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– From Marathon Runners to Atrial Fibrillation

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The originality of this publication has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

ISBN 978-951-29-8828-0 (PRINT)
ISBN 978-951-29-8829-7 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama, Turku, Finland 2022

To my family

UNIVERSITY OF TURKU
Faculty of Medicine
Department of Cardiology and Cardiovascular Medicine
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TUOMAS PAANA: Clinical Challenges of Cardiac Troponin Testing – From Marathon Runners to Atrial Fibrillation
Doctoral Dissertation, 97 pp.
Doctoral Programme in Clinical Research
March 2022

ABSTRACT

Cardiac troponin (cTn) testing is the cornerstone of diagnosis of myocardial infarction. Contemporary assays detect circulating levels of cTn even in healthy populations. Increasing sensitivity has led to an upsurge in the number of patients with myocardial injury not related to acute coronary syndrome. The aim of this dissertation is to evaluate the prevalence of cTn elevation in healthy marathon runners and its association with coronary artery calcification, vulnerable plaques, and exercise-related muscle injury. Furthermore, the aim is to describe the prevalence, etiology, and predictors of minor cTn elevation in patients with atrial fibrillation (AF) presenting to the emergency department (ED), and finally to evaluate the prognostic significance of elevated cTn in these patients. **Methods**: The population of study I consisted of 43 male recreational runners participating in the 2018 Paavo Nurmi marathon. Studies II and III describe the results of the TROPO-AF study, an observational, retrospective cohort study analyzing patients with AF (n = 2911) at ED. **Results**: In study I, elevated cTn levels were found in 95% of the marathon runners after the race. Considerable increases in markers of skeletal muscle injury were seen but without association to markers of myocardial injury. Coronary artery calcium or markers of plaque vulnerability did not correlate with cTn levels. In studies II and III, over 70% of the patients had cTn elevation, but only 4.5% were considered to have acute coronary syndrome. The strongest predictors of cTn elevation were age over 75 years, renal insufficiency, and infections. Even minor cTn elevation in these patients was associated with poor prognosis. **Conclusions**: Contemporary high-sensitivity (hs) assays regularly detect elevated cTn levels after strenuous exercise and in patients with AF during ED visits. cTn elevations after physical exercise are usually benign in subjects without apparent cardiovascular disease. In patients with AF, cTn elevations are typically associated with comorbidities or acute illness and reflect poor short- and long-term prognosis.

KEYWORDS: Cardiac troponin, exercise, atrial fibrillation, mortality

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kardiologia ja kardiovaskulaarilääketiede
Sydänkeskus, Turun yliopistollinen keskussairaala
TUOMAS PAANA: Sydänperäisen troponiinin käytön kliinisiä haasteita – maratonjuoksijoista eteisvärinäpotilaisiin
Väitöskirja, 97 s.
Turun kliininen tohtoriohjelma
Maaliskuu 2022

TIIVISTELMÄ

Sydänperäisen troponiinin (cTn) määritys on sydäninfarktin diagnostiikan kulmakivi. Nykyaikaiset testit pystyvät määrittämään myös terveiden ihmisten cTn-tasoja. Testien herkkyyden lisääntymisen myötä sydäninfarktiin liittymättömiä sydänlihasvaurioita tavataan aiempaa useammin. Väitöskirjan tarkoituksena oli selvittää cTn-nousun yleisyyttä terveillä maratonjuoksijoilla ja sen yhteyttä sepelvaltimoiden kalkkeutumiseen, hauraisiin valtimoplakkeihin ja luurankolihasten kuormitukseen. Lisäksi pyrittiin kuvaamaan cTn-nousun esiintyvyyttä, etiologiaa ja taustatekijöitä eteisvärinäpotilailla ja cTn-nousun ennustevaikutusta tässä potilasryhmässä. **Metodit:** Osatyössä I tutkittiin 43 vapaaehtoista vuoden 2018 Paavo Nurmi maratonille osallistuvaa juoksijaa. Osatöissä II ja III kuvataan havainnoivan, taannehtivan kohorttitutkimuksen (TROPO-AF) tuloksia ensiapuun joutuneilla eteisvärinäpotilailla (n = 2911). **Tulokset:** Osatyössä I cTn-nousuja tavattiin 95 %:lla juoksijoista. Lihaskuormituksen merkkiaineet nousivat huomattavasti, mutta yhteyttä sydänlihasvaurion merkkeihin ei havaittu. Sepelvaltimoiden kalkilla tai valtimoplakkien repeämisherkkyydellä ei ollut havaittavaa yhteyttä cTn-arvoihin. Osatöissä II ja III yli 70 %:lla cTn oli kohonnut, mutta vain 4,5 %:lla kyseessä oli akuutti sepelvaltimotapahtuma. Voimakkaimmat ennustetekijät cTn-nousulle olivat yli 75 vuoden ikä, munuaisten vajaatoiminta sekä infektiot. Vähäisetkin cTn-nousut heikensivät eteisvärinäpotilaan ennustetta. **Päätelmät:** Nykyaikaisilla herkillä testeillä havaitaan usein cTn-nousuja voimakkaan fyysisen kuormituksen jälkeen kuten myös eteisvärinäpotilailla. Fyysisen kuormituksen aiheuttama nousu vaikuttaa hyvänlaatuiselta muutoin terveillä tutkittavilla. Eteisvärinäpotilailla cTn-nousu liittyy usein perussairauksiin tai äkilliseen sairastumiseen, ja siihen liittyy merkittävästi heikentynyt ennuste.

AVAINSANAT: Sydänperäinen troponiini, fyysinen kuormitus, eteisvärinä, kuolleisuus

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Abbreviations

ACS	Acute coronary syndrome
AF	Atrial fibrillation
AST	Aspartate aminotransferase
AMI	Acute myocardial infarction
BMI	Body mass index
CAC	Coronary artery calcium
CAD	Coronary artery disease
CHA2DS2-VASc	Congestive heart failure, Hypertension, Age ≥75 (doubled); Diabetes mellitus, prior stroke, transient ischemic attack or thromboembolism (doubled); Vascular disease, Age 65–74, Sex category female
CK	Creatine kinase
CKD	Chronic kidney disease
cTn	Cardiac troponin
CVD	Cardiovascular disease
ECG	Electrocardiogram
ED	Emergency department
hs	High-sensitivity test, defined as the ability to detect cTn concentrations with coefficient of variation <10% at or below the 99th percentile UNL and measurable in >50% of normal healthy individuals
MI	Myocardial infarction
NSTEMI	Non-ST elevation myocardial infarction
NT-proBNP	N-terminal pro b-type natriuretic peptide
PAPP-A	Pregnancy associated plasma protein A
SCD	Sudden cardiac death
skTnI	Skeletal muscle troponin I
STEMI	ST-elevation myocardial infarction
URL	Upper reference limit

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Paana T, Jaakkola S, Bamberg K, Saraste A, Tuunainen E, Wittfooth S, Kallio P, Heinonen OJ, Knuuti J, Pettersson K, Airaksinen KEJ. Cardiac troponin elevations in marathon runners. Role of coronary atherosclerosis and skeletal muscle injury. The MaraCat Study. Int J Cardiol 2019 Nov15; 295:25–28.

II Jaakkola S, Paana T, Nuotio I, Kiviniemi TO, Pouru JP, Porela P, Biancari F, Airaksinen KEJ. Etiology of Minor Troponin Elevations in Patients with Atrial Fibrillation at Emergency Department – Tropo-AF Study. J Clin Med 2019 Nov 14;8(11):1963.

III Paana T, Jaakkola S, Biancari F, Nuotio I, Vasankari T, Kiviniemi TO, Airaksinen KEJ. Minor troponin T elevation and mortality in patients with atrial fibrillation presenting to the emergency department. Eur J Clin Invest. 2021 Nov; 51(11):e13590.

1 Introduction

Cardiac troponin (cTn) is a structural protein found in the myocardial cells and plays a crucial role in muscle contraction (Sharma, Jackson & Makan, 2004). cTn are highly sensitive, specific biomarkers of cardiac injury and as such a key element in the diagnosis of acute coronary syndromes (Thygesen et al., 2018). In the context of acute coronary syndrome (ACS), troponin values increase shortly after the onset of ischemia and stay elevated for several days. Meta-analysis has demonstrated that elevated cTn values predict increased cardiovascular and all-cause mortality in the general population (Van Der Linden et al., 2016).

Elevated cTn levels are often encountered in conditions other than ACS, such as pulmonary embolism, cerebrovascular accidents, kidney impairment, heart failure, infections, arrhythmias, and other acute noncardiac critical illnesses (Tanindi & Cemri, 2011). In addition, several studies have demonstrated elevated levels of cTn after strenuous exercise (Shave et al., 2010; Gresslien & Agewall, 2016). With the exception of abnormally high or prolonged troponin elevation, this is mostly thought to be of a benign nature (Aengevaeren et al., 2019).

The health benefits of physical exercise have been assumed as a given for centuries and are associated with favorable lipid profile, reduced inflammation, and insulin resistance. On the other hand, strenuous exercise has been linked to transient risk of myocardial infarction (MI) and sudden cardiac death (SCD) (Kim et al., 2012) as well as increased coronary artery calcium (CAC) (Radford et al., 2018). CAC detected through computed tomography is considered a surrogate marker of coronary artery disease (CAD) and a predictor of cardiovascular events (Cardarelli, Hall & Rankin, 2017). High cardiorespiratory fitness has been linked to increased CAC, but the risk of cardiovascular events is attenuated by improved cardiorespiratory fitness levels (Radford et al., 2018), perhaps through increasing plaque density, which is known to be inversely related to cardiovascular risk (Criqui et al., 2014).

As mentioned, a well-known cause of troponin elevation is cardiac arrhythmia. Atrial fibrillation (AF) is the most common cardiac arrhythmia in the adult population, with increasing incidence. Of AF patients, 10–40% are hospitalized annually (Steinberg et al., 2014). cTn is increasingly measured as part of routine laboratory testing in emergency departments (ED) (Makam & Nguyen, 2015), and

elevated high-sensitivity cTn is a common finding in AF patients in this setting (Hijazi et al., 2014). The etiology of troponin elevations in these patients is insufficiently understood, precipitating an increase in additional laboratory testing, imaging studies, and hospitalizations. Most of these elevated values are classified as myocardial injury, as ACS is a rare condition among these patients (Parwani & Boldt, 2014) and troponin elevations are generally related to traditional comorbidities or acute illness. Even in the absence of ACS, the association between elevated cTn and mortality is robust (van den Bos et al., 2011; Stoyanov et al., 2018). cTn levels are likewise independently associated with increased risk of stroke, cardiac death, and major bleeding, elevating AF patients' risk stratification beyond their CHA2DS2-VASc score (Hijazi et al., 2014).

