are the main types. The classic myocardial infarction, caused by coronary plaque rupture, resulting in thrombus in the coronary artery decreasing the blood flow, and ultimately leading to myocardial necrosis, is known as type 1 myocardial infarction (Thygesen et al., 2012b). However about 6 % of patients who suffer from a myocardial infarction have no significant coronary artery disease in coronary angiography (Bertrand et al., 1982, Roe et al., 2000). The myocardial infarction may be caused by other mechanisms than by plaque rupture, such as direct toxic effects of high circulating catecholamine levels or by vasospasm (Bertrand et al., 1982, Suwaidi et al., 2000, Thygesen et al., 2012a). These may lead to imbalance between oxygen supply and demand, leading to a myocardial infarction known as type 2 myocardial infarction, which

accounts for about one fourth of the myocardial infarctions diagnosed (Thygesen et al., 2012b, Saaby et al., 2013). The most common clinical reasons behind this infarction are anemia, respiratory failure, tachyarrhythmias and sepsis (Landes et al., 2016, Saaby et al., 2013). Only about half of patients with type 2 myocardial infarction have significant coronary artery disease, but other comorbidities are significantly more common in these patients (Saaby et al., 2013). Patients suffering from type 2 myocardial infarction may experience chest pain significantly less often than patients with type 1 infarction (Landes et al., 2016), and do not usually have ST elevation (Saaby et al., 2013). However, the distinction between type 1 and 2 myocardial infarctions may not always be simple, leading to the diagnosis of type 2 infarction in some patients with actual plaque rupture indicating type 1 myocardial infarction instead. Type 2 myocardial infarction has been demonstrated to associate with an even worse prognosis than type 1 myocardial infarction (Landes et al., 2016).

2.5 Myocardial injury and infarction in non-cardiac surgery

2.5.1 Incidence, etiology and diagnosis

The reported incidence of postoperative myocardial injury evidenced by troponin elevation in serial measurements has ranged from 17 to 37 %, depending on the type of surgery and patients studied (Lee et al., 1996, Chong et al., 2012b, Devereaux et al., 2017). It is more common in older patients and those with pre-existing comorbidities (Lee et al., 1996, Oscarsson et al., 2004, Chong et al., 2012b). Diagnosis of actual perioperative myocardial infarction is less common (Adams et al., 1994). The incidence of postoperative myocardial infarction during the first postoperative days after non-cardiac surgery has been reported to range from 2 to 17 %, depending largely on the criteria for diagnosis, but also the type of surgery and patients studied (Adams et al., 1994, Devereaux et al., 2011, Alcock et al., 2012, Chong et al., 2012b, Bass et al., 2015). A slight decline in the number of perioperative myocardial infarctions diagnosed per surgeries has been observed recently (Smilowitz et al., 2017). Older age and cardiovascular risks are predisposing factors (Devereaux et al., 2011, Smilowitz et al., 2017). Of the different non-cardiac surgery types myocardial infarctions are most commonly diagnosed in transplant, thoracic and vascular surgeries (Smilowitz et al., 2017).

About one fourth of type 2 myocardial infarctions are diagnosed in patients postoperatively (Landes et al., 2016). Intraoperative hypotension has been found to

independently associate with postoperative troponin elevation, suggesting a mismatch of myocardial oxygen supply and demand as the underlying mechanism (Alcock et al., 2012). This may be caused by an increase in myocardial oxygen demand in response to neuroendocrine factors reactive to stress, but also due to a prothrombotic state, vascular inflammation, altered vasomotion and possibly a stress-induced rupture of an atherosclerotic coronary plaque. The operation also causes shifts of fluid between the body fluid compartments and this can increase the stress response (Kristensen et al., 2014).

Postoperative myocardial injury usually develops during the first two postoperative days, but a later injury is also possible (Metzler et al., 1997, Chong et al., 2012b). Most perioperative myocardial infarctions also occur within 48 hours after the operation (Devereaux et al., 2011). About 10 % of postoperative myocardial infarctions are STEMI, while a third of patients have ST-segment depression on an ECG (Devereaux et al., 2011). The clinical diagnosis of perioperative myocardial infarction requires a rise and or fall of troponin values (Thygesen et al., 2012b). It has been established that routine serial measurement of troponin in operative patients is accurate in the detection of perioperative myocardial infarction (Adams et al., 1994). However, the diagnosis should not be made solely based on troponin elevation (Kristensen et al., 2014). The diagnosis is challenging, since ischemic symptoms are seen in only about a third or fourth of the patients with perioperative myocardial infarction (Adams et al., 1994, Devereaux et al., 2011, Devereaux et al., 2017). Routine measurement of troponin and ECG registrations in asymptomatic patients are usually not performed. This can lead to serious underdiagnosing, and some studies conclude that only about 6 % of perioperative myocardial infarctions are being clinically diagnosed (Bass et al., 2015). Due to the paucity of symptoms, routine postoperative cardiac biomarker testing for myocardial injury has been suggested, at least in high cardiac risk patients (Devereaux et al., 2011).

2.5.2 Management and prognosis

The treatment of perioperative myocardial infarction is often insufficient. In an earlier study about two thirds of patients with previously known cardiac risk factors who were diagnosed with infarction received acetylsalicylic acid (Devereaux et al., 2011). Type 2 infarctions are often treated at some other department than the cardiology department (Saaby et al., 2013). About one fifth of patients who are diagnosed with perioperative myocardial infarction are referred for invasive treatment (Smilowitz et al., 2017).

Operative patients with a perioperative troponin elevation often suffer from a clinical cardiac complication, such as unstable angina or myocardial infarction or heart failure (Metzler et al., 1997). Myocardial injury also increases the risk of nonfatal cardiac arrest and later coronary revascularization (Devereaux et al., 2011). Cardiac risk patients who already have an elevated level of troponin before an operation have a higher incidence of cardiovascular complications during surgery and congestive heart failure postoperatively, and the troponin elevation tends to be higher in those patients who suffer from a clinical cardiac complication (Metzler et al., 1997). The most important risk-factors for perioperative cardiovascular complications are the preoperative clinical condition and pre-existing comorbidities of the patients, but also the surgery characteristics, namely type, urgency, invasiveness, duration and amount of blood loss, are of importance (Kristensen et al., 2014). The urgency of the operation has been suggested to constitute the strongest independent preoperative predictor of short-term mortality (Devereaux et al., 2012).

Mortality seems to be especially high in those cardiac risk patients who already have an elevated level of troponin before surgery (Oscarsson et al., 2004). Previous studies have also shown that higher a postoperative troponin level independently predicts all-cause short- and long-term mortality (Devereaux et al., 2012, Oscarsson et al., 2004, Chong et al., 2012b). Even a minor postoperative troponin elevation is associated with a poorer prognosis (Devereaux et al., 2012, Oscarsson et al., 2004), regardless of the cause for the elevation (Devereaux et al., 2017). A dose-dependent relation between the postoperative troponin level and mortality, with highest troponin levels leading to the highest mortality, has been demonstrated (Oscarsson et al., 2004, Devereaux et al., 2012, Devereaux et al., 2017).

Diagnosis of perioperative myocardial infarction is associated with longer hospitalization (Adams et al., 1994, Smilowitz et al., 2017), and a significantly poorer prognosis compared to other operative patients (Adams et al., 1994, Devereaux et al., 2011, Chong et al., 2012b, Smilowitz et al., 2017). Of those patients diagnosed with a postoperative myocardial infarction, about 12 % die during the first month after the operation, most of these already during the first two postoperative days (Devereaux et al., 2011), but even an in-hospital mortality of 38 % amongst patients with perioperative myocardial infarction has been reported (Adams et al., 1994). Perioperative myocardial infarction is the most common postoperative cause of in-hospital mortality (Adams et al., 1994, Chong et al., 2012b). The prognostic effect of the infarction is not affected by the presence or absence of ischemic symptoms (Devereaux et al., 2011). An earlier study has shown that by taking simple measures in postoperative care, such as increasing the awareness of the personnel and the monitoring of the patients, the incidence of postoperative troponin

elevation and major long-term adverse cardiac events can be significantly reduced (Ausset et al., 2010).

2.5.3 Current guidelines for perioperative cardiac risk assessment

The European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA) have created guidelines on cardiovascular assessment and management in non-cardiac surgery. The guidelines emphasize the importance of preoperative cardiological evaluation in order to minimize patient risks, choice of right treatment policy, operative and anesthetic method and perioperative cardiovascular management measures. According to the guidelines, most patients with stable heart disease undergoing surgery of low- or intermediate cardiac risk only need a standard cardiac risk evaluation, while the patients whose risk is considered small should be operated without further delay. The assessment should cover the patient's pre-existing comorbidities and the clinical condition, as well as the type of surgery. Clinical risk index scores can sometimes be helpful in the evaluation and physical status classification system of the American Society of Anesthesiologists (ASA) and the Revised Cardiac Risk Index value (RCRI, the Lee's score) are commonly used. The ASA classes range from class one to six and describe the patients' general health status and eligibility for surgery (Saklad, 1941). The Lee's score predicts cardiac complications in patients undergoing non-cardiac surgery. The maximum score is six, and one point is given for high-risk surgery, history of ischemic heart disease, congestive heart failure or cerebrovascular disease, insulin therapy for diabetes and an elevated preoperative serum creatinine level exceeding 177 μmol/l. For patients with a Lee's score ≥ 3 the cardiac complication risk is about 10 % (Lee et al., 1999). Routine pre-operative ECG recording is advised for all patients with high cardiac risk, at least when being referred to intermediate- or high-risk surgery. Furthermore, in older patients (aged above 65 years) with no risk factors, who are referred for intermediate-risk surgery, a preoperative ECG may be considered. However, in patients with no risks referred for a low-risk surgery, current guidelines advise that there is no need for routine preoperative ECG recording. Perioperative ECG monitoring is recommended for all patients, and ST segment changes during operation should primarily be considered caused by myocardial ischemia. Preoperative cardiac biomarker determination may be considered in patients with high cardiac risk, but it is not currently advised routinely in all surgery patients. A preoperative chest x-ray is not routinely advised. If the patient requires emergency surgery, then the preoperative cardiac evaluation is limited when necessary. Postoperative measurement of natriuretic peptides and troponin should be considered in high-risk patients for early complication diagnosis (Kristensen et al., 2014).

2.5.4 Pharmacological risk reduction

According to ESC guidelines, administration of low-dose acetylsalicylic acid should be evaluated individually in each patient weighing the risk of thrombosis against bleeding, and continuation of previous acetylsalicylic acid medication may be considered if no problems with hemostasis during surgery are expected. Nitrates do not reduce perioperative myocardial infarctions or cardiac deaths and may even be harmful by causing hypotension and tachycardia. Beta blockers reduce heart rate and blood pressure and decrease contractility. The results of trials evaluating the use of beta blockers in preoperative cardiac risk reduction are controversial. If the patient is already on a beta blocker, it should be continued, but heart rate and blood pressure should be monitored to avoid hypotension and bradycardia. If a patient referred to high-risk surgery has cardiac risks, or a patient with known ischemic heart disease or myocardial ischemia is referred to any kind of surgery, beta blockers could decrease the risk of myocardial infarction and cardiac death and should therefore be commenced preoperatively if this medication is not in prior use. However, in patients with no risk factors, commencing a beta blocker preoperatively could even increase their cardiac risk. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARB) should be continued in heart failure patients. In patients who are using these medications for hypertension, withdrawal for the perioperative period one day prior to the surgery should be considered because of the risk of hypotension during anesthesia. Statins are recommended to be continued through the perioperative period, but preoperative commencing is not needed in patients with no prior statin medication undergoing non-vascular surgery (Kristensen et al., 2014).

2.6 Acute congestive heart failure

Heart failure is defined by a clinical syndrome where structural and/or functional cardiac abnormality leads to reduced cardiac output and/or elevated intracardiac pressure at rest or during stress, and is characterized by typical symptoms such as breathlessness, reduced exercise tolerance, swelling of ankles and fatigue. Elevated jugular venous pressure, pulmonary crackles and peripheral edema are some of the possible clinical findings. The heart failure is considered acute when the signs and symptoms appear, or pre-existing signs and symptoms worsen, rapidly. The stage before the evolvement of symptoms is considered a left ventricular dysfunction. Possible causes for heart failure include conditions of the myocardium, such as ischemic heart disease, cardiomyopathies and toxic damage, abnormal loading condition, such as in valvular defects and hypertension, and arrhythmias.

There are usually one or more precipitating factors, such as acute coronary syndrome, arrhythmia, surgery or perioperative complications, that trigger acute heart failure in patients with pre-existing chronic heart failure.

Diagnosis of acute heart failure is based on the patient's history, symptoms and clinical findings and assessment of potential precipitants, and possibly by ECG, chest x-ray, biomarker testing with natriuretic peptides, and echocardiography. (Ponikowski et al., 2016).

2.6.1 BNP

Brain natriuretic peptide (BNP) is a cardiac hormone, and part of the natriuretic peptide family, originally found in the porcine brain (Sudoh et al., 1988). Later studies revealed the synthesis and secretion to be mainly by the ventricles of the heart (Ogawa et al., 1991, Mukoyama et al., 1991). The main stimulus for secretion is myocardial wall tension or stretch, caused by volume overload (Yasue et al., 1994), and is increased in conditions such as hypertension, dilated cardiomyopathy and congestive heart failure (Ogawa et al., 1991, Yasue et al., 1994, Mukoyama et al., 1991). Increase in BNP leads to increased natriuresis and diuresis, cardiac output and vasodilatation. It strives to prevent cardiac hypertrophy, fibrosis and left ventricular dysfunction (Sudoh et al., 1988, Hunt et al., 1996, Plante et al., 2014, van der Zander et al., 1999). BNP maintains the cardiovascular homeostasis by decreasing angiotensin II and aldosterone (Hunt et al., 1996). It has been discovered that the BNP level reflects the degree of left ventricular dysfunction, and BNP thus serves as a good cardiac biomarker (Yasue et al., 1994, Mukoyama et al., 1991). According to ESC guidelines, the upper limit of normal value in the acute setting is 100 ng/l, and patients with a normal level are unlikely to suffer from heart failure (Ponikowski et al., 2016).

2.6.2 NT-proBNP

Soon after the introduction of BNP, it was discovered that the level of aminoterminal fragment of pro-brain natriuretic peptide (NT-proBNP), which is the end of the biologically inactive secretion form of BNP, is even higher than BNP in patients with heart failure, and the level significantly correlates with the severity of the condition (Hunt et al., 1997). However the level of NT-proBNP is dependent on the level of renal function (Hunt et al., 1997). The recommended NT-proBNP level for upper normal limit in the acute setting is 300 ng/l. Patients with a lower NT-proBNP level are unlikely to suffer from acute heart failure (Ponikowski et al.,

2016). However, elevated level of NT-proBNP can be caused by various other cardiac and non-cardiac causes (Table 2).

Table 2. Other causes for natriuretic peptide elevation than heart failure. Modified from (Ponikowski et al., 2016).

Cardiac	**Non-cardiac**
Acute coronary syndrome	Advancing age
Pulmonary embolism	Ischemic stroke or subarachnoidal hemorragia
Hypertrophic or restrictive cardiomyopathy	Severe infections
Left ventricular hypertrophy	Anemia
Valvular disease	Severe metabolic and hormonal abnormalities
Tachyarrhythmias	Severe burns
Pulmonary hypertension	Renal dysfunction
Myocarditis	Liver dysfunction
Congenital heart disease	Paraneoplastic syndrome
Cardiac contusion, surgery or defibrillator shocks	Chronic obstructive pulmonary disease

2.7 Congestive heart failure in the perioperative period

Postoperative acute heart failure is often atypical and may have a different kind of etiology than in a conventional setting. Postoperatively the large amount of fluids administered during and immediately after the operation may mobilize and cause hypervolemia. When postoperative heart failure is suspected, serial biomarker determinations of troponin and natriuretic peptide, ECG recording, chest x-ray and echocardiography should be combined with the physical examination (Kristensen et al., 2014).

In non-cardiac surgery, higher preoperative BNP and NT-proBNP level have been shown to independently predict postoperative cardiovascular complications (Villacorta Junior et al., 2010, Vetrugno et al., 2014, Dernellis and Panaretou,

2006, Chong et al., 2012a, Yeh et al., 2005, Yun et al., 2008). Furthermore, preoperative BNP and NT-proBNP are independent predictors of long-term cardiovascular events and mortality (Farzi et al., 2013, Chong et al., 2010a, Katsanos et al., 2015). According to current ESC guidelines, routine preoperative measurement of natriuretic peptide, either BNP or NT-proBNP, is recommended in all patients with prior heart failure referred to surgery. These patients should be monitored closely during the perioperative period, especially when using ACE inhibitor or ARB. Diuretics that the patients are using should be continued to the day of the surgery, and then continued when it is orally possible. In case of hypotension and hypovolemia or fluid retention, the dosage of diuretics should be adjusted accordingly. ACE inhibitor and ARB medications should be continued in heart failure patients throughout the perioperative period, and for those with no prior medication, commencing should be considered at least a week preoperatively. However, if hypotension is expected, ACE inhibitor or ARB should be discontinued one day prior to surgery and continued as soon as possible when allowed by the clinical condition of the patient. Beta blocker should be continued without cessation. Medications should be adjusted well in advance, if possible (Kristensen et al., 2014).