The main objectives of this dissertation are to examine the prevalence of troponin elevation in diagnostically challenging and clinically relevant scenarios. In the first study, we aimed to assess the prevalence of cTn elevations in marathon runners and whether such cTn elevation is associated with CAC, plaque vulnerability, or skeletal muscle injury. The second and third studies were conducted to evaluate the etiology and prognostic significance of minor troponin elevations in AF patients presenting to the ED.

2 Review of the Literature

2.1 Biomarkers of cardiac injury or infarction

2.1.1 The history of cardiac biomarkers

At the moment, cardiac troponins are the only generally accepted biomarkers of myocardial injury or myocardial infarction (MI). Historically, the first biochemical marker for diagnosing MI was aspartate aminotransferase (AST), in 1954 (LaDue, Wróblewski & Karmen, 1954), followed by lactate dehydrogenase (LD) in 1956 (Wróblewski, Ruegsegger & LaDue, 1956), creatine kinase (CK) enzyme activity in 1960 (Dreyfus et al., 1960), and creatine kinase MB activity (CK-MB) in 1972 (Roe et al., 1972). These biomarkers were included in 1979 WHO criteria for acute myocardial infarction (AMI) diagnosis (Rapaport, Bernard & Corday, 1979). The myoglobin assay for detection of AMI was introduced in 1987 (Gibler et al., 1987). A method of determining CK-MB mass was developed in 1985, and five years later rapid immunoassays were developed (Brandt et al., 1990). Despite the advantages these biomarkers provided in the diagnosis of acute myocardial injury, they were lacking either sensitivity or specificity in comparison to cTn (Goodman et al., 2006).

2.1.2 Cardiac troponin structure and physiology

The cardiac myocyte muscle cell is composed of myofibrils containing myofilaments. The basic contractile units of myocytes are sarcomeres. These are composed of thick filaments (myosin) and thin filaments. Structurally, thin filaments consist of actin, tropomyosin, and troponin complex. This complex is made of three components: troponin-T, troponin-C, and troponin-I.

Interaction between thick and thin filaments leads to sarcomere shortening and consequential myocyte contraction. This sliding filament theory was described in 1954 in *Nature* (Huxley & Hanson, 1954; Huxley & Niedergerke, 1954). In the 1960s, Professor Setsuro Ebashi published series of articles describing the importance of ca2+ regulation in muscle contraction and the existence of a third factor, in addition to actin and myosin, responsible for the regulation of the process. This protein was called troponin (Ebashi, 1961; Ebashi & Kodama, 1965). A few

years later, in 1971, three subunits of troponin were discovered (Greaser and Gergely, 1971) and named after their distinctive properties: TnC, with ca2+ binding capacity; TnI, responsible for inhibition of ATPase activity; and TnT, for binding tropomyosin.

The cTnI and cTnT are specifically expressed in the cardiac muscle and are hence suitable for diagnosing myocardial damage, while cTnC is also expressed in slow skeletal muscle, making it an unsuitable biomarker for cardiac injury (Parmacek & Solaro, 2004). Most of the cTn is bound to myofilaments, but there is a free portion in the cytosol that is initially released during cardiac injury, followed by the release of cTn from deteriorating myofilaments (Antman, 2002). This cytosolic pool contains approximately 3% TnI (Adams et al., 1994) and 6% TnT (Katus et al., 1991). After myocardial injury, cTn is measurable 3–4 hours later, and elevation persists for 10–14 days.

2.1.3 High-sensitivity cardiac troponin test

The first cTnI assays were developed in 1987 (Cummins, Auckland & Cummins, 1987), and cTnT assays a few years later (Katus et al., 1989). The first-generation cTnT assays had a problem with cross-reactivity in patients with severe skeletal muscle damage, which was overcome in 1997 through the second generation of assays (Müller-Bardorff et al., 1997). The bovine cTnT used for calibration in the second-generation assays was replaced with human recombinant cTnT in 1999, resulting in the third generation of assays (Hallermayer, Klenner & Vogel, 1999). The fourth-generation assay developed in 2007 used FAB (fragment-antigen binding) of two cTnT-specific mouse monoclonal antibodies in a sandwich format (Hermsen et al., 2007).

The contemporary high-sensitivity test is a fifth-generation assay. Developed from the fourth-generation assay, it was introduced in 2010. The detection antibody was modified to minimize interference by heterophilic antibodies. Numerous manufacturers offer high-sensitivity cTnI tests, but at the moment high-sensitivity cTnT assays are available exclusively from Roche Diagnostics due to patent issues. It would be logical to expect cTnI and cTnT to be released from myocytes in equal amounts, but the measurable levels demonstrate poor correlation, possibly due to variations in stability during circulation, differences in effect of kidney function on clearance, or varying amounts of the free form of cTn in the cytoplasm (Wießner et al., 2008).

The term “high-sensitivity” reflects the assay’s characteristics. To be called high-sensitivity (hs), tests are required to measure concentrations below the 99th percentile and over the level of detection in over 50% and ideally >95% in healthy individuals. In addition, the total imprecision at the 99th percentile should be ≤10%. The results

of high-sensitivity tests should be reported as nanograms per liter. The IFCC Task Force on Clinical Applications of Cardiac Bio-Markers has proposed recommendations for determining 99th percentiles. The number of apparently healthy individuals of diverse racial and ethnic background should be minimum 300 for both sexes. The median age should be 60–65 years to correctly present cardiac patients, and the inclusion criteria should be based on medical history, medications taken, natriuretic peptide concentration, and estimated glomerular filtration rate (Apple et al., 2017). To date, no study has compared contemporary high-sensitivity tests among the same reference population, and there is a clear need for direct comparison in contemporary tests and for cTn test standardization. In patients with chronic kidney disease (CKD), decreased renal clearance has been hypothesized as the underlying mechanism behind elevated cTn levels. The data is conflicting, and elevated cTn levels most likely reflect both increased cardiac production of cTn and reduced renal clearance (Parikh et al., 2015).

It is also known that older age and male sex increase cTn values in healthy subjects (McKie et al., 2013) as well as patients with ACS (Widera et al., 2019), but implementing different cut-off points for these patient subgroups has not been shown to be clinically significant (Motiwala et al., 2014; Widera et al., 2019). In 2020, High-STEACS investigators found that implementing high-sensitivity cTn tests in clinical practice increased diagnosis of type 1 MI by 11%, type 2 MI by 22%, and myocardial injury by approximately 40%, respectively. In patients with type 1 MI, this led to a slight modification of treatment strategies, such as intensified antiplatelet therapy and coronary revascularization, as opposed to in patients with type 2 MI or myocardial injury. Using high-sensitivity tests did not improve the outcomes of patients in any group (Chapman et al., 2020). It appears to be of no consequence whether a high-sensitivity cTnI or cTnT test is used with AMI patients, but the diagnostic performance of cTnI might be slightly better in early presenters (3h), perhaps due to an earlier release from cardiomyocytes (Gimenez et al., 2014). The high sensitivity of contemporary cTn assays provide the possibility to assess circadian variability in cTn levels, with peak concentrations measured in the morning. Although this finding might challenge European guidelines for a rapid rule-in/rule-out algorithm, where very low (<5 ng/L) hs-TnT concentration can be used to rule-out AMI, no studies have confirmed the clinical significance of this finding (Zaninotto et al.,2020; Fournier et al., 2017; Klinkenberg et al., 2016).

The 99th percentile upper reference (URL) limit of Roche hs-TnT assay used at the Turku University Hospital is 14 ng/L. This cut-off value was initially validated in 2010 (Giannitsis et al., 2009) and confirmed two years later (Apple, Ler & Murakami, 2012), although the URL has been determined to be sex-specific and naturally dependent on the heterogeneity of reference population (14.5–16 ng/L for men and 10.5–12 ng/L for women) (Giannitsis et al., 2009; Kimenai et al., 2016). In

selected patients, age has been shown to be a strong independent predictor of cTn elevation, and up to 43% of the patients >75 years without known cardiovascular disease (CVD) present with an hs-TnT over URL (Menacer et al., 2013). This finding was confirmed by Webb et al., who concluded age over 70 years to be the strongest independent predictor of elevated cTn in this patient cohort (OR32.1;95%CI13.5–76.3, p <0.001).

2.1.4 Prognostic significance of elevated high-sensitivity cardiac troponin

Even in a healthy population, measurable (over level of detection, [LOD]) and elevated high-sensitivity cTnT have been shown to be associated with increased mortality, coronary heart disease, and heart failure (HF) (Saunders et al., 2011). As expected, association between elevated baseline levels and increased mortality is also present in patients with pre-existing CAD (Reiter et al., 2012) and diabetics (Everett et al., 2011).

In over 90% of patients with chronic HF, hs-TnT is detectable, as opposed to approximately 10% through older generation assays, and increasing hs-TnT deciles are associated with increased mortality (Latini et al., 2007).
In patients with pulmonary artery hypertension, 27.3% have hs-TnT values over the 99th percentile (Filusch et al., 2010), and the respective figure for patients with pulmonary embolism is 64% (Lankeit et al., 2010). In both patient groups, elevated hs-TnT is associated with worsened prognosis.

In patients with CKD, hs-TnT levels are elevated even in those without apparent CAD (Dubin et al., 2013). In patients with renal replacement therapy, hs-TnT is elevated in practically all patients (Jacobs et al., 2009).

Among fifth-generation high-sensitivity tests, TnT demonstrates a more robust association with mortality in non-cardiac etiologies in contrast to TnI, which appears to be more sensitive to CAD (Tveit et al., 2020). Even when taken outside conventional clinical indications, over half of patients in critical care presented with elevated levels of high-sensitivity troponin, and it was found to be an independent predictor of mortality (Hinton et al., 2021). In this setting, the cTn elevation illustrates comorbidities and severe illnesses in the patient cohort, and thus the underlying cause and possible impact on treatment remains elusive, as opposed to in patients with MI.