2.8 Cardiovascular events in hip fracture patients

Major orthopedic surgeries, such as hip surgery, are considered intermediate risk surgeries (Kristensen et al., 2014). However, the urgent nature of surgeries is known to carry a greater risk for perioperative myocardial infarctions than in elective surgeries (Smilowitz et al., 2017). Not only do hip fracture patients share the same risks as orthopedic surgery patients in general, but also the fracture itself brings an additional burden.

In the beginning of the present study, only limited studies had been conducted on perioperative cardiovascular events in hip fracture patients, and the magnitude of the problem was unknown. Recently interest has risen in the subject (Table 3). Previous studies suggest that, similarly to all other operative settings, patients with hip fracture often present an elevated level of troponin perioperatively (Ausset et al., 2009, Dawson-Bowling et al., 2008b, Oscarsson et al., 2009, Fisher et al., 2008b, Izhaki et al., 2011). The myocardial involvement seems to be clinically silent and would in most cases not have been detected without serial troponin measurement (Fisher et al., 2008b, Oscarsson et al., 2009). Hip fracture patients also seem to have high perioperative concentrations of NT-proBNP (Oscarsson et al., 2009). Since most studies conducted on hip fracture patients have concentrated on the operation as the cause for the cardiovascular complications, and only performed serial cardiac biomarker measurements postoperatively, the role of the

fracture itself in the origin of the myocardial complications remains unclear. Furthermore, little is known about the ECG changes associated with the biomarker elevations and the clinical importance of the troponin and NT-proBNP elevations in hip fracture patients.

Table 3. Studies that have measured TnI or TnT in hip fracture patients.

Paper	n	Mean age	Exclusion criteria	Ischemic ECG	Bin-ded	TnI/TnT	Treshold of elevation	Time of routine TnI/TnT measurement	Preop. elevation	Perioperative elevation	Independent predictors of elevation	Prognostic impact of TnI/TnT elevation
(Dawson-Bowling et al., 2008a)	108	-	< 65 years, creatinine >200 µmol/l, polymyositis, injury at hospital, no surgery	-	No	TnT	0.03 ng/mL	On arrival and 1. and 2. postop. day	29 % of elevations on arrival	39 %	-	Higher in-hospital mortality
(Fisher et al., 2008a)	238	82	< 60 years	-	Yes	TnI	0.06 ug/l	Once pre- or postoperatively	27 %	29 %	Higher age	Independent predictor of in-hospital mortality
(Ausset et al., 2009)	75	84	Operation at off-duty hours	"In 5 patients". No systematic report.	No	TnI	0.08 ng/ml / 0.1 ng/ml	1., 2., and 3. postop. days	-	-	-	Independent predictor of 6-month mortality
(Oscarsson et al., 2009)	69	86	ASA class < 3	-	No	TnI	0.06 ug/l	Preop, 12 and 48 hours postop.	58 % of postop.	-	-	Higher 3-month mortality
(Izhaki et al., 2011)	148	81	-	ST-depression was not associated with TnT elevation. No systematic report.	Yes	TnT	0.1 ng/ml	On arrival, 24 hours after arrival and end of hospitalization	67 % of elevations on arrival	35 %	-	Independent predictor of 8-year mortality
(Spurriet et al., 2011)	108	84	< 60 years	-	Yes	TnT	0.03 (unit?)	preop. and 1. postop. day	-	27 %	-	1- and 3-month mortality not affected. Higher 1-year mortality
(Talsnes et al., 2011a)	146 (302)	84-85	< 75 years	-	No	TnT	0.01 ug/l	preop, within 24 hours, 1. and 4. postop. days	-	-	-	Independent predictor of 3-month mortality
(Rostagno et al., 2015)	21 (1025)	85	-	21 (2 %) MI (5 STEMI)	No	TnI	0.5 ng/l	On arrival	-	-	-	Did not study
(Katsanos et al., 2017)	152	80	< 65 years, no surgery	Not reported	Yes	TnI	0.01 ng/mL	4. or 5. postop. day	-	-	-	Independent predictor of 1-year mortality
Vallet, Breining et al. 2017)	312	84-87	< 70 years	Of patients wih TnI elevation 10% had STEMI and 38% NSTEMI	No	TnI	0.05 ng/L	Once during 1-3. postop. days	-	30 %	-	Isolated TnI elevation not a predictor of mortality

3 AIMS OF THE STUDY

The hypothesis of the present study was that elevations in cardiac biomarkers are frequent in hip fracture patients, but do not always present any symptoms or changes in ECG. The aims of the study were:

1. To determine the incidence of and factors associated with TnT and NT-proBNP elevation in hip fracture patients (I, III).

2. To determine the incidence of ECG changes in hip fracture patients (I).

3. To study how often hip fracture patients experience symptoms suggestive of cardiovascular problems (I).

4. To study the association between the hip fracture type, operative method and surgery delay and cardiovascular events (IV).

5. To assess the prognostic impact of the elevated TnT and NT-proBNP level (II, III).

6. To evaluate whether it is justified to conduct routine TnT and NT-proBNP measurements for all hip fracture patients (I-IV).

4 MATERIALS AND METHODS

This was a prospective, single-centre, cohort study carried out at Turku University Hospital. The study protocol was reviewed and approved by the Ethics Committee of the Hospital District of Southwest Finland (meeting records no. 3/2009). After approval, the study was registered at www.ClinicalTrials.gov (identifier NCT01015105). The study was conducted in compliance with the Declaration of Helsinki.

4.1 Subjects and setting

All consecutive patients who were referred to Turku University Hospital during a 7-month period from October 19th 2009 to May 19th 2010 due to a hip fracture (femoral neck, intertrochanteric or subtrochanteric femoral fracture) were enrolled. The inclusion criteria were an age of 18 years or above and admittance to the traumatology ward due to a hip fracture. The primary exclusion criterion was patient refusal, and one patient declined, resulting in a cohort of 200 hip fracture patients (I-II). Informed written consent was obtained from each patient after full explanation of the study protocol. In the case of impaired cognition, approval was asked from the next of kin by phone, and written consent was later obtained on the ward. In Study III, the 18 patients who had no NT-proBNP measurement were excluded, and the final study population consisted of 182 patients. The primary fracture classification was established by the clinician at hospital admission by radiographic imaging, and this classification is presented in Study I. All fracture classifications were re-evaluated by one traumatologist in January 2016 in line with the current AO/OTA and Garden classifications (AO-Foundation, 2018). In Study IV and in this thesis, these latest classifications were used in the analysis. In Study IV, only patients who had a femoral neck or intertrochanteric fracture and who underwent surgery were included, leading to the exclusion of patients with subtrochanteric fracture (n=2), and death prior to surgery (n=1), and resulting in a final study group of 197 patients in this study. Information on the patients' medical history, cardiovascular risk factors and medication were retrieved from the electronic medical records. This data was also used to evaluate the Lee's score for each patient (II-III). In Study II, an ASA physical status class was determined based on the information in the medical records, while in Studies III-IV and in this thesis, the ASA class used in the analysis was the one assigned to each patient preoperatively by an on-call anesthesiologist. The patients were evaluated by the clinician and anesthesiologist in the emergency room.

4.2 Procedures

The patient's usual medications were given on the day of the operation and continued throughout the hospital stay. However, if the patient was on diuretics, these were withdrawn for the day of the operation. Low molecular weight heparin for deep venous thrombosis prophylaxis was started as soon as possible, in most cases in the evening of the day of the operation. After the fracture diagnosis, an on-call anesthesiologist placed a lumbar epidural catheter in each patient for pain control. The patients received a mixture of a local anesthetic (1mg/ml of bupivacaine; Marcain, Astra) and an opiate (1mg/ml of fentanyl; Fentanyl, Jansen) through this until the second postoperative morning. One dose of intravenous antibiotic prophylaxis (1,5 g of cefuroxime; Zinacef, GlaxoSmithKline or in the case of allergy 600 mg of clindamycin; Dalacin, Pfizer) was given prior to surgery. The anesthetic method preferred was spinal anesthesia with isobaric bupivacaine. In the event of significant operative blood loss (leading to a hemoglobin level less than 90 g/l), red blood cell transfusion was performed. In the event of hypotension (blood pressure less than 100/60 mmHg), a rapid fluid challenge, vasopressors and atropine were given, as appropriate. The operation was performed as soon as possible depending on overcrowding in the operative theatres. Since the exact time of the injury was not known in most of the cases, the surgery delay was counted from the moment the patient was registered in the emergency room of the study hospital. If the patient was sent from an affiliate hospital where the primary diagnosis had already been made, the registration time at the first hospital was considered. If the patient was already in the study hospital during the injury, the delay was assessed from the moment of fracture diagnosis. The choice of operative method was made according to the fracture- and patient characteristics by the treating traumatologist. If clinical findings or symptoms were suggestive of a perioperative cardiovascular event, a cardiologist, internist or neurologist was consulted for diagnostics and treatment.

4.3 Laboratory assays, ECG registrations and radiological imaging

Basic blood chemistry tests were performed on admission and later according to the clinical need. Measurements for troponin T (TnT) and NT-proBNP and ECG registrations were done for study purposes only. However, if the clinician suspected an adverse cardiovascular event based on the patients' clinical condition or symptoms, these results were accessible to them. A TnT measurement was performed on admission, before the operation, on 1st and 2nd postoperative days and later when clinically indicated. Measurement of NT-proBNP level was performed at least once during hospital stay. For determination of TnT and NT-proBNP lev-

els, an Electrochemiluminescence immunoassay (ECLIA) on Modular E170 automatic analyser (Roche Diagnostics GmbH, Mannheim, Germany) was used. This detects a TnT level of ≥0.03 µg/l and an NT-proBNP level of ≥50 ng/l. The results were reviewed retrospectively. If there were multiple TnT measurements, the highest of these during the preoperative period until the 5th postoperative days was considered as the peak elevation. A TnT level of ≥0.03 µg/l was considered abnormal; peak TnT elevations from 0.03 to 0.15 µg/l were considered mild and those ≥0.15 µg/L were considered major (I-II). If there were multiple NT-proBNP measurements perioperatively, the highest level was considered. An undetectably low level of NT-proBNP was quoted as 50 ng/l. In Study III and in the additional unpublished analyses presented, measurements during the perioperative period from hospital admission until the 5th postoperative day were included, and in Study IV, until the 4th postoperative day. The patients were divided into tertiles of low, intermediate and high NT-proBNP levels according to the measured level (III). A 12-lead electrocardiogram (ECG) recording was performed on arrival, preoperatively, and on the first and second postoperative mornings. All ECG's were analyzed retrospectively by one cardiologist, and ST elevations, ST depressions ad T-wave inversions were classified according to the guidelines of the European Society of Cardiology as presented previously (Thygesen et al., 2007). A chest x-ray study was performed at arrival and later when clinically indicated. A radiologist assessed the x-rays for signs of decompensation, including cardiomegaly, redistribution of pulmonary blood flow, increased artery to bronchus ratio, interstitial and alveolar edema and pleural effusion. If an acute intracranial process was suspected based on the patients' symptoms or the clinical picture, a computed tomography (CT) of the head was performed. Cultivation of bacteria was performed when clinically indicated.

4.4 Follow-up and end-points

The primary end-points were the TnT and NT-proBNP elevations. The secondary end-points were the perioperative complication diagnoses and all-cause death during follow-up. The patients were followed until January 2016. The mortality data was collected from the electronic medical records. Follow-up data was accessible for all participants. The 30-days (II-IV), 2-year (IV), 1000-days (II-III) and 5-year (IV) mortalities were studied calculated from the date of hospital admission.

4.5 Statistical methods

The computations were performed with an IBM SPSS Statistics Version 16, 17, 22 and 23 (IBM Corporation, Armonk, NY, USA). Normality was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables are presented as frequency and percentages. The Pearson Chi-square test was used for comparison of differences between the categorical variables, and Fisher's exact test was used when the expected cell count was less than 5 in more than 20 % of cells. Normally distributed continuous variables are presented as mean values and standard deviation (SD) and skewed continuous variables as median and range or interquartile range [IQR]. For analysis of the differences in continuous data between the groups, a Student's T-test was used for two groups with normally distributed data and One-way ANOVA was used for multiple groups; while for skewed data a Mann-Whitney U- was used for two groups and a Kruskall-Wallis-test for multiple groups. Differences were considered significant if the null hypothesis could be rejected at a <0.05 probability level. A logistic multivariable regression analysis was performed to identify independent predictors of TnT and NT-proBNP elevation. Because of multiple testing only variables with a two-sided P value <0.05 (I-III) or <0.1 (IV) in the univariate analysis were included in the model. Survival analysis was performed using Kaplan-Meier's method and Cox proportional hazards method (II-IV). A Cox regression analysis with backward selection was performed to analyse the independent predictors of short- and long-term mortality (II-III).

5 RESULTS

5.1 Characteristics of the study population

The median age of the participants was 84 years (range 32 - 98) and 66.0 % were women. A history of cardiovascular disease was common amongst participants, but 55 (27.5 %) had no prior cardiovascular history (Table 7). The median [IQR] ASA class preoperatively assigned by anesthesiologist was 3 [1]. Of the participants 112 (56.0 %) arrived from home, 28 (14.0 %) from a sheltered home, 36 (18 %) from a nursing home, 9 (4.5 %) from a health center ward, 3 (1.5 %) from another ward in the study hospital and 10 (5.0 %) from another hospital. Place of origin was unknown in 2 (1.0 %) participants. Three participants (1.5 %) were bedridden. Prior to the fracture 49 (24.5 %) were known to have been using vitamin D supplementation and 9 (4.5 %) bisphosphonate for osteoporosis.

5.2 Characteristics of the injuries

The injury mechanism was known and recorded in 70 (35.0 %) cases. Most common causes were falls due to stumbling or slipping (Table 4). The original fracture classification established by the clinician was femoral neck fracture in 115 (57.5 %), intertrochanteric fracture in 73 (36.5 %) and subtrochanteric fracture in 12 (6.0 %). When the x-ray images were re-analyzed retrospectively, the fracture classification changed in 13 (6.5 %) participants; Two (2.7 %) femoral neck fractures were considered intertrochanteric, one (1.4 %) intertrochanteric fracture was considered a femoral neck fracture, and 10 (83.3 %) subtrochanteric fractures were considered intertrochanteric (Table 5). Eleven (5.5 %) participants had accompanying injuries; 5 had a fractured humerus, 5 a fractured radius and one a pneumothorax.

Table 4. Causes of injury and contributing factors.

	n (%)
Unknown	130 (64.7)
Stumbling	24 (11.9)
Slipping	14 (7.0)
Dizziness or problems with the balance	11 (5.5)
Falling from a height	6 (3.0)
Alcohol intoxication	5 (2.5)
Traffic accident with non-motorized vehicle	5 (2.5)
Collapse	3 (1.5)
Pathologic fracture	1 (0.5)
Assault	1 (0.5)
Total	200 (100)

Table 5. The fracture classifications according to Garden and AO/OTA classifications.

	n (%)
Femoral neck	114 (56.7)
Garden I	0 (0.0)
Garden II	14 (7.0)
Garden III	19 (9.5)
Garden IV	81 (40.5)
Intertrochanteric	84 (41.8)
A1.1 – A1.3	22 (11.0)
A2.1 - A2.3	52 (26.0)
A3.1 - A3.3	10 (5.0)
Subtrochanteric	2 (1.0)
Total	200 (100)

5.3 Characteristics of the surgery

The surgery delay was less than 24 hours for 99 (49.3 %) participants, from 24 to 48 hours for 78 (38.8 %) participants and more than 48 hours for 22 (10.9 %) participants. One participant died before the operation. The operations were performed by 20 different surgeons. The operative methods were cemented hemiarthroplasty in 25 (12.4 %), uncemented hemiarthroplasty in 70 (34.8 %), trochanteric intramedullary nail in 67 (33.3 %), long intramedullary nail in 16 (8.0 %), cannulated screws in 20 (10.0 %) and locking plate in one (0.5 %) (Table 6). The median [IQR] length of operation was 46 [32] minutes.

Table 6. Characteristics of the operative methods chosen in the re-evaluated fracture types (n=199). Data expressed in count (%) or median [IQR].

	Hemiarthroplasty		**Intramedullary nail**		**Cannulated**	**Locking**
	cemented	**uncemented**	**trochanteric**	**long**	**screws**	**plate**
	n = 25	**n = 70**	**n = 67**	**n = 16**	**n = 20**	**n = 1**
Femoral neck	25 (100)	70 (100)	0	0	19 (95.0)	0
Intertrochanteric	0	0	66 (98.5)	16 (100)	1 (5.0)	0
Subtrochanteric	0	0	1 (1.5)	0	0	1 (100)
Dislocation	23 (92.0)	66 (94.3)	0, n=64	0	8 (40.0)	0
Surgery delay						
<24 hours	12 (48.0)	32 (45.7)	38 (56.7)	7 (43.8)	9 (45.0)	1 (100.0)
24-48 hours	12 (48.0)	29 (41.4)	20 (29.9)	8 (50.0)	9 (45.0)	0
>48 hours	1 (4.0)	9 (12.9)	9 (13.4)	1 (6.3)	2 (10.0)	0
Length of operation (minutes)	68 [41]	57 [23]	31 [19]	59 [44]	26 [20]	124

5.1 TnT elevation

5.1.1 Incidence and associated factors

Perioperative TnT elevation from hospital admission to the 3rd postoperative day was detected in 71 (35.5 %) participants, and in 36 (50.7 %) it was already detected before the fracture surgery. Preoperative samples were obtained in 197 (98.5 %) participants and postoperative in 179 participants (89.5 %). TnT was measured on arrival in 194 participants and the level was elevated in 23 (11.9 %). Measurement of TnT preoperatively on the day of the operation was obtained from 143 participants and TnT was elevated in 29 (20.3 %) of these. TnT was elevated in 52 (30.2 %) of the 172 samples obtained on the 1st postoperative day and in 36 (25.9 %) of the 139 measurements obtained on the 2nd postoperative day. The peak elevated level of TnT ranged from 0.03 to 4.04 µg/l (median 0.07 [IQR 0.17] µg/l). Of the elevations 46 (64.8 %) were considered mild (0.03-0.15 µg/l) and 25 (35.2 %) major (≥ 0.15 µg/l).

Factors associated with TnT elevation were older age, history of coronary artery disease, myocardial infarction and coronary artery revascularization, congestive heart failure and renal insufficiency (Table 7). Prior revascularization (hazards ratio (HR) 3.29, 95% Confidence interval (CI) 1.12 - 9.73; p = 0.03), heart failure (HR 2.42; 95% CI 1.04 - 5.61, p = 0.04) and higher age (HR 1.06, 95% CI 1.02 - 1.10, p = 0.002) remained independent predictors of perioperative TnT elevation in a multivariate logistic regression analysis.

Table 7. Characteristics and details of medical history of all participants and comparison between participants with and without a perioperative TnT elevation. Data are presented in median (range) or count (%).

Variable	All participants n= 200	TnT elevation n=71	No TnT elevation n=129	p - value
Age (years), median (range)	84 (32-98)	86 (51-98)	81 (32-97)	**<0.001**
Women	132 (66.0)	44 (62.0)	88 (68.2)	0.37
Coronary artery disease	65 (32.5)	31 (43.7)	34 (26.4)	**0.012**
Prior myocardial infarction	24 (12.0)	13 (18.3)	11 (8.5)	**0.042**
Prior coronary revascularization	16 (8.0)	10 (14.1)	6 (4.7)	**0.019**
History of TIA or stroke	37 (18.5)	14 (19.7)	23 (17.8)	0.74
Hypertension	103 (51.5)	38 (53.5)	65 (50.4)	0.67
Atrial fibrillation	43 (21.5)	18 (25.4)	25 (19.4)	0.33
Diabetes mellitus	36 (18.0)	15 (21.1)	21 (16.3)	0.39
Congestive heart failure	28 (14.0)	16 (22.5)	12 (9.3)	**0.010**
Pacemaker	6 (3.0)	2 (2.8)	4 (3.1)	1.00
No history of cardiovascular disease	55 (27.5)	15 (21.1)	40 (31.0)	0.13
Impaired renal function	12 (6.0)	8 (11.3)	4 (3.1)	**0.028**
Dementia	81 (40.5)	30 (42.3)	51 (39.5)	0.71
Medicated epilepsy	10 (5.0)	3 (4.2)	7 (5.4)	1.00
Psychiatric medication	94 (47.0)	35 (49.3)	59 (45.7)	0.63
CNS affecting medication	73 (36.5)	30 (42.3)	43 (33.3)	0.21
COPD	9 (4.5)	3 (4.2)	6 (4.7)	1.00
Asthma	13 (6.5)	7 (9.9)	6 (4.7)	0.23
Cancer	19 (9.5)	5 (7.0)	14 (10.9)	0.38
ASA class 4	65 (32.7)	29 (41.1)	36 (27.9)	0.052
Arrival from home	112 (56.0)	35 (49.3)	77 (59.7)	0.16
Mobility aid	82 (41.0)	35 (49.3)	47 (36.4)	0.077

TIA transient ischemic attack; Psychiatric medication, benzodiazepine, selective serotonine or norepinephrine reuptake inhibitor, mirtazapine, buspirone, tricyclic antidepressant or antipsychotic medication); CNS, central nervous system; COPD, chronic obstructive pulmonary disease; Cancer, history of cancer (active or in remission); ASA class, American Society of Anesthesiologists' physical status classification, assigned by anesthesiologist; Mobility aid, known to have been using a stick, buggy, or a wheelchair prior to fracture.

Table 8. Comparison of ECG analysis between participants with vs. without perioperative TnT elevation. All ST-segment changes and Q-waves are reported (old and new). Data are presented in count (%).

	All participants	**TnT elevation**	**No TnT elevation**	**p - value**
ECG on arrival	*n =92*	*n = 37*	*n = 55*	
ST-segment elevation	3 (3.3)	3 (8.1)	0 (0.0)	0.064
ST-segment depression	18 (19.6)	10 (27.0)	8 (14.5)	0.15
T-wave inversion	54 (58.7)	21 (56.8)	33 (60.0)	0.76
Q-waves	33 (35.9)	16 (43.2)	17 (30.9)	0.28
ECG preoperatively	*n =142*	*n = 51*	*n = 91*	
ST-segment elevation	3 (2.1)	2 (3.9)	1 (1.1)	0.29
ST-segment depression	13 (9.2)	10 (19.6)	3 (3.3)	**0.002**
T-wave inversion	82 (57.7)	32 (62.7)	50 (54.9)	0.37
Q-waves	49 (34.5)	25 (49.0)	24 (26.4)	**0.007**
ECG on the 1st postoperative day	*n = 155*	*n = 57*	*n = 98*	
ST-segment elevation	4 (2.6)	4 (7.0)	0 (0.0)	**0.017**
ST-segment depression	27 (17.4)	16 (28.1)	11 (11.2)	**0.008**
T-wave inversion	88 (56.8)	33 (57.9)	55 (56.1)	0.74
Q-waves	50 (32.3)	26 (45.6)	24 (24.5)	**0.005**
ECG on the 2nd - 4th postoperative day	*n = 52*	*n = 28*	*n = 24*	
ST-segment elevation	0 (0.0)	0 (0.0)	0 (0.0)	1.00
ST-segment depression	8 (15.4)	3 (10.7)	5 (20.8)	0.45
T-wave inversion	35 (67.3)	22 (78.6)	13 (54.2)	0.061
Q-waves	23 (44.0)	16 (57.1)	7 (29.2)	0.056

5.1.2 ECG changes

The participants with a perioperative TnT elevation had significantly more frequent ST-segment changes and Q-waves preoperatively and on the 1st postoperative day than participants without TnT elevation (Table 8). New ST-segment changes, including ST-segment elevation, ST-segment depression or T-wave inversion appeared in the ECGs of 50 (70.4 %) participants with a TnT elevation compared to 51 (41.5 %) participants with no TnT elevation ($p < 0.001$). New ST-segment elevation and depression and T-wave inversion were all more common in participants with a TnT elevation (Table 9). Of the participants with a major TnT elevation 80.0 % had new ST-segment changes compared to 65.2 % of the participants with minor TnT elevation, but the difference did not reach statistical significance (20/25 vs. 30/46, $p = 0.192$).

Table 9. New ischemic ECG changes during hospitalization. Data are presented in count (%).

	All (n = 194)	TnT elevation (n = 71)	No TnT elevation (n = 123)	p - value
ST-segment elevation	7 (3.6)	7 (9.9)	0 (0.0)	**0.001**
ST-segment depression	48 (24.7)	29 (40.8)	19 (15.4)	**<0.001**
T-wave inversion	77 (39.7)	37 (52.1)	40 (32.5)	**0.007**
No new ischemic ECG changes	93 (47.9)	21 (29.6)	72 (58.5)	**<0.001**

5.1.2.1 ST elevation myocardial infarction

Seven (3.5 %) participants developed new ST-segment elevation perioperatively, and all of these had a perioperative TnT elevation ranging from 0.05 to 4.04 µg/l. Five of the participants had a major and 2 had a minor TnT elevation. TnT was already elevated at the time of hospital admission in 3 participants, and the elevation appeared on the first postoperative day in 4 others. Three of the participants had a history of coronary artery disease. None of the 7 participants were reported to experience chest pain or sensation of arrhythmias or suffer from disturbances in consciousness, but 5 had shortness of breath and/or hypotension. All 7 participants were reported to be disoriented. During hospitalization three of these seven participants with confirmed ST elevation myocardial infarction in a retrospective analysis were diagnosed with a myocardial infarction and were treated conservatively, while 4 remained undiagnosed during hospitalization.

5.1.3 Laboratory assay results and chest x-ray findings

An elevated TnT level was associated with lower hemoglobin on admission and preoperatively, higher C-reactive protein (CRP) and MB isoenzyme of creatinine kinase (CK-MB) on admission and higher NT-proBNP perioperatively. On admission 9 (4.5 %) participants presented signs of acute cardiac failure in a chest x-ray; 6 of these had a TnT elevation during hospitalization (Table 10).

Table 10. Laboratory assay and chest x-ray results for all participants and comparison between participants with and with no TnT elevation. Results expressed in median [IQR], mean (SD), or count (%).

	All participants n = 200	**TnT elevation n = 71**	**No TnT elevation n = 129**	**p - value**
On hospital admission				
Hemoglobin (g/l)	124 [23]	119 [26]	126 [19]	**0.008**
Leukocytes (E9/l), mean (SD)	10.7 (3.6)	10.6 (3.3)	10.8 (3.8)	0.72
Thrombocytes (E9/l)	210 [75]	218 [89]	208 [66]	0.22
Creatinine (µmol/l)	73 [33]	75 [37]	70 [32]	0.15
CRP (g/l)	6 [31]	13 [36]	4 [23]	**0.002**
Glucose (mmol/l)	7.2 [2.2]	7.3 [2.6]	7.2 [2.0]	0.15
Sodium (mmol/l)	139 [5]	139 [7]	139 [5]	0.62
Potassium (mmol/l)	4.1 [0.6]	4.2 [0.6]	4.1 [0.6]	0.17
CK-MB (ug/l)	3.6 [2.5]	4.5 [3.5]	3.5 [1.8]	**0.001**
Acute decompensation	9 (4.9), n=182	6 (9.1), n=66	3 (2.6), n=116	0.074
Chronic heart failure	20 (11.0), n=182	10 (15.2), n=66	10 (8.6), n=116	0.18
Preoperative hemoglobin (g/l), mean (SD)	113.6 (16.7)	109.0 (16.5)	116.0 (16.5)	**0.007**
Perioperative NT-proBNP (ng/l)	1415 [2932]	3315 [5508]	947 [1456]	**<0.001**

CRP, C-reactive protein; Glucose missing in 6; Potassium missing in 3; CK-MB, creatine kinase MB isoenzyme, missing in 10 participants; Acute decompensation, signs of acute decompensated congestive heart failure on chest x-ray already on arrival; Chronic heart failure, signs of compensated heart failure on chest x-ray on arrival; Preoperative hemoglobin, on the day of the operation, missing in 15; Perioperative NT proBNP, peak N-terminal fragment of brain natriuretic peptide between arrival and the 5th postop day, missing in 18.

5.1.4 Cardiovascular medication

The use of acetylsalicylic acid prior to hospital admission was significantly more common in participants with a perioperative TnT elevation. Cardiovascular medication was seldom started during hospitalization, and at discharge from the traumatology ward the cardiovascular medications of participants with vs. without a TnT elevation only differed significantly concerning the use of statins (Table 11).

Table 11. Cardiovascular medication of participants with and without a TnT elevation on hospital admission and at discharge* from the traumatology ward, expressed in count (%).

	On admission			At discharge		
	TnT elevation (n = 71)	**No TnT elevation (n = 129)**	**p - value**	**TnT elevation (n = 67)**	**No TnT elevation (n = 127)**	**p - value**
Acetylsalicylic acid	33 (46.5)	41 (31.8)	**0.039**	17 (25.4)	23 (18.1)	0.23
Clopidogrel	0 (0.0)	2 (1.6)	0.54	2 (3.0)	2 (1.6)	0.61
Dipyridamole	3 (4.2)	9 (7.0)	0.54	3 (4.5)	8 (6.3)	0.75
Warfarin	13 (18.3)	19 (14.7)	0.51	11 (16.4)	15 (11.8)	0.37
LMWH	2 (2.8)	1 (0.8)	0.29	64 (95.5)	120 (94.5)	1.00
Beta blocker	27 (38.0)	52 (40.3)	0.75	35 (52.2)	52 (40.9)	0.13
Nitroglycerin	16 (22.5)	27 (20.9)	0.79	18 (26.9)	26 (20.5)	0.31
Statin	22 (31.0)	29 (22.5)	0.19	24 (35.8)	28 (22.0)	**0.039**
ACE inhibitor or ARB	17 (23.9)	39 (30.2)	0.34	19 (28.4)	39 (30.7)	0.73
Calcium channel blocker	10 (14.1)	22 (17.1)	0.58	8 (11.9)	23 (18.1)	0.27
Diuretic	24 (33.8)	44 (34.1)	0.97	31 (46.3)	45 (35.4)	0.14
Digoxin	7 (9.9)	9 (7.0)	0.47	3 (4.5)	8 (6.3)	0.75

LMWH, low molecular weight heparin; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker. *Six participants died before discharge from the traumatology ward.

5.2 NT-proBNP elevation

5.2.1 Incidence

During hospitalization NT-proBNP measurements were obtained from 182 participants at least once between hospital admission and the 5th postoperative day. The median [IQR] peak NT-proBNP level was 1415 [2932]; 1260 [2298] ng/l in the preoperative phase (n = 117) and 1600 [3971] ng/l in the postoperative phase (n = 86). There were both pre- and postoperative measurements in 21 participants, and the median [IQR] preoperative NT-proBNP level was 2220 [2964] ng/l and postoperative 3370 [5520] ng/l for those participants (p = 0.001). The NT-proBNP level was < 806 ng/l in the lowest tertile (n = 60), 806 – 2370 ng/l in the intermediate tertile (n = 61) and > 2370 ng/l in the highest tertile (n = 61).

5.2.2 In-patient characteristics

The patient characteristics associated with a higher peak of NT-proBNP were higher age, history of coronary artery disease, hypertension, atrial fibrillation, congestive heart failure, renal insufficiency and use of some mobility aid prior to fracture. Dementia was significantly less common in participants in the lowest tertile than those in the intermediate or high tertile. Nearly half of the participants in the highest NT-proBNP tertile had an ASA class 4 assigned by the on-call anesthesiologist (Table 12). Multivariable logistic regression analysis, with high and intermediate NT-proBNP compared to low NT-proBNP as a dependent variable, and age and the baseline characteristics significantly associated with higher NT-proBNP as covariates, showed that increasing age (HR 1.10, 95% CI 1.06 - 1.14; p < 0.001) and atrial fibrillation (HR 5.88, 95% CI 1.67 - 20.72, p = 0.006) were independent predictors of higher NT-proBNP; whereas when high NT-proBNP was compared to low and intermediate NT-proBNP in a similar model, increasing age (HR 1.10, 95% CI 1.04 - 1.16, p < 0.001), history of atrial fibrillation (HR 4.99, 95% CI 2.12 - 11.75, p < 0.001), renal insufficiency (HR 48.60, 95% CI 3.18 - 741.80, p = 0.005) and heart failure (HR 3.84, 95% CI 1.35 - 10.90, p = 0.012) were the independent predictors of higher NT-proBNP.

Table 12. Comparison of the baseline characteristics and details of the medical history of participants with low, intermediate and high N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) (n = 182). Data are presented as median [IQR] or (range) and count (%).