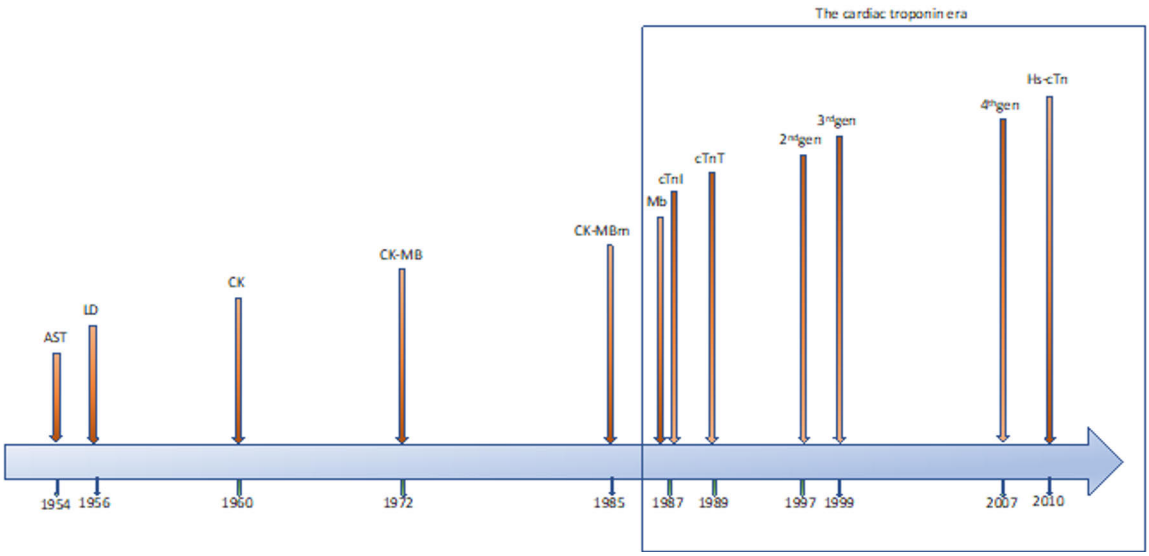

Figure 1. Timeline of development of cardiac biomarkers. AST, aspartate aminotransferase; LD, lactate dehydrogenase; CK, creatine kinase; CK-MB, creatine kinase MB activity; CK-MBm, creatine kinase MB mass; Mb, myoglobin; cTnI, cardiac troponin I; cTnT, cardiac troponin T; 2nd–4th gen, previous generation cTn tests; hs-cTn, contemporary 5th generation high-sensitivity troponin.

2.2 Myocardial injury and infarction

2.2.1 Definition of myocardial injury and infarction

CVDs are among the most widespread global diseases and responsible for almost 18 million deaths worldwide in 2017 (Kaptoge et al., 2019). The vast majority of these deaths are attributable to coronary heart disease and stroke. CVD has been and still is the most common cause of death in Finland, despite a decline from 41% to 34% over the last decade. Of CVDs, coronary artery disease was the most common cause of death, responsible for almost 9000 casualties in Finland in 2019 (Tilastokeskus - Kuolemansyyt 2019).

Coronary atherosclerosis is long-lasting, progressive inflammatory disease caused by and accelerated by a multiplicity of non-modifiable and modifiable risk factors, ranging from genetic disposition to smoking. Clinical manifestations of coronary atherosclerosis vary from stable angina to ACS, HF, and even SCD. At the core of this process is endothelial activation leading to an imbalance between injury and repair. This imbalance may eventually lead to atherosclerotic plaque formation and MI, precipitated by vulnerable plaque erosion or rupture and subsequent thrombosis (Ross & Glomset, 1973; Ross, 1986). This formation of atheroma varies in its structure and composition and includes both reversible and irreversible phases

(Stary et al., 1995). Plaque rupture is defined as a structural defect in the fibrous cap of the atherosclerotic plaque. This mechanism is thought to be the main cause of coronary thrombosis irrespective of clinical presentation. In the 1990s, the term *plaque erosion* was introduced to describe thrombosis without plaque rupture: the lesions at the eroded sites lack endothelium, and the eroded sites indicate signs of inflammation (Falk et al., 2013). Regardless of the actual mechanism, the principal adverse sequela of this process is MI.

In 2018, the European Society of Cardiology, the American College of Cardiology, the American Heart Association, and the World Heart Federation published the Fourth Universal Definition of Myocardial Infarction (Thygesen et al., 2018). In this paper, they defined the term *myocardial injury*, which presents as elevated cTn values with at least one value above the 99th percentile upper reference limit (URL), while *myocardial infarction* should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia, detection of a rise and/or fall in cTn values with at least one value above the 99th percentile URL, and symptoms of myocardial ischemia combined with electrocardiogram (ECG) abnormalities or imaging findings suggestive of ischemic process. At the moment, this consensus document classifies five subcategories of MI, described in detail later.

2.2.2 Diagnosing myocardial injury and infarction

According to Thygesen et al, myocardial injury is defined as an elevated cTn value above the 99th percentile URL. This elevation in troponin is considered acute if a rise or fall in troponin is detected (Thygesen et al., 2010). When baseline levels are markedly elevated, a 20% increase is considered diagnostic, but for hs-TnT values below or close to URL, a relative increase of 50% or absolute increase of 7 ng/L suggests dynamic cTn change (Morrow et al., 2007; Mueller et al., 2011). The latest European Society of Cardiology guidelines advocate the use of a 0 h/1 h algorithm instead of the previously recommended 0 h/3 h (Collet et al., 2021). The efficacy of applying the ESC 0 h/1 h algorithm has been confirmed in multiple studies (Stoyanov et al., 2020; Chapman et al., 2019; Chew et al., 2019). It is notable that the cut-off values used are assay specific. Cardiac troponin I and T are the preferred biomarkers, and high-sensitivity assays are recommended.

As a stand-alone finding, elevated cTn and, thus, myocardial injury is not specific to any cause and can be related to myocardial ischemia caused by atherosclerotic plaque rupture/erosion, ischemia because of oxygen supply/demand mismatch, or various cardiac or systemic conditions. When elevated cTn is detected in association with signs and/or symptoms of clinical myocardial ischemia, MI can be diagnosed. The clinical symptoms of MI propose a significant clinical challenge. Typically, the patient experiences chest pain or epigastric discomfort or occasionally

dyspnea. The pain or discomfort may be difficult to locate and usually is not affected by body movements or positional changes. Sometimes the first manifestation of MI is cardiac arrest or life-threatening arrhythmia.

ECGs play a crucial role in diagnosing MI. Patients with new ST segment elevation in 2 contiguous leads or a new bundle branch block are classified as suffering from ST elevation myocardial infarction (STEMI) and patients without ST segment elevation either as NSTEMI (non-ST elevation myocardial infarction) or unstable angina. The Fourth Universal Definition of Myocardial Infarction further classifies MI into five categories based on pathological, clinical, and prognostic differences. Type 1 MI is caused by coronary artery thrombosis following plaque rupture or erosion. Type 2 MI is caused by a mismatch between oxygen supply and demand unrelated to coronary thrombosis. Type 2 MI is often difficult to distinguish from myocardial injury, but diagnosis of type 2 MI requires signs or symptoms of myocardial ischemia. To make things even more complex, type 2 MI and myocardial injury can coexist. Type 3 MI refers to a patient manifesting a typical MI presentation, after which cardiac death occurs while biomarker evidence of MI is lacking. Type 4 and 5 MI are associated with coronary procedures: type 4a specifically with percutaneous coronary intervention, type 4b with stent or scaffold thrombosis, 4c with restenosis, and type 5 with coronary artery bypass grafting. In type 4 MI, cTn values are expected to rise to at least 5 times the URL, and in type 5 MI to at least 10 times the URL, with new ischemic ECG changes, development of pathological Q waves, imaging evidence of loss of viable myocardium or ventricular wall motion abnormality, or angiographic finding suggestive of flow-limiting occlusion.

2.3 Non-ACS causes of cardiac troponin elevation

2.3.1 Physical exercise

High levels of physical exercise have been linked to increased coronary calcification (Jafar et al., 2019), and although contradictory data has also been published (Aengevaeren et al., 2019), this phenomenon has mostly been considered benign (Defina et al., 2019). An increase in SCD rates during or after physical exercise has been described, but the absolute risk is extremely low (1 death per 1.42 million hours of vigorous exercise) and decreases with increasing baseline physical activity (Albert et al., 2000). SCD in younger individuals are thought to be the result of congenital or inherited cardiac diseases, such as hypertrophic or right ventricular cardiomyopathy (Maron et al., 2009; Corrado et al., 2003).

In older individuals, SCD is mostly caused by CAD. Plaque rupture is caused by increased shear forces and increased bending and flexing of epicardial coronary

arteries (Thompson et al., 2007). Exercise has been found to affect left ventricular ejection fraction. This reduction is usually small, and improvement to pre-exercise levels are generally seen within 48 hours post- exercise (Middleton et al., 2006; McGavock et al., 2002). The thinner wall and greater wall stress during exercise has an even bigger impact on right ventricular function (La Gerche et al., 2011). A reduction of left ventricular diastolic function has been observed in a meta-analysis (Middleton et al., 2006). There is no evidence that this transient change in ventricular function is of clinical significance.

Minor myocardial injury observed during physical training is usually considered reversible and followed by myocyte repair and possibly hypertrophy. However, it has been hypothesized that myocyte injury might cause scarring and fibrotic replacement (Rowe, 1992). Some studies have found myocardial fibrosis in endurance athletics, but the findings are contradictory (Eijsvogels et al., 2016). Increased parasympathetic tone and left atrial enlargement are thought to be responsible for increased incidence of AF in endurance athletes. The findings suggests a U-shaped relationship, as light-to-moderate exercise is associated with lower incidence of new-onset AF (Mozaffarian et al., 2008). A meta-analysis suggests up to 5-fold risk of AF in endurance athletes (Abdulla & Nielsen, 2009). Elevated cTn is often encountered after intense physical exercise, proposing a major clinical challenge in the event of cardiac symptoms. Exercise intensity and duration specifically have been linked to elevated cTn, with cTn peaking at approximately 3 hours after exercise (Gresslien & Agewall, 2016; Marshall et al., 2020). In a North Sea Race Endurance Exercise Study (NEEDED) published in 2013, Kleiven et al. established that baseline systolic blood pressure and exercise duration predicted elevated cTn (Kleiven et al., 2019), and a 2020 analysis from the same study indicated duration of heart rate >150bpm is a significant predictor of cTn (Bjørkavoll- Bergseth et al., 2020). In most cases, this elevation can be considered clinically nonsignificant, but prolonged or unexpectedly high cTn elevation after exercise might be indicative of obstructive CAD (Skadberg et al., 2017; Kleiven et al., 2020). Although hs-TnT levels after physical exercise are elevated beyond URL in apparently healthy subjects, there is emerging evidence of elevated levels of cTn caused by secondary, smaller fragments (Vroemen et al., 2019) similar to those found in patients with end-stage renal disease (Mingels et al., 2017) and different from the forms seen in patients with AMI (Cardinaels et al., 2013). The exact mechanism behind the exercise-induced release of cTn is unclear. It has been proposed to be a result of increased energy demand in the myocardium, ventricular strain/wall tension, or neuro-hormonal stimulation (Gresslien & Agewall, 2016; Weil et al., 2018).

2.3.2 Non-ACS cardiac diseases

High-sensitivity tests have shown elevated circulating levels of cTn to be present in patients with HF and ventricular dysfunction, providing both diagnostic and prognostic information on these patients. The prevalence of HF has been increasing over recent decades, rising from 3/1000 cases to 20/1000 cases, and as expected is more common in the elderly (McMurray & Stewart, 2000). Approximately half of these patients have preserved left ventricular ejection fraction (Bursi et al., 2006). High-sensitivity cardiac troponin T is measurable in over 90% of patients with HF, with almost half the patients presenting with cTn levels above the normal upper limit (Latini et al., 2007). Hs-cTn levels above the normal upper limit or increasing hs-cTn levels are associated with a significant increase in all-cause mortality and adverse events in patients irrespective of left ventricular function (Masson et al., 2012; Fudim et al., 2018). The underlying pathophysiology behind cTn elevation in heart failure is heterogeneous and dependent on mechanistical and structural changes in cardiac function (Harrison et al., 2019). Even transient cardiac volume or pressure overload may lead to increased wall stress causing cTn release mediated by integrins (Hessel et al., 2008). Increases in circulating levels of cytokines, catecholamines, and oxidative stress caused by neurohumoral activation further promote cTn elevation (Eggers & Lindahl, 2017).

In over 90% of patients with AF, both high-sensitivity cTnT and cTnI are measurable (Hijazi et al., 2015). cTn levels are associated with increased risk of stroke and cardiac death (Roldán et al., 2012; Z. Hijazi et al., 2014). In smaller studies, elevations in cTn levels have also been reported in atrial flutter and re-entrant tachycardia (Costabel et al., 2016). In paroxysmal supraventricular tachycardia (SVT), fast heart rates (150/min) and history of CAD predicted cTn elevation (Ghersin et al., 2020). In SVT patients without cardiac comorbidities, major adverse cardiac events are rare, and cTn testing does not seem to play a significant prognostic role (Fernando, Adams & Mitra, 2019). Most likely, cTn elevations in these patients represent tachycardia-induced myocardial stretch, possible coronary vasospasm, or relative ischemia caused by a shortened diastole (Higgins & Higgins, 2003).

In elderly patients with isolated systolic hypertension without heart failure detectable and elevated high-sensitivity cardiac TnT is more common than in normotensive patients (Madan et al., 2019) and elevated hs-TnT is associated with both left ventricular hypertrophy and incident hypertension (McEvoy et al., 2015; Lyngbakken et al., 2020). Elevation of cTn levels in hypertensive patients could be explained by increased amount of cTn in hypertrophic myocardial cells, or high mechanical left ventricular load causing subendocardial hypoperfusion or myocardial fibrosis (Aesbacher et al., 2014).

In cases of pulmonary embolism (PE), cardiac troponins are considered to indicate myocardial injury and right heart failure. In addition to cardiac biomarkers, risk stratification in these patients is based on hemodynamic status and right ventricular dysfunction (Konstantinides et al., 2014). The prognostic value of elevated cTn in patients with low-risk PE was evaluated in a meta-analysis published in 2018. In this study, patients with right ventricular dysfunction had early all-cause mortality of 1.8%, escalating to 3.8% if elevated cTn levels were observed (Barco et al., 2019). This deleterious effect of elevated cTn in the event of PE was confirmed in another meta-analysis published a year later (El-Menyar, Sathian & Al-Thani, 2019). It is assumed that the mechanism of cTn elevation in PE depends on the severity of PE. Non-massive PE causes reversible injury to the myocytes and release of free cytosolic cTn into circulation. In massive PE, pronounced RV overload is responsible for irreversible myocyte necrosis and possibly coronary artery hypoperfusion (Chauin, 2021).

Valvular heart diseases are a common finding with increasing age. Of significant valvular diseases, aortic stenosis (AS) is the most common, with a prevalence of 2.9% (calculated valve area <0.8 cm^2) in Finnish patients over 75 years (Lindroos et al., 1993). Over 70% of patients with significant AS have been shown to have elevated baseline hs-TnT levels (Røsjø et al., 2011; Kim et al., 2014). A study by Røsjø et al. found significant correlation between hs-TnT levels and LV mass, LV dimension and peak gradient, and peak velocity across the aortic valve. Confirmed CAD did not cause additive hs-TnT elevation in this study, but there was a strong association with elevated hs-TnT and mortality (Røsjø et al., 2011). In AS, cTn elevations are usually caused by left ventricular hypertrophy, replacement myocardial fibrosis and elevated pulmonary artery pressure (Nunes et al., 2003).

Hypertrophic cardiomyopathy (HCM) is an often-inherited and frequent heart disease with diverse clinical presentation and a presumed prevalence of 1:200–1:500 (Maron, 2018). Diagnosis is based on echocardiography and magnetic resonance imaging in which a non-dilated, hypertrophied left ventricle is identified. These patients often present elevated cTn levels. When using high-sensitivity tests, cTn is elevated over URL in over half these patients and is an independent predictor of cardiovascular mortality and adverse events (Kubo et al., 2013). The exact mechanism behind cTn elevation in HCM is unknown, but supply–demand mismatch causing relative myocardial ischemia as well as myocardial fibrosis have been proposed as possible explanations.

Dilated cardiomyopathy (DCM) is defined by the presence of a dilated left ventricle in the absence of other predisposing conditions. Multiple mechanisms behind cTn elevation in DCM patients have been suggested: apoptosis, necrosis, calcium handling abnormalities, cytokines, nitric oxide, and oxidative stress, among others. The prevalence of hs -cTn elevation in DCM appears to be 20–30% (Connelly

et al., 2016). Irrespective of the actual mechanism, persistent cTnT elevation in DCM patients suggests ongoing myocyte degeneration and is associated with increased mortality (Sato et al., 2001).

Contrary to HCM and DCM, in patients with Takotsubo cardiomyopathy (TCM), cTn elevation does not seem to be of prognostic significance (Elesbar et al.,2007; Looi et al.,2012), albeit these studies have been conducted with earlier-generation assays. TCM is characterized by reversible ventricular dysfunction, with mortality rates similar to those of ACS (Templin et al., 2015). cTn elevation is usually less pronounced in comparison to ACS patient with a similar degree of left ventricular dysfunction. The pathological mechanism behind cTn elevation is presumed to be cardiotoxicity and microvascular dysfunction caused by catecholamine excess.

Infiltrative cardiomyopathies often cause elevated cTn levels. The common denominator among these cardiomyopathies is the deposit of abnormal substances in the heart tissue, causing diastolic and/or systolic dysfunction. The most common types are cardiac amyloidosis and sarcoidosis, while hemochromatosis and Fabry disease remain less common causes (Bejar et al., 2015). Cardiac amyloidosis is characterized by increased wall thickness, diastolic dysfunction, and conduction disturbances. Persistent elevation of cTn levels are common and reflect subclinical myocardial damage caused most likely by microvascular dysfunction, elevated left ventricular filling pressure, and impaired endothelial function. In a study by Palladini et al., over 70% of patients with cardiac amyloidosis had cTnT levels over URL, and a high-sensitivity assay seemed to be the best baseline prognostic marker in this patient group, as 52% of the patients with cTnT over 77 ng/L die within one year compared to 9% in a group with lower baseline cTn levels (Palladini et al., 2010). cTn levels in cardiac amyloidosis appear to be higher than in patients with non-infiltrative cardiac hypertrophy, with a cut-off value of 31.2 ng/l suggesting amydoidosis (Takashio et al.,2018).

Sarcoidosis is an idiopathic granulomatous disease primarily affecting young adults, with the highest incidences in northern Europe and Japan, and among African-Americans. The lungs are most commonly affected, but cardiac involvement is thought be present in 25–30% of cases. Serious cardiac dysfunction is reported in 5–10% of cases. Often the first presentation of cardiac sarcoidosis is sudden death, but congestive heart failure, ventricular tachycardia, and advanced heart blocks are also frequent findings (Silverman et al., 1978). More than 50% of treatment-naive patients present with elevated high-sensitivity cTn and decreasing levels are observed after initiation of steroid therapy. Elevated cTn levels are associated with increased risk of adverse events (Kandolin et al., 2015).

2.3.3 Renal impairment

CKD is considered one of the strongest risk factors for CVD, an effect that is intensified by the comorbidities often seen in conjunction with CKD, such as hypertension or diabetes. As seen in the ARIC study, CKD is associated with various CVDs, such as AF, HF, peripheral artery disease, and CAD (Astor et al., 2006; Kottgen et al., 2007; Wattanakit et al., 2007; Alonso et al., 2011). Impaired kidney function significantly increases the likelihood of all-cause and cardiovascular mortality at eGFR levels below 75 ml/min/1.73m2 (Matsushita et al., 2010). In patients with CKD, hs-TnT levels are higher than in patients with normal kidney function even without apparent CAD (Dubin et al., 2013). The correlation between diminishing eGFR and elevated baseline hs-cTn assays is stronger with TnT than TnI (Twerenbold et al., 2015), and cTn levels are elevated in practically all dialysis patients (Jacobs et al., 2009). Thus, the optimal cTn cutoff levels in patients with CKD are 1.9–3.4 higher than in subjects with normal kidney function (Twerenbold et al., 2015). CKD patients with elevated cTn present a challenging clinical scenario in which prognostic implications must be weighed against possible risk of further diagnostic procedures. The European Society of Cardiology 0 h/1 h algorithm for rapid rule-in/rule-out of NSTEMI has been studied in this setting and found to be safe in CKD patients but lacking in rule-out efficacy (Twerenbold et al., 2018).