Variable	Peak NT-proBNP level			p - value
	Low n = 60	Intermediate n = 61	High n = 61	
Peak NT-proBNP	441 [342]	1390 [860]	5170 [6045]	
TnT elevation	7 (11.7)	18 (29.5)	41 (67.2)	**<0.001**
Age (years)	78 [19]	84 [8]	87 [8]	**<0.001**
Women	40 (66.7)	43 (70.5)	40 (65.6)	0.83
History of coronary artery disease	12 (20.0)	19 (31.1)	25 (41.0)	**0.044**
Prior myocardial infarction	3 (5.0)	6 (9.8)	10 (16.4)	0.12
Prior coronary revascularisation	2 (3.3)	4 (6.6)	8 (13.1)	0.12
History of TIA or stroke	11 (18.3)	11 (18.0)	8 (13.1)	0.68
Hypertension	22 (36.7)	31 (50.8)	38 (62.3)	**0.019**
Atrial fibrillation	3 (5.0)	10 (16.4)	26 (42.6)	**<0.001**
Diabetes mellitus	10 (16.7)	9 (14.8)	13 (21.3)	0.62
Congestive heart failure	3 (5.0)	5 (8.2)	18 (29.5)	**<0.001**
Pacemaker	0 (0.0)	3 (4.9)	3 (4.9)	0.22
No history of cardiovascular disease	24 (40.0)	18 (29.5)	10 (16.4)	**0.016**
Renal insufficiency	0 (0.0)	1 (1.6)	9 (14.9)	**<0.001**
Dementia	16 (26.7)	32 (52.5)	25 (41.0)	**0.015**
COPD	4 (6.7)	3 (4.9)	2 (3.3)	0.69
Cancer	6 (10.0)	7 (11.5)	6 (9.8)	0.95
ASA class 4	14 (23.3)	18 (30.0)	29 (47.5)	**0.014**
Arrival from home	40 (66.7)	33 (54.1)	29 (47.5)	0.099
Mobility aid	18 (35.3)	23 (56.1)	33 (76.7)	**<0.001**
Use of bisphosphonate	2 (3.3)	3 (4.9)	3 (4.9)	0.89
Medication affecting the CNS	19 (31.7)	20 (32.8)	26 (42.6)	0.38

TnT, troponin T; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; Cancer, history of cancer (active or in remission); ASA class, American Society of Anesthesiologists' physical status classification, assigned by anesthesiologist; CNS, central nervous system.

5.2.3 Laboratory assay results and chest x-ray findings

On arrival, significant differences were seen in the hemoglobin, creatinine, CRP and potassium levels between the participants in the NT-proBNP tertiles. Perioperative TnT elevation was detected in 7 (11.7 %) participants in the low tertile, 18 (29.5 %) in the intermediate tertile and 41 (67.2 %) in the high tertile ($p < 0.001$). Acute decompensation was rare in x-rays on arrival, but 14 (25.5 %) participants in the high tertile showed signs of compensated heart failure (Table 13).

Table 13. Laboratory assay and chest x-ray results in the different NT-proBNP tertiles. Results expressed in median [IQR], mean (SD) or count (%).

	Low n = 60	**Intermediate n = 61**	**High n = 61**	**p - value**
On hospital admission				
Hemoglobin (g/l), mean (SD)	127 (16)	119 (16)	123 (18)	**0.043**
Leukocytes (E9/l), mean (SD)	11.3 (3.9)	9.9 (3.4)	10.7 (3.7)	0.12
Thrombocytes (E9/l)	221 [70]	196 [68]	210 [87]	0.12
Creatinine (µmol/l)	68 [32]	67 [17]	84 [40]	**0.001**
CRP (g/l)	2 [23]	5 [19]	14 [42]	**0.001**
Glucose (mmol/l)	7.1 [1.8]	7.3 [2.2]	7.3 [2.7]	0.44
Sodium (mmol/l)	139 [4]	139 [4]	137 [7]	0.38
Potassium (mmol/l)	4.0 [0.7]	4.0 [0.5]	4.3 [0.8]	**0.004**
CK-MB (ug/l)	3.5 [2.3]	3.6 [2.0]	3.9 [2.6]	0.23
Acute decompensation on arrival, n (%)	1 (1.9)	2 (3.4)	5 (9.1)	0.18
Chronic heart failure on arrival, n (%)	3 (5.7)	1 (1.7)	14 (25.5)	**<0.001**
Preoperative hemoglobin (g/l), mean (SD)	116 (14)	111 (16)	113 (19)	0.32
Perioperative TnT elevation, n (%)	7 (11.7)	18 (29.5)	41 (67.2)	**<0.001**

CRP, C-reactive protein; Glucose missing in 6; Potassium missing in 3; CK-MB, creatine kinase MB isoenzyme, missing in 10 participants; Acute decompensation, signs of acute decompensated congestive heart failure on chest x-ray, missing in 16; Chronic heart failure, signs of compensated heart failure on chest x-ray on arrival, missing in 16; Preoperative hemoglobin, on the day of the operation, missing in 15.

5.2.4 Cardiovascular medication

The medications significantly associated with higher NT-proBNP on admission were warfarin, beta blockers, and diuretics. At discharge from the traumatology ward, the use of beta blockers, ACE inhibitors or ARBs and diuretics were associated with a higher NT-proBNP (Table 14).

Table 14. Cardiovascular medication at hospital admission (n = 182) and at discharge from the traumatology ward (to home, facility or another ward or hospital) (n = 176*) in low, intermediate and high NT-proBNP tertiles. Data expressed in counts (%).

	On admission				At discharge			
	Low n = 60	**Intermediate n = 61**	**High n = 61**	**p-value**	**Low n = 60**	**Intermediate n = 57**	**High n = 59**	**p-value**
Acetylsalicylic acid	20 (33.3)	22 (36.1)	26 (42.6)	0.55	11 (18.3)	16 (28.1)	8 (13.6)	0.14
Clopidogrel	1 (1.7)	0 (0.0)	1 (1.6)	0.60	2 (3.3)	1 (1.8)	1 (1.7)	0.79
Dipyridamole	4 (6.7)	3 (4.9)	2 (3.3)	0.69	4 (6.7)	3 (5.3)	1 (1.7)	0.41
Warfarin	3 (5.0)	11 (18.0)	14 (23.0)	**0.018**	3 (5.0)	8 (14.0)	11 (18.6)	0.073
LMWH	0 (0.0)	0 (0.0)	2 (3.3)	0.14	59 (98.3)	54 (94.7)	54 (91.5)	0.24
Beta blocker	14 (23.3)	25 (41.0)	31 (50.8)	**0.007**	17 (28.3)	24 (42.1)	36 (61.0)	**0.001**
Nitroglycerin	8 (13.3)	13 (21.3)	17 (27.9)	0.14	8 (13.3)	13 (22.8)	17 (28.8)	0.12
Statin	14 (23.3)	17 (27.9)	15 (24.6)	0.84	14 (23.3)	17 (29.8)	16 (27.1)	0.73
ACE inhibitor or ARB	9 (15.0)	20 (32.8)	19 (31.1)	0.050	9 (15.0)	21 (36.8)	20 (33.9)	**0.017**
Calcium channel blocker	7 (11.7)	10 (16.4)	12 (19.7)	0.48	6 (10.0)	11 (19.3)	11 (18.6)	0.30
Diuretic	13 (21.7)	17 (27.9)	31 (50.8)	**0.002**	15 (25.0)	16 (28.1)	39 (66.1)	**<0.001**
Digoxin	4 (6.7)	3 (4.9)	7 (11.5)	0.37	3 (5.0)	2 (3.5)	5 (8.5)	0.49

LMWH, low molecular weight heparin; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker. *6 participants died before discharge from the traumatology ward.

5.3 Symptoms

Participants with a TnT elevation or higher NT-proBNP level rarely had any symptoms. During hospitalization, chest pain was experienced by 8.5 % participants with TnT elevation compared to 1.6 % participants with no TnT elevation (6/71 vs. 2/129; p = 0.025), but not significantly different in the NT-proBNP tertiles (3.3

vs. 3.3 vs. 4.9 %, p = 0.867). Dyspnea and hypotension were significantly more common in participants with a TnT elevation compared to participants with no TnT elevation (32.4 % vs 14.0 %; p = 0.002 and 35.2 % vs. 9.3 %; p < 0.001, respectively). Even though participants in the highest NT-proBNP tertile experienced dyspnea and hypotension numerically more often than participants in the intermediate and low tertiles, the difference was not statistically significant (31.1 vs. 16.4 vs. 16.7 %; p = 0.076 and 23.0 vs. 16.4 vs. 11.7 %; p = 0.253, respectively). Sensation of arrhythmia was not associated with elevated TnT or NT-proBNP (2.8 % vs. 0.8 %; p = 0.288 and 0 vs 1.6 vs 3.3 %, respectively; p = 0.355). Disorientation was a frequent observation made for all participants on the ward but was more common for participants with a TnT elevation (69.0 % vs 51.9 %, p = 0.019) and participants in the higher NT-proBNP tertiles (75.4 % vs. 59.0 % vs. 38.3 %, p < 0.001).

5.4 Clinical cardiovascular adverse event diagnoses

Traumatologists consulted an internist, cardiologist or anesthesiologist concerning 31 (15.5 %) participants; 24 (33.8 %) of the 71 participants with an elevated level of TnT and 7 (5.4 %) of the 129 participants with no TnT elevation (p < 0.001). A clinical diagnosis of a cardiovascular complication was made for 28 (14.0 %) participants; for 21 (29.6 %) participants with a perioperative TnT elevation and 7 (5.4 %) participants with no TnT elevation (p < 0.001). Myocardial infarction was clinically diagnosed in 12 (16.9 %) of the participants with an elevated level of TnT, and the peak TnT level ranged from 0.09 to 4.04 µg/l (median 0.81 [IQR 1.51]) for these. Acute decompensated heart failure was diagnosed in 12 (16.9 %) participants with an elevated TnT level and 4 (3.0 %) participants with a normal TnT level (p = 0.001) and these 16 participants had a median [IQR] peak NT-proBNP level of 5295 [22683] ng/l. Other cardiovascular complications diagnosed were new atrial fibrillation or flutter (n = 4) and a stroke (n = 1). No diagnoses of deep venous thrombosis or pulmonary embolism were made.

5.5 The role of fracture type and operative characteristics

5.5.1 The fracture types

Participants with a femoral neck fracture had a significantly higher hemoglobin level on admission and before the operation than the other participants. Participants with an intertrochanteric fracture were more likely to arrive from somewhere else

than home. No significant age- or gender difference was seen between the fracture types (Table 15). In a subanalysis, with only participants who were operated on with femoral neck and intertrochanteric fracture types (n = 197), the preoperative TnT elevation was significantly more common in participants with a femoral neck fracture compared to intertrochanteric fracture (26/113, 23.0 % vs 9/81, 11.1 %; p = 0.034). In this subanalysis, multivariable regression analysis, with age, preoperative ASA class, coronary artery disease, prior coronary revascularization and renal insufficiency as covariates, showed that a femoral neck fracture (HR 2.95, 95% CI 1.21 - 7.19, p = 0.018), increasing age (HR 1.06, 95% CI 1.01 - 1.11, p = 0.03) and renal insufficiency (HR 5.89, 95% CI 1.44 - 24.1, p = 0.014) were independent predictors of preoperative TnT elevation. No statistically significant differences were seen in the median NT-proBNP levels or clinical diagnoses of adverse cardiovascular events between the different fracture types (Table 15).

5.5.2 The treatment choices

Cannulated screws were more often chosen for those arriving from home and those who did not need any mobility aids. No other patient characteristics were significantly associated with the operative method. Participants treated with a long intramedullary nail required most red blood cell transfusions but also had the lowest preoperative hemoglobin levels. Of those participants treated with cemented hemiarthroplasty 56.0 % developed a TnT elevation, compared to 25.0 – 43.8 % when some other operative method was chosen, but the difference did not reach statistical significance (p = 0.053). Peak NT-proBNP levels or clinical diagnoses of adverse cardiovascular events did not significantly differ between the treatment methods (Table 16).

TnT was elevated perioperatively in 40.0 % of participants who received blood transfusion and in 28.0 % of participants who did not receive blood transfusion during hospitalization, but the difference was not statistically significant (50/125 vs. 21/75, p = 0.086).

Table 15. Comparison between participants with different fracture types. Data are presented in counts (%), median [IQR] or mean (SD).

Variable	Femoral neck n = 114	Intertrochanteric n= 84	Subtrochanteric n = 2	p - value
Age (years), median (range)	84 (43 – 98)	84 (32 – 97)	66.5 (54 – 79)	0.098
Women	72 (63.2)	58 (69.0)	2 (100.0)	0.41
Coronary artery disease	39 (34.2)	26 (31.0)	0 (0.0)	0.55
Hypertension	57 (50.0)	44 (52.4)	2 (100.0)	0.37
Atrial fibrillation	22 (19.3)	21 (25.0)	0 (0.0)	0.48
Diabetes	23 (20.2)	12 (14.3)	1 (50.0)	0.28
Congestive heart failure	12 (10.5)	16 (19.0)	0 (0.0)	0.20
Renal insufficiency	6 (5.3)	6 (7.1)	0 (0.0)	0.81
Dementia	46 (40.4)	35 (41.7)	0 (0.0)	0.49
Use of vitamin D supplementation	25 (21.9)	24 (28.6)	0 (0.0)	0.41
Use of bisphosphonate	4 (3.5)	5 (6.0)	0 (0.0)	0.68
ASA class 4	38 (33.3)	27 (32.5)	0 (0.0)	0.61
Arrival from home	71 (62.3)	39 (46.4)	2 (100.0)	**0.038**
Mobility aid	43 (37.)	38 (45.2)	1 (50.0)	0.55
Perioperative TnT elevation	46 (40.4)	25 (29.8)	0 (0.0)	0.18
TnT elevated preoperatively	26 (23.0), n=113	10 (12.2), n=82	0 (0.0)	0.12
TnT elevated postoperatively	40 (37.0), n=108	22 (31.9), n=69	0 (0.0)	0.46
Peak NT-proBNP (ng/l)	1480 [3929]	1280 [2102]		0.49
Admission hemoglobin (g/l), mean (SD)	126 (16)	118 (17)	123 (1)	**0.004**
Preoperative hemoglobin (g/l), mean (SD)	118 (15)	107 (17)	105 (5)	**<0.001**
Transfusion	62 (54.4)	61 (72.6)	2 (100.0)	**0.018**
Length of hospitalization (days)	6 [4]	6 [5]	5	0.51
Diagnosis of cardiovascular complication	20 (17.5)	8 (9.5)	0 (0.0)	0.23

ASA class, American Society of Anesthesiologists' physical status classification, assigned by anesthesiologist (missing in one participant); Mobility aid, known to have been using a stick, buggy, or a wheelchair prior to fracture; Peak NT-proBNP, highest level of N-terminal fragment of pro-B-type natriuretic peptide between arrival and the 5th postoperative day (missing in 18); preoperative hemoglobin on the day of the operation, missing in 15; Transfusion, received red blood cells during hospitalization.

Table 16. Comparison of the different operative methods (n = 198*). Data are presented in count (%), median [IQR] or mean (SD).

Variable	Hemiarthroplasty		Intramedullary nail			
	cemented n = 25	uncemented n = 70	trochanteric n = 67	long n = 16	Cannulated screws n = 20	p-value
Age (years)	84 [8]	84 [11]	83 [12]	85 [11]	74 [28]	0.062
Women	19 (76.0)	45 (64.3)	46 (68.7)	12 (75.0)	9 (45.0)	0.20
Coronary artery disease	7 (28.0)	27 (38.6)	18 (26.9)	7 (43.8)	5 (25.0)	0.43
Hypertension	12 (48.0)	35 (50.0)	37 (55.2)	7 (43.8)	10 (50.0)	0.92
Atrial fibrillation	5 (20.0)	13 (18.6)	20 (29.9)	1 (6.3)	4 (20.0)	0.25
Diabetes	3 (12.0)	15 (21.4)	8 (11.9)	3 (18.8)	5 (25.0)	0.47
Congestive heart failure	3 (12.0)	8 (11.4)	12 (17.9)	4 (25.0)	1 (5.0)	0.38
Renal insufficiency	0 (0.0)	5 (7.1)	6 (9.0)	0 (0.0)	1 (5.0)	0.43
Dementia	11 (44.0)	30 (42.9)	27 (40.3)	7 (43.8)	5 (25.0)	0.67
Use of bisphosphonate	0 (0.0)	2 (2.9)	5 (7.5)	0 (0.0)	2 (10.0)	0.28
ASA class 4	7 (28.0)	25 (35.7)	21 (31.3)	6 (37.5)	6 (30.0)	0.94
Arrival from home	15 (60.0)	40 (57.1)	30 (44.8)	9 (56.3)	17 (85.0)	**0.033**
Mobility aid	13 (52.0)	29 (41.4)	30 (44.8)	7 (43.8)	1 (5.0)	**0.014**
TnT elevation						
perioperatively	14 (56.0)	27 (38.6)	17 (25.4)	7 (43.8)	5 (25.0)	0.053
preoperatively	7 (28.0)	15 (21.7), n=69	7 (10.8), n=65	2 (12.5)	4 (20.0)	0.28
postoperatively	12 (50.0), n=24	24 (34.3)	15 (27.3), n=55	7 (50.0), n=14	4 (26.7), n=15	0.22
Peak NT-proBNP (ng/l)	1200 [3096]	1580 [4277]	1170 [1897]	1695 [3049]	1230 [4039]	0.77
Admission hemoglobin (g/l), mean (SD)	126 (17)	126 (15)	118 (17)	116 (18)	127 (19)	**0.012**
Preoperative hemoglobin (g/l), mean (SD)	115 (17)	120 (14)	108 (17)	102 (16)	119 (16)	**<0.001**
Transfusion	17 (68.0)	40 (57.1)	47 (70.1)	14 (87.5)	5 (25.0)	**0.001**
Length of operation (min)	68 [41]	57 [23]	31 [19]	59 [44]	26 [20]	**<0.001**
Length of hospitalization (days)	6 [3]	7 [6]	6 [5]	5 [4]	6 [3]	0.12
Diagnosis of cardiovascular complication	5 (20.0)	12 (17.1)	7 (10.4)	1 (6.3)	3 (15.0)	0.70

ASA class, American Society of Anesthesiologists' physical status classification, assigned by anesthesiologist (missing in one participant); Mobility aid, known to have been using a stick, buggy, or a wheelchair prior to fracture; TnT, troponin T elevation, data measurement missing for 3 preoperatively and for 20 postoperative; Peak NT-proBNP, highest level of N-terminal fragment of pro-B-type natriuretic peptide between arrival and the 5th postoperative day (missing in 18); Preoperative hemoglobin on the day of the operation (missing in 14); Transfusion, received red blood cells during hospitalization.*Not presented are one participant operated with locking plate and one participant who died before the operation.