2.3.4 Infections

The risk of both MI and injury is substantially increased in patients with respiratory or urinary tract infections as well as in patients with bacteremia or sepsis (Smeeth et al., 2004; Jafarzadeh et al., 2016). The mechanisms behind the increased risk include inflammatory activation of atherosclerotic plaques, prothrombotic milieu, increased metabolic demand, ventilation–perfusion mismatch, shock, direct myocyte damage, and cytokine storm (Musher, Abers and Corrales-Medina, 2019). Elevated cTn in the context of infection is strongly associated with poor prognosis, especially in patients with non-cardiac troponin elevation (Ilva et al., 2010; Sheyin et al., 2015).

Over 80% of patients with infective endocarditis are found to have elevated cTn levels. The elevated cTn is associated with over 3-fold in-hospital mortality, and these patients are more often treated surgically (Postigo et al., (2020).

Myocarditis is an inflammatory disease of the myocardium. Incidence is estimated at 1–10:100,000. Damage to the myocardium is thought to be a result of direct cytotoxic effects, secondary immune responses, cytokine expression in the myocardium, or induction of apoptosis. Most patients with acute myocarditis have elevated levels of circulating cTn, albeit absence of elevated cTn does not rule out myocarditis (Aquaro et al., 2017). When using hs-TnT assays, a concentration of

>50 ng/L has been found to be predictive for acute myocarditis when other causes have been excluded and other findings support the diagnosis (Ukena et al., 2014).

As of 2020, coronavirus disease (COVID-19) has emerged as a global health emergency. CVD or cardiovascular risk factors appear to increase sensitivity to COVID-19. In this setting, cTn elevation is usually associated with myocardial injury caused by non-ischemic processes: hypoxia, sepsis, systemic inflammation, PE, adrenergic stimulation, or perhaps myocarditis (Imazio et al., 2020). Elevated cTn values have been observed in 8–12% of COVID-19 patients, with magnitude of elevation associated with severity of disease (Lippi et al., 2020). Cardiac injury has been reported in 22% of patients admitted to intensive care units and in over 50% of the patients who died (Zhou et al., 2020). A prothrombotic milieu also predisposes the patients to ACS, and in-hospital and out-of-hospital STEMI patients with COVID-19 have significantly elevated mortality rates (Saad et al., 2021).

2.3.5 Neurological emergencies

Elevated cTn is a common finding in patients with cerebrovascular disease. Patients are often elderly and have various comorbidities (hypertension, valvular heart disease, AF, CKD) affecting their baseline cTn levels. With conventional assays, one in five patients with acute ischemic stroke present with elevated cTn (Kerr et al., 2009). High-sensitivity assays increase this prevalence to 60% (Scheitz et al., 2015). Similar findings have been demonstrated in patients with intracerebral hemorrhage and subarachnoid hemorrhage (Alkhachroum et al., 2019). Dynamic cTn elevations are linked with simultaneous ACS, whereas constant elevation of cTn is usually an indication of a pre-existing condition, such as heart failure, hypertension, or kidney failure (Anders et al., 2013). Even moderately elevated high-sensitivity cTn is associated with poor prognosis, and dynamic changes increase in-hospital death (Scheitz et al., 2014). In epilepsy patients, up to 5% present with elevated cTn levels after seizure. cTn elevation is associated with longer seizures, higher maximal ictal heart rate, and dynamic heart rate change (Faria et al., 2020).

2.3.6 Alternative causes

Sometimes a cTn test result is considered a “false positive”. In normal situations, cTnT is not expressed in adult skeletal muscle, but there is some debate as to whether there might be a re-expression of cardiac TnT isoforms in skeletal myopathies (Jaffe et al., 2011). The other possible explanation for elevated cTnT levels in skeletal myopathy patients is cross-reactivity between skeletal muscle troponin isoforms and the currently used cTnT immunoassay (Schmid et al., 2018). If such cTn elevation is observed, a possible third explanation is subclinical myocardial injury, as observed

in 23% of the patients in the aforementioned study by Schmid et al. TnI was seldom elevated in either of these studies, probably reflecting variations in cTn assays from different manufacturers or an inappropriately established 99th percentile for the cTnI assays (Kimenai et al., 2016).

In patients with occult cTn elevations, strict investigations for underlying cardiac disease are mandated, and serial testing is of special importance in identifying the possible dynamics most likely reflecting primary cardiac etiology. It has historically been thought that elevated levels of circulating cTn denote myocardial necrosis and, thus, irreversible damage to the myocardium, establishing their application as highly sensitive, specific markers of myocardial injury. There is evidence that cardiac myocytes may have limited regenerative capabilities (Eschenhagen et al., 2017), leading to the assumption that increased cell turnover might be responsible for elevated levels of circulating cTn. In addition, there is evidence of apoptosis in mammalian hearts, which might explain detectable levels of circulating cTn in patients with myocardial ischemia or myocardial wall stress in the absence of necrosis (Weil et al., 2017). The third possible explanation is an increase in cell membrane permeability due to cell wounds or membranous blebs (HM et al., 1984) leading to the release of a cytosolic pool of cTn. Delayed biomarker clearance is also a possible mechanism, especially in patients with stable elevated concentrations of cTnT; renal clearance is another contributing factor (Fridén et al., 2017).

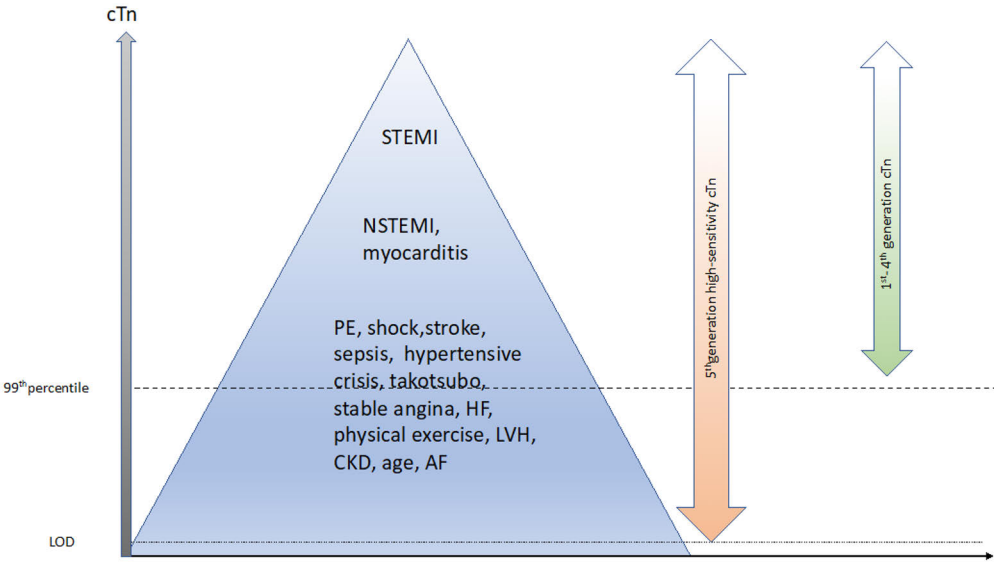

Figure 2. Magnitude and incidence of cTn elevation in various clinical conditions in relation to detection sensitivities of cTn assays. STEMI, ST elevation myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; PE, pulmonary embolism; HF, heart failure; LVH, left ventricular hypertrophy; CKD, chronic kidney disease; AF, atrial fibrillation; cTn, cardiac troponin; LOD, level of detection; 99th percentile, upper normal limit of cTn assay

2.4 Atrial fibrillation and cardiac biomarkers

2.4.1 Epidemiology and clinical significance of atrial fibrillation

AF has been defined as a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and, consequently, ineffective atrial contraction (Hindricks et al., 2021). It is considered the most common sustained arrhythmia, with a prevalence in adults of 2–4% (Benjamin et al., 2019). The number of patients suffering from AF is expected to rise significantly in the future due to the extended life expectancy of the general population and improved diagnostics.

The lifetime risk of AF is thought to be over 30% in patients over the age of 55 (Staerk et al., 2018). In addition to age, male sex, genetics, and modifiable risk factors such as hypertension, CAD, obesity, sleep apnea, heart failure, diabetes, and CKD are relevant to incidence of AF. In addition to often-significant impairment of quality of life and depression (Schnabel et al., 2013; Freeman et al., 2015), AF increases mortality 1.5–3.5-fold (Andersson et al., 2013; Magnussen et al., 2017), stroke risk over 2–5-fold (Wolf, Abbott & Kannel, 1991; Andrew, Thrift & Cadilhac, 2013; Yiin et al., 2018).

The risk for dementia and cognitive impairment is increased (Kwok et al., 2011; Kalantarian et al., 2013), and AF may lead to left ventricular dysfunction or heart failure, with age, CKD, CAD, hypertension, previous stroke, and uncontrolled ventricular rate being predisposing factors (Stewart et al., 2002; Ziff et al., 2018). Annually 10–40% of AF patients are hospitalized, primarily due to heart failure, elevated heart rate, or severe symptoms caused by AF (Steinberg et al., 2014).

2.4.2 Myocardial infarction and injury in atrial fibrillation

The risk of MI is significantly increased in patients with AF (Soliman et al., 2014; Guo et al., 2016; Ruddox et al., 2017). A potential cause can be coronary embolism related to AF, with a reported prevalence of 2.9% (Shibata et al., 2015). AF also leads to a prothrombotic state and is associated with an increase in inflammatory markers and mediators (Guo, Lip & Apostolakis, 2012), which may be either cause or consequence but are nonetheless associated with increased risk of MI. In addition, a significant overlap in risk factors is found between AF and MI: for example, age, smoking, diabetes mellitus, hypertension, and prevalent CAD— all widely accepted risk factors for MI—are known to predispose patients to AF (Benjamin et al., 1994). Despite increased MI risk, ACS seems to be an infrequent diagnosis in AF patients presenting to the ED despite quantum patients presenting with minor cTn elevations (Meshkat et al., 2011). This finding is supported by a study McCarthy et al, in which

they found strict adjudication of contemporary MI guidelines (Thygesen et al., 2018) to alter primary MI diagnosis to myocardial injury in 42% of patients (McCarthy et al., 2019).