5.5.3 Surgery delay

A surgery delay exceeding 48 hours was more common for men. There were no other differences seen in the characteristics between the groups of participants with a shorter or longer surgery delay. The surgery delay did not significantly affect TnT or NT-proBNP levels (Table 17).

5.6 Complications and length of hospitalization

5.6.1 Length of hospitalization

The median [IQR] length of stay at the traumatology ward was 6 [4] days, ranging from 1 to 29 days, and was not significantly affected by possible TnT or NT-proBNP elevation. The median [IQR] length of stay was 7 [5] days for participants with a TnT elevation and 6 [4] days for participants with no TnT elevation ($p = 0.36$), and 6 [4] days in the low, 6 [5] days in the intermediate and 6 [6] days in the high NT-proBNP tertile ($p = 0.65$). The length of stay at the traumatology ward did not significantly differ between participants who were diagnosed with an adverse cardiovascular event and those who were not (8 [6] vs. 6 [4] days, $p = 0.68$). Furthermore, no differences were seen in lengths of hospitalization between different fracture types or operative methods (Tables 15 and 16).

5.6.2 Technical and mechanical complications

Two (1.0 %) participants suffered from a technical complication during the operation; one participant had the wrong hip incised initially and one participant had an anesthetic problem during epidural catheter insertion. During hospitalization 3 (1.5 %) participants were diagnosed with a pressure ulcer and 1 (0.5 %) with intestinal occlusion.

Table 17. Comparison of participants with a surgery delay of less than and more than 48 hours (n = 199*). Data presented in median [IQR] or (range), count (%) or mean (SD).

	Surgery delay		p-value
	<48 hours (n=177)	**≥48 hours (n=22)**	
Age, median (range)	84 (32 – 98)	83 (49 – 92)	0.37
Women	124 (70.1)	8 (36.4)	**0.002**
ASA class, median [IQR]	3 [1]	3 [1]	0.39
ASA class 4	56 (31.6)	9 (40.9)	0.38
Arrival from home	103 (58.2)	9 (40.9)	0.12
Mobility aid	73 (41.2)	8 (36.4)	0.66
Coronary artery disease	57 (32.2)	7 (31.8)	0.97
Atrial fibrillation	38 (21.5)	5 (22.7)	1.00
Heart failure	27 (15.3)	1 (4.5)	0.33
Any cardiovascular disease	127 (71.8)	17 (77.3)	0.59
Warfarin medication	27 (15.3)	5 (22.7)	0.36
Acetylsalicylic acid medication	66 (37.3)	7 (31.8)	0.62
Diabetes	31 (17.5)	4 (18.2)	1.00
Renal insufficiency	10 (5.6)	2 (9.1)	0.63
Dementia	69 (39.0)	11 (50.0)	0.32
Femoral neck fracture	102 (57.6)	12 (54.5)	0.83
Intertrochanteric fracture	73 (41.2)	10 (45.5)	0.83
Hemoglobin on arrival (g/l), mean (SD)	123 (17)	124 (16)	0.69
TnT elevation			
perioperatively	62 (35.0)	8 (36.4)	0.90
on arrival to hospital	21 (12.2), n=172	1 (4.8), n=21	0.48
preoperatively	31 (17.7), n=175	4 (19.0), n=21	1.00
postoperatively	56 (34.8), n=161	6 (33.3), n=18	0.90
Peak NT-proBNP (ng/l), median [IQR]	1330 [2868]	1760 [3452]	0.58
Diagnosis of cardiovascular complication	23 (13.0)	5 (22.7)	0.21
30-day mortality	14 (7.9)	3 (13.6)	0.41
1000-day mortality	80 (45.2)	13 (59.1)	0.22

ASA class, American Society of Anesthesiologists' physical status classification, assigned by anesthesiologist; Mobility aid, known to have been using a stick, buggy, or a wheelchair prior to fracture; TnT, troponin T; Peak NT-proBNP, highest NT-proBNP level between hospital admission and the 5th postoperative day, missing in 18. *One participant died before the operation.

5.6.3 Infections

Three (1.5 %) participants were diagnosed with an infection of the fractured hip; one participant had a general infection originating from the fractured hip already on hospital admission, and another suffered from a local infection of the operated hip postoperatively, and a third had a local infection of the operated hip one month after surgery. During the whole stay in the study hospital 12 (6.0 %) participants were diagnosed with pneumonia, 21 (10.5 %) with a urinary tract infection, 3 (1.5 %) with other infections (gastroenteritis, pyelonephritis and indeterminate bacterial infection), and 1 (0.5 %) with an infection of the intravenous cannule cite. Infections were more common in participants with a perioperative TnT elevation, of whom 31.0 % were diagnosed with some infection in the study hospital, compared to 11.6 % of those with no TnT elevation (22/71 vs 15/129, p = 0.001). Pneumonia was more common in men, those with a history of cardiovascular disease or renal insufficiency, perioperative TnT elevation and higher NT-proBNP level (Table 17). The surgery delay, the fracture type, or fixation method did not affect the occurrence of pneumonia (Table 18 and 21).

5.6.4 Re-operations and new fractures

During the follow-up until January 2016 a new operation was performed in 15 (8 %) cases; one participant was re-operated on the second postoperative day due to a reduction of the fracture and 14 were later re-operated during the follow-up. Operation renewals were performed on 30 % of those who had been originally operated with cannulated screws, compared to 0 - 12.5 % when some other fixation method had been selected (p = 0.002) (Table 21). During the follow-up 15 (8 %) participants had a new hip fracture of the same or adjacent hip.

Table 18. Characteristics of participants who were diagnosed with pneumonia compared to the other participants. Data expressed in counts (%) and median [IQR].

	Pneumonia n = 12	**No diagnosis of pneumonia n = 188**	**p- value**
Age, median (range)	88 (52 – 94)	83 (32 – 98)	0.063
Women	3 (25.0)	129 (68.6)	**0.003**
ASA class 4	6 (50.0)	59 (31.6)	0.21
Some cardiovascular disease	12 (100.0)	133 (70.7)	**0.039**
Coronary artery disease	5 (41.7)	60 (31.9)	0.53
Hypertension	6 (50.0)	97 (51.6)	0.92
Atrial fibrillation	4 (33.3)	39 (20.7)	0.29
Heart failure	4 (33.3)	24 (12.8)	0.069
Renal insufficiency	3 (25.0)	9 (4.8)	**0.027**
Diabetes	4 (33.3)	32 (17.0)	0.24
Dementia	5 (41.7)	76 (40.4)	1.00
Arrival from home	5 (41.7)	107 (56.9)	0.30
Mobility aid prior to fracture	5 (41.7)	77 (41.0)	1.00
Bedfast patients	0 (0.0)	3 (1.6)	1.00
Fracture type			0.75
Femoral neck	8 (66.7)	106 (56.4)	
Intertrochanteric	4 (33.3)	80 (42.6)	
Surgery delay < 24 hours	8 (66.7)	92 (49.2), n=187	0.24
Surgery delay > 48 hours	1 (8.3)	21 (11.2), n=187	1.00
TnT elevation			
perioperatively	9 (75.0)	62 (33.0)	**0.005**
preoperatively	6 (50.0)	30 (16.2), n=185	**0.010**
postoperatively	8 (66.7)	54 (32.3), n=167	**0.025**
Peak NT-proBNP (ng/l), median [IQR]	3865 [16515]	1275 [2729]	**0.005**
Disorientation	10 (83.3)	106 (56.4)	0.067
Length of hospital-stay, median [IQR]	9.00 [5]	6.00 [4]	**0.003**
30-day mortality	4 (33.3)	14 (7.4)	**0.015**
1000-day mortality	10 (83.3)	84 (44.7)	**0.009**
5-year mortality	10 (83.3)	115 (61.2)	0.22

ASA class, American Society of Anesthesiologists' physical status classification, assigned by anesthesiologist, missing in 1; Mobility aid, known to have been using a stick, buggy, or a wheelchair prior to fracture; TnT, troponin T; NT-proBNP, N-terminal fragment of pro-B-type natriuretic peptide from admission to 5th postoperative day, missing in 18.

5.7 Factors affecting mortality

5.7.1 Patient characteristics

Within the first 30 days of hospital admission, 18 (9.0 %) participants had died. None of the patient characteristics were predictive of short-term mortality. By the 1000 day follow-up 94 (47.0 %) participants had died. A higher age, a history of coronary artery disease (diagnosed by prior myocardial infarction, coronary artery revascularization, cardiac stress testing or based on symptoms only), atrial fibrillation, congestive heart failure and dementia, arrival from another location than home, ASA class 4 and higher Lee's score, were significantly associated with long-term mortality. Coronary artery disease determined by prior myocardial infarction or coronary artery revascularization was not predictive of mortality (Table 19).

Table 19. Comparison of the participants who died vs survived 30 and 1000 days. Data expressed in median (range) or [IQR] or count (%).

Variable	Died during 30 days n=18	Alive after 30 days n=182	p – value	Died during 1000 days n = 94	Alive after 1000 days n = 106	p - value
Age (years), median (range)	86 (68 – 97)	83 (32 – 98)	0.115	86 (32 – 98)	80 (43 – 97)	**<0.001**
Women	9 (50.0)	123 (67.6)	0.133	58 (61.7)	74 (69.8)	0.23
Coronary artery disease	6 (33.3)	59 (32.4)	0.937	40 (42.6)	25 (23.6)	**0.004**
Prior myocardial infarction	4 (22.2)	20 (11.1)	0.242	15 (16.0)	9 (8.5)	0.11
Prior coronary revascularization (CABG or PCI)	2 (11.1)	14 (7.7)	0.642	11 (11.7)	5 (4.7)	0.069
History of TIA or stroke	2 (11.1)	35 (19.2)	0.536	18 (19.1)	19 (17.9)	0.82
Hypertension	11 (61.1)	92 (50.5)	0.392	53 (56.4)	50 (47.2)	0.19
Atrial fibrillation	7 (38.9)	36 (19.8)	0.073	30 (31.9)	13 (12.3)	**0.001**
Congestive heart failure	2 (11.1)	26 (14.3)	1.000	19 (20.2)	9 (8.5)	**0.017**
Diabetes mellitus	6 (33.3)	30 (16.5)	0.103	19 (20.2)	17 (16.0)	0.44
Renal insufficiency	2 (11.1)	10 (5.5)	0.295	8 (8.5)	4 (3.8)	0.16
Dementia	9 (50.0)	72 (39.6)	0.389	49 (52.1)	32 (30.2)	**0.002**
Medicated epilepsy	0 (0.0)	10 (5.5)	0.604	3 (3.2)	7 (6.6)	0.34
Psychiatric medication	9 (50.0)	85 (46.7)	0.789	47 (50.0)	47 (44.3)	0.42
Medication affecting the CNS	8 (44.4)	65 (35.7)	0.463	33 (35.1)	40 (37.7)	0.70
COPD	1 (5.6)	8 (4.4)	0.580	5 (5.3)	4 (3.8)	0.74
Cancer	3 (16.7)	16 (8.8)	0.388	9 (9.6)	10 (9.4)	0.97
Lee's score	0.5 [1.3]	0 [1]	0.887	1 [2]	0 [1]	**0.006**
ASA class 4	7 (41.2)	58 (31.9)	0.434	40 (43.0)	25 (23.6)	**0.004**
Arrival from home	9 (50.0)	103 (56.6)	0.591	40 (42.6)	72 (67.9)	**<0.001**
Mobility aid	6 (66.7)	79 (55.6)	0.732	41 (65.1)	44 (50.0)	0.065

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; TIA, transient ischemic attack; Psychiatric medication, benzodiazepine, selective serotonine or norepinephrine reuptake inhibitor, mirtazapine, buspirone, tricyclic antidepressant or antipsychotic medication; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; Cancer, history of cancer (active or in remission); ASA class, American Society of Anesthesiologists' physical status classification, assigned by anesthesiologist; Mobility aid, known to have been using a stick, buggy, or a wheelchair prior to fracture.

5.7.2 TnT

Within 30 days of admission, 6 (24.0 %) participants with a major perioperative TnT elevation, 6 (13.0 %) participants with a minor TnT elevation and 6 (4.7 %) participants with no TnT elevation had died (p = 0.005). The short-term mortality was highest in participants with an already elevated level of TnT on arrival compared to participants with a normal level of TnT at hospital admission (6/23, 26.1 % vs. 11/171, 6.4 %; p = 0.007). Participants with a preoperative TnT elevation had a 30-day mortality of 19.4 % compared to 6.2 % for participants with a normal preoperative TnT level (7/36 vs. 10/161; p = 0.019), while participants with a postoperative TnT elevation had a 30-day mortality of 16.1 % compared to 5.1 % for participants with a normal postoperative TnT level (10/62 vs. 6/117; p = 0.014).

In a Cox regression model with age, atrial fibrillation, renal insufficiency and dementia as covariates, perioperative TnT elevation (HR 3.87, 95% CI 1.45-10.30, p = 0.007) was the only independent predictor of 30-day mortality. This result remained even when new ECG changes, red blood cell transfusion and the Lee's score were added to the model (II). When preoperative TnT elevation was used instead of perioperative TnT elevation, preoperative TnT elevation remained as the only independent predictor of short-term mortality (HR 3.36, 95% CI 1.28 - 8.84, p = 0.014) and adding ECG changes, red blood cell transfusion and the Lee's scores did not change the result. In a similar model postoperative TnT elevation (HR 3.13, 95% CI 1.13 - 8.65, p = 0.028) was an independent predictor of short-term mortality together with atrial fibrillation (HR 2.83, 95% CI 1.05 - 7.62, p = 0.04), and ECG changes, red blood cell transfusion and the Lee's scores did not change this result either.

During the1000 days after hospital admission, 43 (60.6 %) participants with and 51 (39.5 %) participants with no perioperative TnT elevation died (p=0.004). In a Cox regression model with age, atrial fibrillation, renal insufficiency and dementia as covariates, TnT elevation (HR 1.73, 95% CI 1.14 - 2.64, p = 0.011) remained an independent predictor of mortality together with atrial fibrillation (HR 1.86, 95% CI 1.18 - 2.93, p = 0.007), dementia (HR 1.84, 95% CI 1.22 - 2.78, p = 0.004), and increasing age (HR 1.03, 95% CI 1.01 - 1.06, p = 0.013). Adding red blood cell transfusion, new ECG changes and the Lee's score to the model did not alter the results (II). When age, coronary artery disease, atrial fibrillation, congestive heart failure, dementia and ASA class 4 were used as covariates in the Cox regression model, TnT elevation (HR 1.60, 95 % CI 1.04 - 2.47, p = 0.032), higher age (HR 1.03, 95 % CI 1.00 – 1.06, p = 0.03), atrial fibrillation (HR 1.88, 95 % CI 1.20 - 2.95, p = 0.006), and dementia (HR 1.83, 95 % CI 1.21 - 2.77, p = 0.004) were still the independent predictors of 1000-day mortality. Preoperative TnT elevation (HR 1.77, 95 % CI 1.08 - 2.90, p = 0.024) was also an independent predictor of

1000-day mortality when used in this model instead of perioperative TnT elevation, while postoperative TnT elevation was not.

5.7.3 NT-proBNP

The participants who died during the first 30 days had a median [IQR] peak NT-proBNP level of 2700 [10435] ng/l compared to 1230 [2736] ng/l for survivors (p = 0.002). The 30-day mortality was 1.7 % in the low NT-proBNP tertile, 11.5 % in the intermediate and 14.8 % in the high (p = 0.037). For the 182 participants who had NT-proBNP samples taken, a Cox regression model including age, renal insufficiency, TnT elevation, NT-proBNP tertiles, ASA class and Lee's score was created for analysis of independent predictors of 30-day mortality. Intermediate and high NT-proBNP level compared to low level (HR 7.8, 95% CI 1.03 - 59.14, p = 0.047) was the only independent predictor of short-term mortality (III).

By the end of the 1000-day follow-up, 26.7 % of the participants in the low NT-proBNP tertile, 49.2 % of those in the intermediate and 68.9 % of those in high NT-proBNP tertile died (16/60 vs. 30/61 vs. 42/61, p < 0.001). In a Cox regression model (with only participants with NT-proBNP samples taken included) intermediate and high NT-proBNP levels compared to low NT-proBNP (HR 2.27, 95% CI 1.30 - 3.96, p = 0.004) together with dementia (HR 1.74, 95% CI 1.13 - 2.66, p = 0.011) and higher ASA class (HR 1.59, 95% CI 1.06 - 2.38, p = 0.024) were independent predictors of 1000-day mortality (III).

When participants with perioperative TnT elevation were analysed separately in similar Cox regression models, NT-proBNP was not an independent predictor of 30-days or 1000-days mortality in these participants. However, when participants with no perioperative TnT elevation were analysed separately in similar models, high and intermediate NT-proBNP compared to low NT-proBNP (HR 3,17, 95% CI 1.64 - 6.10, p = 0.001) was the only independent predictor of 1000-days mortality, but no independent predictors for 30-days mortality appeared.

5.7.4 Ischemic ECG changes and symptoms

Ischemic ECG findings were not statistically significantly associated with higher mortality (Table 20). Participants with new ST-elevation had a 30-day mortality of 28.6 % compared to 8.6 % in participants with no new ST elevation and a 1000-day mortality of 71.4 % compared to 46.5 %, but the differences did not reach statistical significance (2/7 vs. 16/187; p = 0.129 and 5/7 vs. 87/187; p = 0.26).

Furthermore, when participants with a TnT elevation were analyzed separately, new ischemic ECG changes did not affect the 30-day or 1000-day mortality.

Of the symptoms, dyspnea was associated with higher 30-day mortality, and hypotension with higher 30- and 1000-day mortalities (Table 20).

Table 20. Comparison of new ischemic ECG findings and symptoms between participants who died and who survived. Data presented in count (%).

	30-day follow-up			1000-day follow-up		
	Deceased (n=18)	**Survivors n=176)**	**p-value**	**Deceased (n=92)**	**Survivors (n=102)**	**p-value**
New ST elevation	2 (11.1)	5 (2.8)	0.13	5 (5.4)	2 (2.0)	0.26
New ST depression	6 (33.3)	42 (23.9)	0.39	23 (25)	25 (25)	0.94
New T wave inversion	10 (55.6)	67 (38.1)	0.15	40 (43.5)	37 (36.3)	0.31
	(n=18)	**(n=182)**		**(n=94)**	**(n=106)**	
Chest pain	0 (0.0)	8 (4.4)	1.00	1 (1.1)	7 (6.6)	0.069
Hypotension	10 (55.6)	27 (14.8)	**<0.001**	24 (25.5)	13 (12.3)	**0.016**
Dyspnea	9 (50.0)	32 (17.6)	**0.003**	23 (24.5)	18 (17.0)	0.19
Disorientation	14 (77.8)	102 (56.0)	0.075	61 (64.9)	55 (51.9)	0.063

5.7.5 Fracture characteristics

The fracture type did not affect the mortality. At 30 days 7.0 % of participants with a femoral neck fracture, 11.9 % of participants with an intertrochanteric fracture and none of participants with a subtrochanteric fracture, and at 1000 days 46.5 % participants with a femoral neck fracture, 48.8 % with an intertrochanteric fracture, and none with a subtrochanteric fracture had died ($p = 0.447$ and $p = 0.388$, respectively).

5.7.6 Treatment characteristics

The operative method did not significantly affect the short-term or long-term mortality (Table 21). Of the participants with a surgery delay exceeding 48 hours 13.6 % had died by the end of the first 30 days compared to 7.9 % of participants with a surgery delay below 48 hours (3/22 vs. 14/177; $p = 0.410$) and at 1000 days this

percentage was 59.1 % vs. 45.2 % (13/22 vs. 80/177; p= 0.218), but the difference was not statistically significant.

Those who received blood transfusion during hospitalization had a 30-day mortality of 8.8 % compared to 9.3 % of those who did not (11/125 vs. 7/75; p = 0.898) and at 1000 days 47.2 % vs 46.7 % (59/125 vs. 35/75; p = 0.942).

Table 21. Comparison of different operative methods on the outcome (n = 198*). Data presented in count (%).

Variable	Hemiarthroplasty		Intramedullary nail			
	cemented n = 25	uncemented n = 70	trochanteric n = 67	long n = 16	Cannulated screws n = 20	p-value
All infections	6 (24.0)	18 (25.7)	9 (13.4)	3 (18.8)	1 (5.0)	0.25
Pneumonia	3 (12.0)	4 (5.7)	4 (6.0)	0 (0.0)	1 (5.0)	0.74
Re-operations	0 (0.0)	5 (7.1)	2 (3.0)	2 (12.5)	6 (30.0)	**0.002**
30-day mortality	3 (12.0)	5 (7.1)	9 (13.4)	0 (0.0)	0 (0.0)	0.30
1000-day mortality	13 (52.0)	34 (48.6)	36 (53.7)	4 (25.0)	6 (30.0)	0.16
5-year mortality	18 (72.0)	43 (61.4)	45 (67.2)	7 (43.8)	11 (55.0)	0.29

*One patient died before the operation and one was treated with a locking plate.

5.7.7 Adverse cardiac event diagnoses and cardiac medications

Of the 28 participants who were diagnosed with some adverse cardiovascular event 9 (32.1 %) died during the 30-day follow-up compared to 9 (5.2 %) of those 172 with no clinical adverse event diagnosis (p < 0.001), and during the 1000-day follow-up 21 (75.0 %) compared to 73 (42.4 %) (p = 0.001). Of the 12 participants with a diagnosed myocardial infarction, 3 (25.0 %) died during the first 30 days compared to 15 (8.0 %) in the other 188 participants, but the difference did not reach statistical significance (p = 0.081). The 1000-day mortality did not significantly differ either (58.3 %, 7/12 vs. 46.3 %, 87/188; p = 0.42). The 30-day or 1000-day mortality did not significantly differ between participants who had a TnT elevation and a clinical diagnosis of myocardial infarction and those with a TnT elevation but no diagnosis of myocardial infarction (25.0 %, 3/12 vs. 15.3 %, 9/59; p = 0.41; and 58.3 %, 7/12 vs. 61.0 %, 36/59; p = 1.00).

Of those 31 participants who had a consultation with an internist, cardiologist or anesthesiologist, 9 (29.0 %) died during the first 30 days, compared to 9 (5.3 %)

of the169 who did not undergo consultation (p<0.001). Eight (33.3 %) of the 24 participants with a troponin elevation and had a consultation died during the first 30 days compared to 4 (8.5 %) of the participants with a TnT elevation but no consultation (p = 0.016). However, the 1000-day mortality did not significantly differ between these participants (62.5 %, 15/24 vs. 59.6 %, 28/47; p = 0.81).

Participants who had used a / calcium channel blocker prior to fracture had a 30-day mortality of 18.7 % compared to 7.1 % for those who had not (6/32 vs. 12/168; p = 0.047). The 1000-day mortality was 65.6 % in participants who had used warfarin prior to fracture compared to 43.5 % in the other participants (21/32 vs. 73/168; p = 0.021), and 60.3 % for those who had used diuretic compared to 40.2 % for those who had not (41/68 vs. 53/132; p = 0.007). No other home cardiac medications were significantly associated with a greater mortality. When participants with a TnT elevation were analyzed separately, calcium channel blocker (50.0 %, 5/10 vs. 11.5 %, 7/61; p = 0.01) was significantly associated with 30-day mortality and digoxin (100.0 %, 7/7 vs. 56.3 %, 36/64; p = 0.037) with 1000-day mortality.

Concerning the medication at discharge from traumatology ward, the use of low molecular weight heparin was associated with a lower 1000-day mortality (43.5 %, 80/184 vs 80.0 %, 8/10; p = 0.045), use of a diuretic was associated with a higher 30-day (11.8 %, 9/76 vs. 2.5 %, 3/118; p = 0.013) and 1000-day mortality (63.2 %, 48/76 vs. 33.9 % 40/118; p < 0.001) and nitroglycerin with a higher 1000-day mortality (59.1 %, 26/44 vs. 41.3 %, 62/150; p = 0.037). When participants with a TnT elevation were analyzed separately, calcium channel blockers were associated with an increased 30-day mortality (42.9 %, 3/7 vs. 8.5 %, 5/59; p = 0.048), and diuretics with an increased 1000-day mortality (74.2 %, 23/31 vs. 44.4 %, 16/36; p = 0.014).

5.7.8 The 5-year survival

The prognostic impact of perioperative TnT elevation remained during the whole 5-year follow-up, with 56 (78.9 %) of the participants with a perioperative TnT elevation dying compared to 69 (53.5 %) of participants with no TnT elevation ($p < 0.001$), as shown in Figure 2.

In a Cox regression model including age, the preoperative ASA class assigned by the anesthesiologist, atrial fibrillation, coronary artery disease, prior revascularization, heart failure, dementia and TnT elevation, TnT elevation (HR 1.65, 95% CI 1.13 - 2.40, p = 0.009) remained an independent predictor of 5-year mortality together with increasing age (HR 1.03, 95% CI 1.01 - 1.06, p = 0.008), atrial fibrillation (HR 1.68, 95% CI 1.12 - 2.53, p= 0.013), higher ASA class (HR 1.58, 95% CI 1.10 - 2.25, p = 0.012) and dementia (HR 1.75, 95% CI 1.22 - 2.50, p = 0.002).

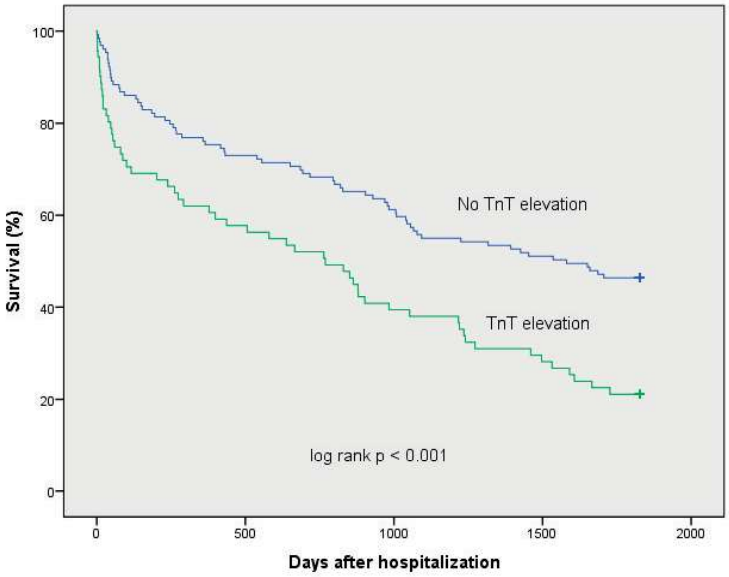

Figure 2. 5-year survival of participants with and with no TnT elevation.

Concerning the 182 participants who had perioperative NT-proBNP measurements, 40.0 % of the participants in the low tertile, 67.2 % in the intermediate and 85.2 % in the high tertile had died by the end of the 5-year follow-up, as shown in Figure 3 (24/60 vs. 41/61 vs. 52/6; $p < 0.001$). In a similar Cox regression model for TnT elevation, intermediate and high compared to low NT-proBNP (HR 1.98, 95 % CI 1.22 - 3.23, $p = 0.006$), ASA class (HR 1.65, 95% CI 1.15 - 2.36, $p = 0.006$) and dementia (HR 1.56, 95 % CI 1.07 - 2.27, $p = 0.021$) were independent predictors of 5-year mortality.

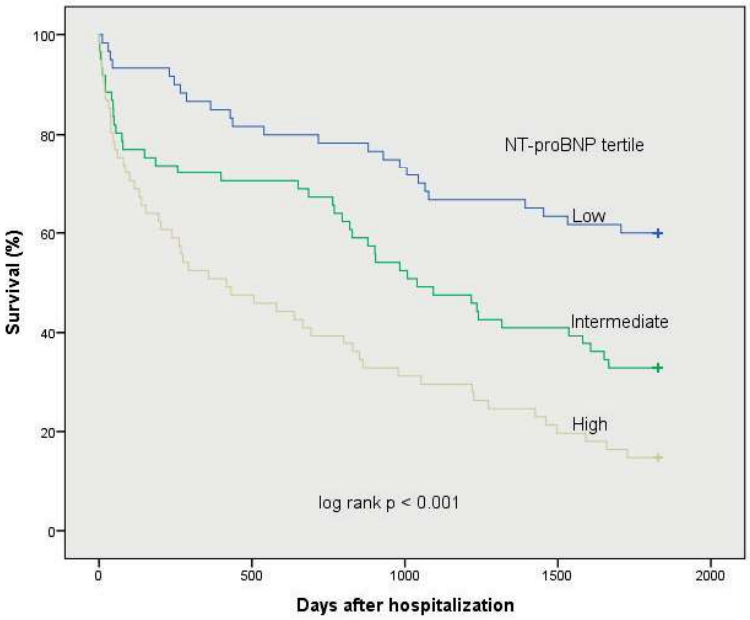

Figure 3. 5-year survival of participants in the low, intermediate and high NT-proBNP-tertiles.

6 DISCUSSION

6.1 TnT elevation and ECG changes

6.1.1 Incidence of and factors associated with TnT elevation

Perioperative TnT elevation was common amongst hip fracture patients with a third of participants having a level of 0.03 µg/l or higher. Not surprisingly, TnT elevation was more common in older participants and those with prior cardiovascular diseases. However, TnT elevations were also seen in younger participants and those with no prior cardiovascular co-morbidities.

Prior to October 2017, 10 other prospective studies measuring perioperative TnI or TnT in hip fracture patients have been published (Table 3). Two of these did not report the incidence of perioperative troponin elevation (Rostagno et al., 2015, Talsnes et al., 2011b), while eight others, with populations ranging from 69 to 312 hip fracture patients and mean ages from 80 to 86 years, reported an incidence of 27 - 51 %, similar to the present study (Ausset et al., 2009, Dawson-Bowling et al., 2008b, Fisher et al., 2008b, Izhaki et al., 2011, Katsanos et al., 2017, Oscarsson et al., 2009, Spurrier et al., 2011, Vallet et al., 2017). In addition, three similar studies with orthopedic populations consisting partly of hip fracture patients have been conducted, and the incidence of perioperative troponin elevation was 13 - 62 % in these, however the study with the lowest incidence also included participant undergoing elective surgeries (Ausset et al., 2008, Chong et al., 2009, Chong et al., 2010b). The differences in inclusion criteria and the timing of troponin measurements and assays used in the studies most likely explain the wide variation of the incidence. Only one prior study on hip fractures has evaluated independent predictors of troponin elevation. In accordance with the results of the present study, that study found higher age to independently predict troponin elevation (Fisher et al., 2008b). An earlier study on emergency orthopedic surgery patients found coronary artery disease to be the clinical characteristic independently predicting perioperative troponin elevation (Chong et al., 2009).

The medications used prior to injury were similar in participants with and without TnT elevation. The only significant difference was found concerning acetylsalicylic acid, which was used by 47 % of participants with TnT elevation compared to 32 % of those with no TnT elevation. This is not surprising considering the higher incidence of prior coronary artery disease in participants with a TnT elevation.

As expected, participants with perioperative TnT elevation had a significantly higher level of CRP and CK-MB on admission than participants with no TnT elevation. They also had a lower level of hemoglobin on admission and before the operation. Earlier studies have demonstrated that anemia is significantly more common for hip fracture patients, and even other orthopedic surgery patients, who are diagnosed with perioperative myocardial infarction (Smilowitz et al., 2017, Gupta et al., 2012). A similar association of lower preoperative hemoglobin and perioperative TnT elevation has been reported for hip fracture patients (Spurrier et al., 2011). An earlier study with an orthopedic population, consisting mostly of hip fracture patients, also found an independent association between postoperative red blood cell transfusions and postoperative TnI elevation (Chong et al., 2009). Contrary to these findings, a recent study on hip fracture patients using conventional troponin assay did not find a significant difference in preoperative hemoglobin levels for those with and those with no TnI elevation (Vallet et al., 2017).

6.1.2 Timing of TnT elevation

Interestingly, a third of TnT elevations were already seen on admission to the hospital and altogether half of TnT elevations occurred in the preoperative phase. Most prior studies have viewed surgery as the cause of the myocardial injury in hip fracture patients, while the present study is the first to perform and report the results of repeated preoperative troponin measurements and shows that the fracture itself may have been the cause for the injury in at least half of the cases. This finding is in accordance with the three earlier studies on hip fracture patients that have performed and reported the results of both pre- and postoperative troponin measurements. However, these studies only measured troponin once in the preoperative phase. Two studies measured troponin on admission, and 29-67 % of perioperative troponin elevations were already detectable then, while one study, measuring troponin one hour prior to surgery, found that 58 % of postoperative troponin elevations were already detectable preoperatively (Dawson-Bowling et al., 2008b, Izhaki et al., 2011, Oscarsson et al., 2009).