2.4.3 Cardiac troponin elevations in patients with atrial fibrillation

cTn elevations in anticoagulated AF patients have been the subject of recent studies. In the RE-LY biomarkers substudy, the percentage of AF patients with elevated cTnI levels was 24.6%, and in the ARISTOTLE trial, cTnI was elevated in 9.2% of patients and cTnT in 34.4% of patients, respectively (Hijazi et al., 2012).

In unselected patients seeking care at an ED, one in eight present with elevated cTn. In AF patients, cTn elevation over the 99th percentile is even more common, with a prevalence of 30–50% (Roldán et al., 2012; Stoyanov et al., 2018). In a study by Van den Bos et al., the prevalence of elevated cTnI was 19% (Van den Bos et al., 2011). The differences here most likely reflect the integral properties of various assays and different clinical decision values. In patients with AF, it has been suggested that a higher cutoff point or change in cTn levels is required to diagnose AMI. For cTnI, it has been proposed that a relative change of 40% or absolute change of 50 ng/L would improve diagnostic accuracy (Sörensen et al., 2016). The underlying mechanism behind cTn elevation in AF patients is most likely "demand ischemia," a mismatch between myocardial oxygen demand and supply precipitated by shortened diastole in the tachycardia.

2.4.4 Clinical significance

Cardiac biomarker testing is often used in ED, even without clinical suspicion of an ACS (Makam & Nguyen, 2015). In these unselected patients, the prevalence of elevated hs-TnT exceeds 12% (Lee et al., 2019). Troponin elevation is even more common in AF patients, and the advent of high-sensitivity testing significantly increases the number of patients with elevated cTn. Only a few of these patients present with ACS, and most elevations are caused by myocardial injury. A study by Parwani et al. evaluated AF patients with elevated cTn and symptoms suggestive of myocardial ischemia, and angiograms revealed 26% of the patients had significant coronary artery stenosis, but no difference between cTn levels was found when compared to patients without obstructive CAD (Parwani et al., 2013). Alghamry et al. studied a similar patient cohort and found that cTn over URL was not predictive of CAD (Alghamry et al., 2016).

2.4.5 Confounding factors

Multiple factors, such as age, sex, and comorbidities, influence cTn levels. In an article by Pouru et al. investigating AF population, a nonlinear association between peak hs-TnT and admission heart rate above 125 bpm was observed, and a heart rate over 140 bpm was associated with dynamic change in cTn (>50%) irrespective of the presence of CAD (Pouru et al., 2020). Similar cTn elevations have been observed in patients with other types of supraventricular tachycardia (Redfearn et al., 2005; Xue et al., 2014). Also of interest in this context is data supporting the benefit of improved rate control in patients with AF and consequential reduction in circulating levels of cTn (Ulimoen et al., 2014).

In selected patients with AF and heart failure, catheter ablation has been shown to reduce mortality (Turagam et al., 2019), a benefit most likely a result of reduced AF burden. One hypothesis is whether circulating troponin levels could be used as a surrogate marker of this benefit, but so far this has not been proven. In general, rhythm control has not been shown to reduce mortality in patients with AF (Carlsson et al., 2003; Purmah et al., 2018; Packer et al., 2019), although a mortality reduction trend has been observed in long-term follow-up in particular (Ionescu-Ittu et al., 2012). Also, the heterogeneity of cTn assays, with their disparate analytic sensitivities and possible analytical errors, pose significant challenges to clinicians (Herman et al., 2017).

2.4.6 Prognostic effect of cTn elevation in patients with atrial fibrillation

The association between elevated cTn levels and mortality in AF patients is clear and has been confirmed in multiple studies irrespective of the assay used (van den Bos et al., 2011; Stoyanov et al., 2018). This association is observed in patients with type 1 MI, type 2 MI, and in patients with myocardial injury notwithstanding the type of AF and even the absence of confounding comorbidities at presentation. Even cTn levels below UNL increase mortality in comparison to patients with undetectable cTn, which was shown in a study by Stoyanov et al. where detectable hs-TnT and elevated hs-TnT were associated with a nearly 5-fold and over 13-fold risk of mortality (Stoyanov et al., 2018). Furthermore, in clinical practice, dynamic elevations in cTn are considered to possess strong predictive value regarding ACS. In patients with AF and tachycardia (at least with minor cTn elevations), this proposition is challenged by the findings of Thelin et al., who found no association between dynamic cTn elevation and increased risk of coronary events (Thelin & Melander, 2017).

3 Aims of the study

This dissertation is based on the findings of the MARACAT and TROPO-AF studies. The primary aims of the dissertation are to:

1. Identify predictors of high-sensitivity cardiac troponin T (cTnT) elevations in male marathon runners and define the association between coronary atherosclerosis, plaque vulnerability, and muscle injury in exercise-related cTnT release (Study I).
2. Evaluate the etiology of minor cardiac cTnT elevations in AF patients presenting to the ED and assess the factors distinguishing ACS from alternative diagnoses causing elevated cTnT in the study population (Study II).
3. Gauge the effect of minor cTnT elevation on mortality and hospitalizations for MI in AF patients (Study III).

4 Materials and Methods

4.1 Patient populations

The study population in Study I consisted of 43 male recreational runners (age <35 years, n = 12; age >44 years, n = 31) who participated in the 2018 Paavo Nurmi Marathon in Turku, Finland. Participants were recruited through an open email invitation. Three runners did not participate or finish the race for various reasons, hence the study presented data on 40 patients.

Study II and Study III were pre-specified analyses included in the Troponins in Atrial Fibrillation Study (Tropo-AF Study, Clinicaltrials.gov Identifier: NCT03683836). Patients were selected from the Turku University Hospital catchment area, and a laboratory database search was carried out to identify patients with cTnT samples taken between 1 March 2013 and 11 April 2016. All subjects were required to have a history of AF or AF at admission to the ED and required to have an ECG and at least two serial cTnT measurements taken 8–72 hours after admission. Patients with cTnT levels below 100 ng/L were selected for the studies. A total of 2911 patients met the inclusion criteria.

4.2 Methods

Study I participants were asked to complete an online questionnaire on personal characteristics, physical activity, exercise experience, medical history, and medications. The protocol included two visits: a control visit either the day before the race or 2–4 weeks after the race and a post-race visit within 30 minutes of finishing the race. During the post-race visit, the finish time was recorded for all participants, along with maximum heart rate for 29 participants, taken from their personal heart rate monitors. A second questionnaire was used to evaluate perceived exertion on the Borg scale, physical complaints, and race-induced muscle soreness. The control visit included laboratory tests, echocardiography, an ECG, and a physical examination. Echocardiographic parameters were obtained according to current recommendations (Lang et al. 2015). Computed tomography was performed for participants > 44 years of age, and CAC scores were calculated at the Turku PET Centre, Turku University Hospital, using a GE Discovery 690 MI PET/CT 128-slice

CT/positron emission tomography device (GE Healthcare, Milwaukee, Wisconsin) and the Agatston method. The presence of CAC was defined as a score of 1 or greater. Basic laboratory work was performed by Turku University Hospital laboratory services (TYKSLAB). A commercial high-sensitive assay (Roche Diagnostics GmbH, Mannheim, Germany) was used to analyze cTnT, with a 99th percentile upper normal limit of 14ng/l, as determined by the manufacturer. The biotechnology unit at the University of Turku provided analysis for skeletal muscle TnI (skTnI) (Bamberg et al., 2020), cardiac troponin I (cTnI) (Savukoski et al., 2015), and free pregnancy-associated plasma protein A (fPAPP-A) (Tuunainen et al., 2018).

In Studies II and III, the clinical characteristics and comorbidities of patients meeting the inclusion criteria were reviewed by the research team using a standardized protocol including clinical and laboratory data from the index hospitalization. Mortality data on the patients was retrieved from a database managed by Statistics Finland, the national statistical institution.

In Study II, a commercially available high-sensitivity cTnT assay (Roche Diagnostics Gmbh, Mannheim, Germany) was used to determine cTnT levels. The patients were thereafter divided into two groups according to maximum cTnT level: patients with normal cTnT (<15 ng/l) and patients with minor cTnT elevation (<100 ng/L). Dynamic changes in cTnT were calculated from the highest and the lowest cTnT levels and reported as percentages. A standard 12-lead ECG was used to confirm the diagnosis of AF and two adjacent leads were used to screen for ST segment depression ≥1 mm. The patients were categorized into six groups according to discharge diagnosis. The study aimed to report the prevalence and predictors of minor cTnT elevation in AF patients seeking ED care and exhibiting various symptoms and diagnoses.

Study III focused on the 30-day and 1-year mortality of the same patient cohort studied in Study II. Again, ECGs were screened for ST depression ≥1mm in two adjacent leads, and diagnosis of AF was confirmed by a 12-lead ECG. If AF terminated, either spontaneously or through intervention, within 7 days of onset, it was defined as paroxysmal. If no attempts to terminate the AF were made and rate control was accepted by the patient and physician, AF was considered permanent. Irrespective of the duration or the presence of symptoms, AF was considered first diagnosed AF if no AF was detected previously. Again, all cTnT samples were analyzed using a commercial high-sensitivity assay (Roche GmbH, Mannheim, Germany) with a UNL of 14 ng/L as determined by the manufacturer. Based on maximum cTnT level, the patients were divided into three groups: cTnT <15 ng/L, cTnT 15–50 ng/L, and cTnT 50–100 ng/L. The patients were then grouped into six categories according to main discharge diagnosis: AF, infections, stroke/transient ischemic attack, ACS, heart failure, and other conditions. All-cause mortality at 30

days and 1 year were the primary outcomes of the study, and the secondary outcomes were all-cause mortality at 3 years and MI at 30 days and 1 year.

The study protocols were approved by the Ethics Committee of the Hospital District of Southwest Finland.