6.1.3 Incidence of ischemic ECG changes and causes for myocardial injury

According to ESC guidelines, diagnosis of myocardial infarction requires that troponin elevation is accompanied by either ischemic symptoms, new ischemic ECG changes or Q-waves or a coronary angiographic confirmation (Thygesen et al., 2012b). However, only less than one fourth of hip fracture patients who have been diagnosed with perioperative myocardial infarction using these criteria have new

ischemic ECG findings (Gupta et al., 2012). In the present study, about 70 % of participants with TnT elevation had new ST segment changes in ECG. Unfortunately, ST segment changes are rather nonspecific for ischemia, and about 40 % of participants with no perioperative TnT elevation also had new ST segment changes in ECG. The poor correlation of ischemic ECG findings and troponin elevation has been recognized by two earlier hip fracture studies (Dawson-Bowling et al., 2008b, Izhaki et al., 2011). No previous hip fracture studies have performed repeated ECG recordings and systematically reported the results. One hip fracture study reports that 2 % of all the study participants had troponin elevation and ECG findings consistent with myocardial infarction, but the percentage of troponin elevations was not reported (Rostagno et al., 2015). Another study found half of perioperative troponin elevations to be caused by myocardial infarction (Vallet et al., 2017). Whether all 71 participants with perioperative TnT elevation in the present study had an actual myocardial infarction remains uncertain. Some of the minor TnT elevations might have been caused by minor myocardial injury instead of an actual infarction.

About a third of participants with TnT elevation had a rise that was considered major, and 80 % of these had new ST segment changes in their ECG. There were seven participants, accounting for 10 % of all participants with a TnT elevation, who in the retrospective analysis were determined to have suffered from STEMI. The exact same incidence of STEMI amongst hip fracture patients with troponin elevation was found in another study (Vallet et al., 2017). Almost all participants with STEMI had a major TnT elevation. Three of the infarctions occurred pre- and four postoperatively. None of these participants experienced chest pain and two were considered asymptomatic. Clinical diagnosis of myocardial infarction was reached in only three, and the clinical suspicion was raised by hypotension or shortness of breath.

It is possible that participants with major TnT elevation suffered from type 1 myocardial infarction with critical coronary artery stenosis. However, since no immediate coronary angiography was performed, this remains unconfirmed. An earlier study on hip fracture patients found echocardiographic findings indicative of stress-induced cardiomyopathy (Takotsubo cardiomyopathy), without significant coronary artery lesions in coronary angiography, in all participants with preoperative STEMI who underwent these examinations (Rostagno et al., 2015). Another study retrospectively observed that one fourth of patients with perioperative NSTEMI or STEMI undergoing diagnostic coronary angiography required PCI, and the culprit vessel was most commonly the left anterior descending or the left circumflex artery. However, the study in question had a dominance of participants undergoing vascular surgery and only 9 % of the participants undergoing PCI were orthopedic patients (Parashar et al., 2016).

There are no prior studies on myocardial injury caused by different fractures. The mechanism behind the myocardial injury can only be speculated. The painful fracture triggers a thrombotic process and an adrenergic storm. The circulating catecholamines can cause a direct toxic effect on the myocardium, but they are also known to increase myocardial oxygen demand (Vasu et al., 1978). Previous studies have shown that preoperatively initiated continuous epidural infusion of local anesthetic and opioid can significantly reduce, not only pain, but also ischemia and adverse cardiac events in hip fracture patients. It has been speculated that this effect might be caused by analgesia, sympatholytic effects, and attenuation of the stress response (Matot et al., 2003, Scheinin et al., 2000). Two recent studies have demonstrated the association of intraoperative hypotension and tachycardia with postoperative troponin elevation in non-cardiac surgery patients (Abbott et al., 2017, Hallqvist et al., 2016). At least some of the minor TnT elevations in the present study were probably type 2 myocardial infarctions. It can also be hypothesized that some of the participants presenting with an elevated level of TnT on arrival might have had an adverse cardiac event leading to the fall and fracture.

6.2 NT-proBNP elevation

The NT-proBNP levels of the participants were higher than expected. ESC guidelines for the diagnosis and treatment of heart failure advise that a level less than 300 ng/l in an acute setting excludes acute congestive heart failure (Ponikowski et al., 2016). In the present study, only 16 (8.8 %) participants who had a NT-proBNP measurement had a level this low.

Thus far, only two other studies have studied NT-proBNP elevation in hip fracture patients. The first of these measured preoperative NT-proBNP in 69 frail hip fracture patients with a preoperative ASA class 3 - 4, and found half of the patients to have a level exceeding 3984 ng/l. Patients with higher NT-proBNP had a lower mean BMI and a higher mean creatinine level, and less often a history of having a stoke, compared to participants with lower NT-proBNP (Oscarsson et al., 2009). The second study measured preoperative NT-proBNP in a younger population of 328 hip fracture patients with a median ASA class 2, excluding those with renal insufficiency, and found a median NT-proBNP level of 299 ng/l (Ushirozako et al., 2017). Neither of these studies determined the independent predictors of a higher NT-proBNP level. Even though higher age, atrial fibrillation, renal and heart failure were independent predictors of a NT-proBNP level exceeding 806 ng/l in the present study, there were also participants with no prior cardiovascular diseases or renal insufficiency presenting with a higher level of NT-proBNP. Prior

use of warfarin, beta blockers and diuretics were expectedly more common in the intermediate and high NT-proBNP tertiles.

The median admission creatinine level was higher in participants in the high NT-proBNP tertile. It is known that the renal function effects the NT-proBNP level (Hunt et al., 1997). Admission CRP was also higher in those with higher NT-proBNP and perioperative TnT elevations were more common in participants with higher NT-proBNP. Since simultaneous NT-proBNP and TnT elevations were common, some of NT-proBNP elevations may have resulted from acute myocardial injury.

NT-proBNP measurements that were taken postoperatively were higher than those taken preoperatively. This finding is consistent with an earlier study on emergency orthopedic surgery patients (Chong et al., 2010a). Furthermore, an earlier study with a small population of 37 patients referred for elective orthopedic surgery found the NT-proBNP measurements taken on the third postoperative day to be significantly higher than those taken preoperatively or 4 hours postoperatively (Montagnana et al., 2006). The heavy perioperative use of intravenous fluids and the surgery itself may account for some of the rise in NT-proBNP. An earlier small study found that the perioperative amount of fluids that was administered independently predicted a postoperative NT-proBNP increase from the original preoperative level in elective orthopedic surgery patients (Montagnana et al., 2006). However, in the current study even preoperative NT-proBNP levels were high, leading to the possibility that the fracture was influencing the elevation in NT-proBNP.

6.3 Symptoms of cardiovascular origin

Chest pain is a classic manifestation of myocardial ischemia, yet it was reported in only 9 % of participants with TnT elevation; whilst both dyspnea and hypotension were reported in approximately a third. Similarly, an earlier study reported no symptoms in more than 80 % of orthopedic patients with troponin elevation (Ausset et al., 2008). A retrospective study with a population of 1212 hip fracture patients reported that only one fourth of the patients who fulfilled the official criteria for perioperative myocardial infarction (Thygesen et al., 2012b) were symptomatic (Gupta et al., 2012). The participants in the present study were on heavy pain medication, and also medications affecting the nervous system were common. This might have led to the masking of ischemic symptoms. Disorientation was a common finding especially in participants with TnT or NT-proBNP elevation, and

this might be a clinical manifestation of ischemia. Other potential causes for postoperative disorientation might be cerebral hypoperfusion and systemic inflammation caused by the surgery (Kristensen et al., 2014).

6.4 Diagnosis and treatment of adverse cardiovascular events

A perioperative cardiovascular complication was clinically diagnosed in 14 % of all participants, and in 30 % of participants with a TnT elevation. A cardiologist, internist or anesthesiologist was consulted in a third of the cases where the participants had a TnT elevation. However, cardiovascular medications were seldom initiated. The use of a beta blocker and an ACE inhibitor or ARB by participants with a perioperative TnT elevation increased only modestly during hospitalization. At discharge, of all cardiovascular medications only the use of statins was significantly more common for participants with TnT elevation compared to participants with no TnT elevation. Of note, the use of acetylsalicylic acid amongst participants with TnT elevation reduced from almost a half on admission to a quarter at discharge from the traumatology ward as a dual antithrombotic therapy was probably considered by the treating traumatologist to increase the bleeding risk too much.

A prior study reported that - against current guidelines - antiplatelet therapy was ceased perioperatively in 80 % of the high cardiac risk patients referred for elective non-cardiac surgery (Alcock et al., 2012). The perioperative cessation of antiplatelet therapies in hip fracture patients has been demonstrated to be associated with an increased risk of acute coronary syndromes (Collyer et al., 2011), but another study on non-cardiac surgery patients did not find any reduction in postoperative myocardial infarctions, but rather a higher incidence of bleeding, when using low-dose acetylsalicylic acid compared to a placebo during the perioperative period (Devereaux et al., 2014).

In the present study, acute decompensated heart failure was clinically diagnosed in 16 (8 %) participants. It is of note that clinical congestive heart failure was seldom present on admission, although signs of chronic heart failure on chest x-ray were seen on admission in a fourth of participants in the high NT-proBNP tertile. All participants with a higher NT-proBNP level most probably did not fulfill criteria for acute congestive heart failure, although an earlier study has shown that the preoperative BNP level is indicative of major preoperative echocardiographic abnormalities in hip fracture patients (Pili-Floury et al., 2012).

Perioperative myocardial infarction was clinically diagnosed in only 12 participants, accounting for 17 % of participants with a perioperative TnT elevation and 6 % of all study participants. The incidence of perioperative myocardial infarction

has been 10 - 14 % in prior hip fracture studies using the criteria in the Universal definition of myocardial infarction (Vallet et al., 2017, Huddleston et al., 2012).

Platelet inhibitors (acetylsalicylic acid and P2Y12 inhibitors), heparin, beta blockers, ACE inhibitors and statins are essential in the treatment of NSTEMI (Roffi et al., 2016). Although conservative treatment was started for those participants with a clinical diagnosis of myocardial infarction, these medications were used at discharge in less than half of the patients with a TnT elevation. In line with the present findings, a large multicentre POISE trial demonstrated that almost half of patients with perioperative myocardial infarction do not receive evidence-based medication during hospitalization or at discharge, and only two thirds are on acetylsalicylic acid (Devereaux et al., 2011). Perioperative bleeding risks may create a challenge in the treatment of postoperative myocardial infarction and explain these findings.

The treatment for STEMI is urgent reperfusion and the preferred strategy is PCI (Ibanez et al., 2017). However, no patient suffering from a STEMI was referred for urgent coronary revascularization in the present study. The reasons behind this are probably the poor clinical detection of the patients in need of coronary revascularization and on the other hand delayed diagnostics at a stage when symptoms of decompensated heart failure were already present. A retrospective study found that one fifth of all kinds of operative patients who are diagnosed with perioperative myocardial infarction are referred for invasive treatment, and 37 % of these undergo coronary revascularization with PCI or CABG (Smilowitz et al., 2017). It should be acknowledged that bleeding is a major factor impairing the outcome of patients with perioperative myocardial infarction treated with PCI (Parashar et al., 2016). However, a recent study on a large national cohort found the short-term mortality to be greatest in conservatively treated patients with perioperative myocardial infarction, despite the increased bleeding associated with invasive treatments (Smilowitz et al., 2017).

6.5 The role of fracture type and operative characteristics

In line with previous findings, participants with a femoral neck fracture had a higher preoperative hemoglobin level than participants with an intertrochanteric fracture (Fisher et al., 2010, Fisher et al., 2012). They also needed less blood transfusions and were more frequently home-dwelling. However, participants with a femoral neck fracture had a 3-fold risk of preoperative TnT elevation compared to participants with an intertrochanteric fracture. Two other studies have measured perioperative troponin elevation in different hip fracture types. The first of these did not find a difference in peri- or postoperative TnI levels between 761 femoral

neck and intertrochanteric fracture patients (Fisher et al., 2010, Fisher et al., 2012), while the other, measuring postoperative TnI in 312 patients, reported numerically greater incidence in femoral neck, compared to intertrochanteric, fractures, but the significance of this finding was not reported (Vallet et al., 2017). No prior studies have compared NT-proBNP levels in different hip fracture types. In the present study, no differences were seen in NT-proBNP levels between the fracture types. Although the comorbidities of femoral neck and intertrochanteric fracture patients do not differ, the biochemical parameters of mineral and bone metabolisms have previously been shown to significantly differ (Fisher et al., 2010), and differences in the mechanisms behind the fractures have been speculated (Fisher et al., 2012).

Of note, no statistically significant differences were seen in TnT and NT-proBNP levels between the different operative methods. However, more than half of participants who were treated with cemented hemiarthroplasty had an elevated level of TnT perioperatively, compared to 25-44 % of those treated with some other operative method. Although this result did not quite reach statistical significance, this might be due to a bias in the small subgroups. An earlier study on 312 hip fracture patients also found a numerically greater amount of postoperative troponin elevation in participants treated with hemiarthroplasty compared to those treated with a gamma nail (Vallet et al., 2017), while another study with 148 hip fracture patients observed no differences between different operative methods, although they did not report the incidences (Izhaki et al., 2011).

Cemented hemiarthroplasty is commonly preferred to uncemented hemiarthroplasty (Rogmark et al., 2014, Hongisto et al., 2014). Earlier studies comparing cemented and uncemented hemiarthroplasty in the treatment of dislocated femoral neck fractures have found no significant differences in the incidence of postoperative cardiovascular complications (Khan et al., 2002, Taylor et al., 2012, Deangelis et al., 2012, Figved et al., 2009, Parker et al., 2010). The present study is in line with this finding observing no differences in the diagnoses of cardiovascular complications between all the different operative methods. However, inclusion of only clinically diagnosed cardiovascular complications in the comparison will inevitably lead to a substantial number of complications being unrecognized. In the present study, participants treated with cemented arthroplasty had a 56 % incidence of perioperative TnT elevation compared to 39 % with uncemented, but the difference was not statistically significant. Another study has compared cemented and uncemented hemiarthroplasty in the treatment of hip fracture by performing routine troponin measurements, but the results of these measurements have not been reported (Deangelis et al., 2012).

Bone cement implantation syndrome is a complication especially associated with cemented hip arthroplasty but may occur in any surgical procedure that compromises the femoral canal (Donaldson et al., 2009, Griffiths et al., 2015). It is a phenomenon featuring hypotension, hypoxia, arrhythmia, cardiac arrest or unconsciousness occurring during or within minutes after the cementation (Donaldson et al., 2009, Qi et al., 2015, Rutter et al., 2014). Although the pathophysiology behind the phenomenon is not fully understood, different mechanisms have been proposed, one of them includes the release of cement or emboli into the circulation (Donaldson et al., 2009). No bone cement implantation syndrome or emboli were suspected in the present study. An earlier hip fracture study found a statistically significant greater incidence of intraoperative oxygen saturation drops and diagnoses of fat-embolic events when performing cemented compared to uncemented hemiarthroplasty (Yli-Kyyny et al., 2013). Contrary to this finding, another study did not find an association of cemented hemiarthroplasty with intraoperative drop in oxygen saturation or blood pressure compared to uncemented hemiarthroplasty (Khan et al., 2002). Furthermore, a third study could not associate cemented hemiarthroplasty with a greater intraoperative blood pressure drop than when using uncemented hemiarthroplasty (Miyamoto et al., 2017).

TnT and NT-proBNP elevations were equally common for participants with a shorter and longer surgery delay. No prior data exist on the effect of delayed surgery on these biomarker levels. An earlier hip fracture study has reported a surgery delay of more than 48 hours to independently predict postoperative cardiovascular complications (Smeets et al., 2012). The present study also found a greater incidence of cardiovascular events being diagnosed in those 22 participants with a surgery delay exceeding 48 hours, but the difference did not reach statistical significance.

6.6 Complications and length of hospitalization

Participants with TnT elevation had significantly more often pneumonia, and infections in general, than participants with no TnT elevation. Almost a third of participants with a TnT elevation suffered from some infection during hospitalization. The greater incidence of pneumonia amongst patients with postoperative troponin elevation was also observed in an earlier study on orthopaedic surgery consisting mainly of hip fracture patients (Chong et al., 2009). Furthermore, another study on hip fracture patients reported a high co-incidence of pneumonia and other postoperative complications (Lv et al., 2016).

In accordance with the present results, previous studies have found a greater incidence of postoperative cardiac complications in hip fracture patients with perioperative troponin elevation (Ausset et al., 2009, Dawson-Bowling et al., 2008b), and similar results have been reported amongst populations that also included other orthopedic patients (Chong et al., 2009). Two studies on hip fracture patients and one orthopedic study, partly on hip fracture patients, have also addressed the association of perioperative troponin elevation and long-term cardiac events, and both found increased incidence in patients with perioperative troponin elevation during index hospitalization (Ausset et al., 2009, Izhaki et al., 2011, Ausset et al., 2008). Hip fracture patients seem to have a high risk of myocardial infarction for years after the hospitalization (Chiang et al., 2013).

The effect of perioperative troponin elevation on the length of hospitalization has been conflicting in earlier studies (Fisher et al., 2008b, Spurrier et al., 2011, Dawson-Bowling et al., 2008b), while the current study found no significant effect.

6.7 Mortality

6.7.1 Overall prognosis and impact of clinical characteristics

The prognosis after hip fracture surgery was poor. The overall 30-day mortality was 9 %, in accordance with other studies on hip fractures reporting 5 – 12 % mortalities (Izhaki et al., 2011, Oscarsson et al., 2009, Ercin et al., 2017, Khan et al., 2013, Grimes et al., 2002, Moran et al., 2005). No patient characteristic was associated with higher short-term mortality in the present study, while higher age, male gender and higher ASA class were independent predictors of short-term mortality in a previous hip fracture study (Talsnes et al., 2011b). One-year mortality of hip fracture patients has ranged from 20 to 28 % in previous studies (Izhaki et al., 2011, Katsanos et al., 2017, Spurrier et al., 2011). The present study found a 1000-day mortality of 47 %. Atrial fibrillation, dementia and older age were the patient characteristics independently associated with higher long-term mortality in the present study, compared to older age and higher admission creatinine in another hip fracture study (Izhaki et al., 2011).

6.7.2 Prognostic impact of elevated TnT

TnT proved to be a strong and independent predictor of short-term mortality. Only two other studies have studied the independent association of peri- or postoperative

troponin elevation and short-term mortality in hip fracture patients, and the results are in line with the current study (Fisher et al., 2008b, Talsnes et al., 2011b). In addition, two studies have reported a univariate association of peri- or postoperative troponin elevation and short-term mortality (Oscarsson et al., 2009, Dawson-Bowling et al., 2008b). Contrary to these findings, an earlier study on 108 hip fracture patients, although reporting numerically greater 3-month mortality and statistically significantly greater one-year mortality in the 29 patients with perioperative troponin elevation, did not find statistical significance in 30-days or 3-month mortalities in univariate analysis. However, it is possible that the lack of significance results from the small sample size, since only 3 participants died during the 30-day follow up and 10 during the 90-day (Spurrier et al., 2011). The current study was the first to show significant graded association between TnT level and short-term mortality, and that even minor TnT elevation affected the prognosis.

There are no prior reports on the independent association of preoperative troponin elevation and short-term mortality in hip fracture patients. Although there probably were different mechanisms in pre- and postoperative TnT elevations, the current study found a similar prognosis in participants with a TnT elevation at some point preoperatively compared to postoperatively, and both pre- and postoperative TnT elevations were independently associated with a more than three-fold increase in short-term mortality compared to a normal TnT level. However, the prognosis was especially poor in those patients presenting with a TnT elevation on arrival at the hospital and more than a fourth of these participants died during the first 30 days.

In line with three other hip fracture studies, troponin elevation remained an independent predictor of mortality over the long-term (Ausset et al., 2009, Izhaki et al., 2011, Katsanos et al., 2017). The independent predictive value of perioperative TnT elevation remained during the whole 5-year follow-up, with 79 % participants with TnT elevation during index hospitalization dying, compared to 59 % of participants with no TnT elevation. An earlier small study on 33 severely frail orthopedic patients did not find an association between perioperative TnI elevation and 6-month mortality (Chong et al., 2010b).

Furthermore, consistent with an earlier study using admission troponin levels in analyses, preoperative TnT elevation was an independent predictor of long-term mortality after the fracture (Izhaki et al., 2011). Postoperative troponin elevation was not an independent predictor of long-term mortality in the present study. A recent study concludes that isolated postoperative troponin elevation is not an independent predictor of long-term mortality in hip fracture patients, while troponin elevation that is associated with other clinical criteria of myocardial infarction is. However, in that study the treating geriatric unit was aware of the troponin results,

and patients with troponin elevation received treatment which might have improved the prognosis of those with isolated troponin elevation (Vallet et al., 2017). Contrary to these and the present study findings, two earlier studies on hip fracture patients and two partially including hip fracture patients have reported independent association of postoperative troponin elevation and long-term mortality (Ausset et al., 2009, Katsanos et al., 2017, Ausset et al., 2008, Chong et al., 2009).

6.7.3 Prognostic impact of elevated NT-proBNP

There was a graded association between the level of NT-proBNP and both short- and long-term mortality. NT-proBNP elevation was the only independent predictor of 30-day mortality in the present subanalysis, and a NT-proBNP level of 806 ng/l or higher was associated with a nearly 8-fold short-term mortality. Only two other studies have addressed the impact of NT-proBNP on short-term prognosis in hip fracture patients. One of these studies found a preoperative NT-proBNP level exceeding 3984 ng/l to independently predict troponin elevation, myocardial infarction or death within 30 days of surgery in high-risk patients, but no association of NT-proBNP with 3-month mortality was found (Oscarsson et al., 2009). Another study that had excluded patients with renal insufficiency found a preoperative NT-proBNP level exceeding 600 ng/l to independently predict postoperative cardiac complications in hip fracture patients (Ushirozako et al., 2017).

The present study is to our knowledge the only one thus far to assess the long-term effects of perioperative NT-proBNP elevation in hip fracture patients. In the current study, perioperative NT-proBNP was the strongest independent predictor of long-term mortality even after the 5-year follow-ups. Only 15 % of participants in the high NT-proBNP tertile were alive after 5 years compared to 60 % of participants in the low NT-proBNP tertile. In line with the present findings, the predictive value of pre- and postoperative BNP on long-term prognosis of hip fracture patients was later shown in a study (Katsanos et al., 2017). Furthermore, pre- and postoperative NT-proBNP analyses have proven to be useful in predicting the long-term prognosis after other types of orthopaedic surgery (Chong et al., 2010a).

In patients with a perioperative TnT elevation, the prognosis was poor and the NT-proBNP level did not bring additional information. Similarly, a previous study on a limited population of 28 very frail orthopedic patients did not find an association between perioperative NT-proBNP elevation and 6-month mortality (Chong et al., 2010b) thus, supporting the view that NT-proBNP does not provide additional prognostic information in high-risk patient groups. Consequently, some of the predictive value of NT-proBNP on the short-term prognosis may be related to acute

myocardial injury and overlap with the prognostic value of TnT elevation. Perioperative NT-proBNP elevation was, however, an independent predictor of long-term mortality in participants with no TnT elevation.

It is of note that NT-proBNP was superior to the commonly used risk scores in predicting both short- and long-term outcome. Other studies have also shown that perioperative measurement of natriuretic peptide BNP is superior to clinical risk scores in predicting postoperative adverse cardiac events in surgery patients (Villacorta Junior et al., 2010, Vetrugno et al., 2014).

6.7.4 Prognostic impact of ischemic ECG findings and symptoms

New ischemic ECG findings carried no independent prognostic information even when participants with TnT elevation were analyzed separately. The prognosis of the small number of STEMI patients was poor. During hospitalization dyspnea was associated with a higher short-term mortality and hypotension with higher short- and long-term mortality. Intraoperative hypotension for even a period of five minutes has been shown to predict a worse short-term outcome in non-cardiac surgery patients (Monk et al., 2015), while the prognostic value of dyspnea has not been reported before.

6.7.5 Prognosis of participants with an adverse cardiovascular event

Those 28 participants who were diagnosed with a perioperative cardiovascular adverse event had a high mortality, with a third dying within 30 days and three quarters over 1000 days. In line with this finding, an earlier study on orthopedic patients found postoperative cardiac events to independently predict 1-year mortality (Chong et al., 2009).

There were 12 participants who were diagnosed with and treated for a perioperative myocardial infarction. These participants probably represented the most severe cases of myocardial infarction and death shortly after diagnosis was common in these participants. The poor long-term prognosis of perioperative myocardial infarction in hip fracture and other orthopedic patients has been acknowledged (Vallet et al., 2017, Chong et al., 2009, Gupta et al., 2012, Huddleston et al., 2012). However, in line with an earlier study, the current study did not find differences between the mortality of participants with a diagnosed myocardial infarction and those with troponin elevation but no diagnosis of myocardial infarction (Huddleston et al., 2012); this is contrary to the findings of another study (Vallet et al., 2017).

Similarly, there were 24 participants with TnT elevation who underwent consultation, and these had a higher short-term mortality than participants with TnT elevation and no consultation. The participants who underwent consultation were probably the ones who were managing the worst, and the higher short-term mortality in these participants is not surprising. However, the long-term mortalities for these participants did not differ. It is possible that the treatments given might have improved the prognosis of these participants. This hypothesis is supported by the findings of a prior study that performed routine preoperative troponin measurements and ECG registrations in hip fracture patients and treated all patients with findings suggestive of myocardial infarction with acetylsalicylic acid and beta blocker; this study did not find any differences in the short- or long-term outcome of those hip fracture patients treated for NSTEMI compared to those with no troponin elevation (Rostagno et al., 2015).

6.7.6 Traumatological aspects

In line with other studies, the fracture type and surgery method did not significantly affect the mortality in hip fracture patients (Panula et al., 2011, Fisher et al., 2012, Ercin et al., 2017, Talsnes et al., 2013, Figved et al., 2009, Deangelis et al., 2012, Lu et al., 2017, Khan et al., 2013).

In the present study, participants with a surgery delay exceeding 48 hours had a 30-day mortality of 14 % compared to 8 % for those with a shorter surgery delay, and a 1000-day mortality of 59 % vs 45 %, but the difference did not reach statistical significance. It should be noted, however, that only 22 participants had a surgery delay exceeding 48 hours leading to a possible bias. Other hip fracture studies have found patients with a surgery delay exceeding 24 or 48 hours to have higher short-term mortality (Grimes et al., 2002, Bottle and Aylin, 2006, Smeets et al., 2012, Orosz et al., 2004, Khan et al., 2013), but patients with a longer surgery-delay tend to have more comorbidities that might cause a delay in the surgery (Grimes et al., 2002, Bottle and Aylin, 2006, Orosz et al., 2004). An independent association of surgery delay with mortality has been demonstrated by few studies (Smeets et al., 2012, Khan et al., 2013, Bottle and Aylin, 2006).

It is noteworthy that while the surgery methods did not differ significantly concerning cardiovascular complications or mortality, 30 % of participants treated with cannulated screws were re-operated during the follow-up. In addition, another study has demonstrated the greater need for reoperations in those hip fracture patients treated with cannulated screws compared to hemiarthroplasty (Lu et al., 2017).

6.8 Limitations

The present study is limited by the relatively small number of participants from a single center. This limitation is evident when comparing smaller subgroups, such as participants with different operative methods or surgery delays.

Since the exact timing of the injury was unknown in most cases, the surgery delay was counted from hospital admission. This brings a potential inaccuracy since some participants were brought to the hospital immediately after the injury while some were admitted hours or even days later. Decisions concerning the operative method and timing of the surgery were at the discretion of the treating traumatologists. Spinal anaesthesia with isobaric bupivacaine was the preferred anaesthetic method. However, there may have been exceptions to this, and the anaesthetic method was not taken into consideration in the analyses.

This study measured TnT with a conventional sensitivity assay that was used at the time of enrollment. Later, higher sensitivity troponin assays were introduced and the measurement of TnT with such high-sensitive assays would have led to the detection of lower concentrations of TnT and increased the number of participants with a TnT elevation.

Originally, the idea was to obtain NT-proBNP measurements from all participants preoperatively. However, obtaining study approval from participants and next of kin prior to measurements and the lack of measurements on public holidays and weekends led to the inclusion of all participants with at least one measurement perioperatively. Since postoperative measurements are higher than preoperative measurements, the actual levels are not directly comparable and should be viewed with caution.

Data on smoking status was missing in most participants and it could not be included in the analyses.

Patients with renal insufficiency were not excluded. Data on weight and height were missing in most participants and the glomerular filtration rate could not be calculated using the Cockcroft-gault formula. After data collection, the CKD-EPI formula was introduced and using this in the analyses could have allowed a more precise estimation of the renal function. However, creatinine was only measured on arrival at the hospital. Ideally, the glomerular filtration rate would have been estimated at every blood sampling. The renal function is known to affect the level of NT-proBNP and participants in the high NT-proBNP tertile had a significantly higher admission creatinine level than participants in the low and intermediate tertiles. However, the independent predictive value of NT-proBNP on 30- and 1000-

day mortalities was shown in the Cox regression analyses where a history of renal insufficiency was one covariate.

Since the measurements were made for study purposes only, and the clinicians were unaware of these results unless clinical suspicion of a perioperative cardiovascular event arose, it is not possible to evaluate how pharmacological or invasive treatment might have impacted the prognosis.

6.9 Clinical implications

Currently, there are no separate guidelines for diagnosis of myocardial infarction in patients undergoing surgery, most likely due to the paucity of data on the subject. Acknowledging the differences between myocardial infarctions in conventional and perioperative settings and by creating separate diagnostic criteria might improve the diagnostics. It should be noted that hypotension and shortness of breath, together with disorientation, were the most common symptoms of perioperative myocardial infarction and, further considering their prognostic value, observation of these symptoms in hip fracture patients should be viewed with caution. Other studies have demonstrated that more postoperative complications are clinically diagnosed when a geriatrician is involved in the treatment of hip fracture patients (Wagner et al., 2012, Frenkel Rutenberg et al., 2017).

Currently, routine pre-operative ECG recording is also advised, in addition to high-cardiac risk patients, for all patients aged over 65 years who are about to attend intermediate or high-risk surgery (Kristensen et al., 2014). These criteria apply to most hip fracture patients. Combining the poor sensitivity and predictive value of perioperative ST segment changes in hip fracture patients contradicts the need fo routine ECG registrations for screening of ischemia in hip fracture patients. However, in patients with a detected troponin elevation the ECG findings could have an impact on the treatment choices and thus be useful.

According to current ESC guidelines, routine preoperative measurement of troponin may be considered in high-risk patients, and BNP or NT-proBNP is recommended in all patients with prior heart failure (Kristensen et al., 2014). However, the results of the present study show that perioperative cardiovascular events are not only a problem of the aged and those with a cardiac history. Since patients with perioperative myocardial infarction are often asymptomatic, routine testing of cardiac biomarker in surgery patients has been suggested earlier (Devereaux et al., 2011). The findings of the current study support routine troponin and NT-proBNP measurements in all hip fracture patients. In Turku University Hospital, the current price for TnT analysis is 2,50 euros and for NT-proBNP analysis 20 euros. Further

studies with larger populations and repeated biomarker measurements are needed to determine the ideal moment for testing to benefit the most. Special attention should be given to those patients who already have a troponin elevation on admission to the hospital, since the prognosis of these patients was poor.

There is an obvious need for more active treatment of patients with troponin or NT-proBNP elevation. Consultation with a cardiologist should be done promptly so that evidence-based treatment could be started. Future research is needed to compare the treatment methods of hip fracture patients with TnT or NT-proBNP elevation.

Of interest is the fact that the current study also found other needs for improvement in the management of hip fracture patients. Only one fourth of the participants were known to have been using vitamin D supplementation prior to injury, and one third were prescribed vitamin D supplementation at discharge from the traumatology ward. The cause of the injury was undocumented in two thirds of the participants, leading to the lack of a possible intervention in the underlying causes. These underlying factors could increase the number of hip fractures, and thus cardiovascular complications, in the future.

The present study emphasizes the paucity of symptoms, the need for better diagnostics, and the prognostic impact of elevated TnT and NT-proBNP in hip fracture patients.

7 CONCLUSIONS

The data of the present study lead to the following conclusions:

1. Perioperative TnT and NT-proBNP level elevation are common in hip fracture patients. Higher age, prior revascularization and heart failure were independent predictors of TnT elevation, while higher age, renal insufficiency and atrial fibrillation were independent predictors of a higher NT-proBNP level.

2. Perioperative new ischemic ECG changes are common in hip fracture patients.

3. Since symptoms of cardiovascular origin are rare, the myocardial injury often remains unrecognized in hip fracture patients.

4. Fracture characteristics play a minor role in preoperative myocardial injury, and the operative method or surgery delay does not have a major impact on TnT or NT-proBNP elevations or prognosis. Therefore, the operative method may be chosen by the treating clinician based on other criteria.

5. TnT and NT-proBNP elevation are strong independent predictors of short-term and long-term mortality in hip fracture patients, superior to the commonly used clinical risk scores.

6. Routine measurement of TnT and NT-proBNP should be considered in all hip fracture patients to enable starting evidence-based cardiac treatments.

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