4.3 Statistical analysis

The statistical analysis for all studies was performed using SPSS statistical software v. 25.0 (IBM Corporation, New York, USA). Unless stated otherwise, the continuous variables were reported as mean±standard deviation when normally distributed and as median [interquartile range (IQR)] when skewed. The data were tested for normal distribution using a Shapiro-Wilk test. In all studies, p-values <0.05 were considered statistically significant.

4.3.1 Study I

A comparison of control and post-race tests was performed with a paired Student's t-test and a Wilcoxon signed-rank test. Linear regression analysis with backward selection was performed to identify factors correlating to post-race cTnT levels. All univariate predictors with p-value <0.1 (Δhemoglobin, Δcreatine kinase total and subunit MB mass, Δskeletal troponin I, age, body mass index, number of completed marathons, maximum heart rate during the race) were included in the final regression model, and correlation between clinical parameters and cTnT were estimated using Spearman's correlation.

4.3.2 Study II

In order to identify independent predictors of cTnT elevation and patients with ACS, a logistic regression analysis using backward Wald elimination was applied. All variables in univariate analysis with p <0.1 were entered into the regression model. To identify the independent risk factors for cTnT elevation, a classification and regression tree (CART) (Moore, 1987) analysis was performed. Gini's method was used as an impurity measurement, and a minimum change in improvement was set at 0.0001. Covariates identified as independent risk factors for minor cTnT elevation (cTnT 15–100 ng/L) in logistic regression and normalized importance >20% were included in the final CART model (age >75 years, male gender, chest pain, ST depression on ECG, ventricular rate ≥100 bpm, eGFR <45 mL/min/1.73 m^2, C-reactive protein (CRP) ≥50 mg/L, and hemoglobin <10.0 g/dL).

4.3.3 Study III

The Cox regression model was used to analyze the association between cTnT elevation and mortality at 30 days, 1 year, and 3 years. Significant univariate predictors of mortality ($p < 0.1$; age >75 years, male gender, AF at admission, heart failure, hypertension, diabetes mellitus, CAD, prior MI, prior stroke or transient ischemic attack, peripheral artery disease, active malignancy, dyspnea, chest pain, heart rate >120/min at admission, ST depression on ECG, anemia, CRP >30 mg/L and eGFR <30 ml/min/1.73 m^2) were included in the multivariate model using backward Wald elimination. To estimate 30-day and 1-year mortality, the Kaplan-Meier method was used, along with a log-rank test for comparison between the groups.

4.4 Ethics

Studies I–III were conducted according to the principles of the Declaration of Helsinki, and study protocols were approved by the local ethics committee of the Hospital District of Southwest Finland. Informed consent was obtained from Study I participants. Due to their observational and retrospective nature, Studies II and III did not require participants' informed consent.

5 Results

5.1 Cardiac troponin elevations in marathon runners. Role of coronary atherosclerosis and skeletal muscle injury (Study I)

In Study I, all participants were male with a mean (SD) age of 47.7 (13.0) years. Younger participants (<35 y, n = 12) had a mean age (SD) of 30.1±3.9 years, while older participants (>44 y, n = 31) had a mean age of 54.9±7.0 years. The participants had a median body mass index (BMI) of 24 (IQR 23–25) and had trained for 14 (IQR 8–20) years. The median number of completed marathons before the 2018 Paavo Nurmi marathon was 10 (IQR 3–30), with weekly training sessions for the last 3 months before index event 4 (IQR 3–5). The mean (SD) finishing time of the marathon was 4.1±0.6 hours. Maximum heart rate was recorded by 29 of 40 runners, with a median 175 bpm (IQR 165–183). None of the runners had cardiac symptoms during or after the race.

Echocardiography showed a left ventricular end-diastolic diameter of 51 (IQR 49–55) mm, left ventricular ejection fraction of 70 (IQR 65.3–71.8) % and left ventricular mass 197 (IQR 172.3–241.3) grams.

Pre-race cTnT was 7.00 (IQR 5.25–8.75) ng/L, and only one of 40 participants had a baseline cTnT level exceeding the URL of 14 ng/L (baseline value of 15 ng/L). Post-race cTnT levels rose above the URL in 38 (97.5%) runners, with a median cTnT of 41 (IQR 26.0–65.5) ng/L. Significant ($p < 0.005$) increases in all measured laboratory parameters excluding hemoglobin were observed, including markers of muscle injury (10-fold rise in skTnI and significant elevations of CK and CK-MBm). Possible plaque vulnerability was evaluated with a free pregnancy-associated plasma protein (fPAPP-A) assay, with elevated levels present in 82.5% (n = 33) of the runners post-race. The elevation in fPAPP-A was statistically significant, rising from 1.14 (IQR 0.86–1.44) mIU/L to 1.63 (IQR 1.31–1.92) mIU/L ($p < 0.001$), but no association with post-race cTnT was evident ($r_s = -0.26$, $p = 0.11$). Numerically, the greatest increase was seen in N-terminal pro b-type natriuretic peptide (NT-proBNP). Baseline values were under lower limit of detection (50 ng/L) in all participants, with post-race levels of 82.0 (IQR <50–162) ng/L and maximum value of 1250 ng/L, $p < 0.001$ (Tables 1 and 2).

Table 1. Baseline and post-marathon laboratory data of all 40 participants.

Variable	Baseline	Post-race	*p-value*
Hemoglobin, g/l	142± 9.95	146± 1.14	0.065
Potassium, mmol/l	3.87± 0.24	4.06± 0.42	0.008
Sodium, mmol/l	141± 1.88	144± 3.25	<0.001
Creatinine, µmol/l	91.6± 9.57	130± 29.8	<0.001
Creatine kinase total, U/l	158[103–203]	376[274–601]	<0.001
Creatine kinase subunit MB mass, µg/l	3.05[2.00–4.65]	5.75[4.95–85.0]	<0.001
cTnT, ng/l	7.00[5.25–8.75]	41.0[26.0–65.5]	<0.001
cTnI, ng/l	<2.9*	12.0[4.30–21.9]	<0.001
skTnI, ng/ml	1.80[0.00–4.05]	19.3[10.3–31.5]	<0.001
D- Dimer, mg/l	0.00[0.00–0.30]	0.3[0.20–0.68]	<0.001
fPAPP-A, mIU/l	1.14[0.86–1.44]	1.63[1.31–1.92]	<0.001
NT- proBNP, ng/l	<50*	82.0[<50–162]	<0.001

Values are mean ± standard deviation, median [inter-quartile range 25th–75th percentiles]. cTnI = cardiac troponin I; cTnT= high-sensitivity cardiac troponin T; skTnI = skeletal troponin I; fPAPP-A = free pregnancy-associated plasma protein A; NT-proBNP= N-terminal pro b-type natriuretic peptide. *Values under lower limit of detection

Table 2. Correlations between clinical parameters and high-sensitivity troponin T (cTnT) in all runners.

	Spearman's r	*p-value*
Age	-0.542	<0.001
Body mass index	-0.286	0.073
Years of active training	0.111	0.494
Completed marathons	-0.274	0.087
Kilometers run/week in the last 3 months	0.022	0.894
Maximum heart rate during race	0.541	0.003
Echocardiography		
LV end diastolic diameter	0.097	0.550
LV ejection fraction	-0.160	0.324
LV mass	0.009	0.961
Laboratory parameters		
ΔHemoglobin	-0.389	0.017
ΔCreatinine	0.070	0.668
ΔCreatine kinase subunit MB mass	0.312	0.050
ΔCreatine kinase, total	0.341	0.031
ΔSkeletal troponin I	0.292	0.068
ΔN-terminal proBNP	0.068	0.6778
ΔfPAPP-A	0.078	0.633
ΔD-Dimer	0.042	0.795
Multivariate regression analysis	β	*p* value
Age	-4.049	<0.001

LV = left ventricular; proBNP = pro brain natriuretic peptide; fPAPP-A = free pregnancy-associated plasma protein A; Δ = change between baseline sample and post-race sample.

Over half (53.6%) of patients >44 years had detectable coronary artery calcification (CAC) in their CT scan (median CAC score 2.0, range 0–608 [IQR80]), without significant association between CAC and post-race cTnT (r_s = -0.013, p = 0.95) or fPAPP-A (r_s = -0.23, p = 0.24). Furthermore, no correlation between post-race cTnT and skTnI (r_s = 0.25, p = 0.12), fPAPP-A (r_s = -0.26, p = 0.11), NT-proBNP (r_s = 0.052, p = 0.75) or D-Dimer (r_s = 0.07, p = 0.67) was observed. In multivariate linear regression analysis, no baseline characteristic, clinical or laboratory parameter, or electrocardiographic or echocardiographic parameter except younger age was associated with post-race cTnT levels (β = -4.049, p <0.001.

5.2 Etiology of Minor Troponin Elevations in Patients with Atrial Fibrillation at Emergency Department-Tropo-AF Study (Study II)

The study cohort included 2911 patients with a median (IQR) age of 79.3 (70.5–85.4) years. The sexes were equally distributed (50.1% male), and prevalence of comorbidities was high, with hypertension in 68.4% (n = 1990), hypercholesterolemia in 39.5% (n = 1151), CAD in 29.9% (n = 869), diabetes in 25.6% (n = 745), heart failure in 21.0% (n = 610), stroke in 19.0% (n = 553), and previous MI in 15.4% (n = 449) of patients. The mean (SD) CHA2DS2-VASc score was 3.89 (1.76). The median cTnT of the entire cohort was 27 (IQR 14.0–48.9) ng/L, and 2116 patients (72.7%) had elevated cTnT (15–100 ng/L). The patients with elevated cTnT were older, more often male, and apart from prior strokes, had significantly more comorbidities. They also had significantly lower hemoglobin and eGFR values, more often presented with ST segment depression on the admission ECG, and had lower systolic blood pressure and higher heart rate at admission. A marker of infection, CRP, was also significantly higher, as was a marker of myocardial strain, proBNP (Table 3).

From the primary diagnostic groups, the most common was AF (21.6%, n = 628), followed by infections (14.4%, n = 410), ischemic stroke/transient ischemic attack (13.0%, n = 378), decompensated heart failure (11.9%, n = 346), and ACS (4.5%, n = 130). When the normal troponin and elevated troponin groups were compared, AF was the primary diagnosis in 30.7% (n = 244) vs. 18.1% (n = 384), infection 4.0% (n = 32) vs. 18.3% (n = 388), stroke/transient ischemic attack 19.0% (n = 151) vs. 10.7% (n = 227), ACS 4.4% (n = 35) vs. 4.5% (n = 95), and heart failure 5.0% (n = 40) vs. 14.5% (n = 306), respectively (Figure 3). In both cTnT groups, miscellaneous (bone fractures, trauma, intoxication, bleeding, renal insufficiency, inflammatory disease, various other symptoms) diagnoses were most common at discharge (34.7%, n = 1009). Linear-by-linear association test showed statistically significant differences ($p < 0.001$) in the distribution of diagnostic categories between the cTnT cohorts (Table 3).

Table 3. Patient characteristics according to troponin T levels at hospital.

Characteristic	cTnT <15 ng/L (*n* = 795)	cTnT 15–100 ng/L (*n* = 2116)	
	No. (%)	No. (%)	*p*
Age, median (IQR)	72.0 (14)	81.0 (12)	<0.001
Women	431 (54.3)	1026 (48.5)	0.005
CHA_2DS_2-VAS_c, mean (SD)	3.30 (1.85)	4.11 (1.68)	<0.001
Heart failure	86 (10.8)	524 (24.8)	<0.001
Hypertension	505 (63.5)	1485 (70.2)	0.001
Diabetes mellitus	155 (19.5)	590 (27.9)	<0.001
Prior stroke	119 (15.0)	346 (16.4)	0.39
Prior myocardial infarction	99 (12.5)	350 (16.5)	0.007
Hypercholesterolemia	340 (42.8)	811 (38.3)	0.03
Coronary artery disease	186 (23.4)	683 (32.3)	<0.001
Heart rate at admission, median (IQR), bpm	81 (66–102)	87 (72–109)	<0.001
Systolic blood pressure, median (IQR), mmHg*	144 (126–163)	140 (122–160)	0.002
ST depression on admission ECG*,†	42 (5.8)	305 (15.9)	<0.001
Laboratory tests at admission			
cTnT, median (IQR), ng/L	9 (6–11)	30 (21–48)	<0.001
Hemoglobin, median (IQR), g/dL	13.8 (12.8–14.7)	12.8 (11.5–14.2)	<0.001
Creatinine, median (IQR), µmol/L	79.4 (70.7–97.2)	97.2 (79.6–124)	<0.001
eGFR, median (IQR), mL/min/1.73m^2	71.3 (58.8–83.8)	55.1 (40.0–72.3)	<0.001
NT-ProBNP, median (IQR), ng/L*	998 (454–2335)	3370 (1580–6355)	<0.001
CRP, median (IQR), mg/L	3 (2–7)	10 (3–37)	<0.001

CHA2DS2-VASc 1 point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65–74 years, and female sex, and 2 points for prior stroke, transient ischemic attack, or thromboembolism, and age ≥ 75 years; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration equation); cTnT, high- sensitivity cardiac troponin T; NT-ProBNP, N-terminal pro-brain natriuretic peptide. *, the number of patients with missing data for CRP was n = 261 (9.0%), for ST depression n = 265 (9.1%), for systolic blood pressure n = 352 (12.1%), and for NT-proBNP n = 1507 (51.8%). †, ≥1 mm ST depression in two adjacent leads; IQR, interquartile range; SD, standard deviation.

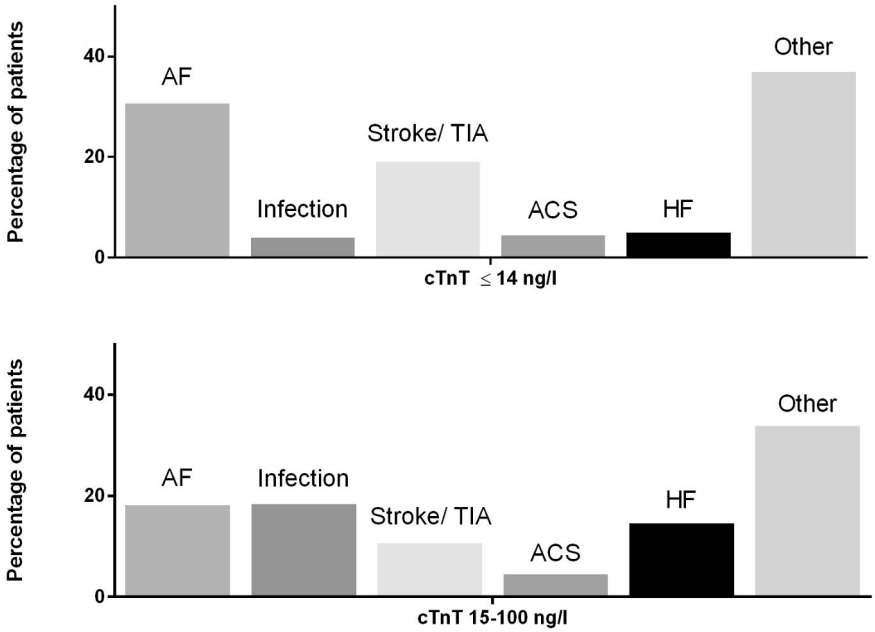

Figure 3. Distribution of different primary discharge diagnoses in patients with normal cTn (top) and minor cTn elevation (bottom). ACS, acute coronary syndrome; AF, atrial fibrillation; HF, heart failure; and TIA, transient ischemic attack.

The most common symptom was dyspnea (28.3%, n = 823), followed by nausea/malaise/dizziness (21.6%, n = 629) and chest pain (17.6%, n = 513). Chest pain was present in 27.0% (n = 215) of patients with normal cTnT and 14.1% (n = 298) of patients with elevated cTnT (p = 0.002), respectively. Over half (65.4%, n = 85) of the patients diagnosed with ACS experienced chest pain, but only one in eight patients with minor troponin elevation and chest pain were diagnosed with ACS (12.8%, n = 38), thus leading to a positive predictive value of 16.5% and negative predictive value of 98%. ST depression in the admission ECG was seen in 11.9% (n = 347) of patients and was more common in patients with elevated troponin (15.9% vs. 5.8%, p <0.001). Prevalence of ST depression did not differ significantly between patients with ACS when compared to other diagnostic groups (10.7% vs 13.2%, p = 0.27).

In the univariate analysis, eGFR <45 ml/min/1.73m2, hemoglobin <10.0 g/dL, CRP ≥50 mg/L and age ≥75 years were associated with troponin T elevation (Table 4). After adjusting for baseline variables eGFR <45ml/min/1.73 m^2, hemoglobin <10.0 g/dL, age >75 years, CRP ≥50 mg/L, male gender, ST depression in admission ECG, ventricular rate ≥100 bpm at admission, and chest pain were independently associated with troponin elevation (Table 4). The classification and regression tree model (AUC 0.763, 95%CI, 0.745–0.782) shows that over 90% of the patients ≥75

years with eGFR <45 ml/min/1.73m2 or CRP ≥ 50 mg/L had elevated TnT levels (Figure 4).

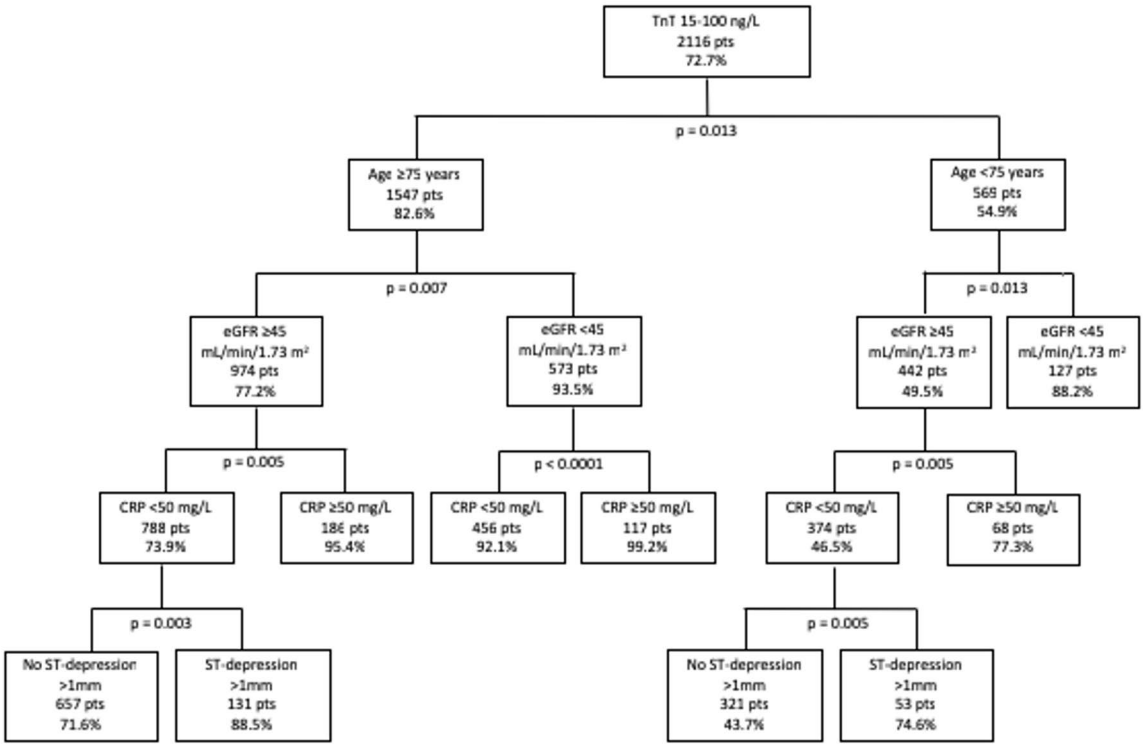

Figure 4. Classification and regression tree analysis showing the independent importance of covariates predicting troponin T elevations in patients with atrial fibrillation. %: percentage of patients with TnT 15–100 ng/L among patients with covariates indicated in each box. CRP, C- reactive protein; eGFR, estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration equation); TnT, high- sensitivity cardiac troponin T; ST depression, ≥1 mm ST depression in two adjacent leads.

Table 4. Univariate predictors of troponin T elevation in patients with atrial fibrillation.

Univariable	Odds Ratio (95% CI)	*p*-Value
Age ≥ 75 years	3.89 (3.28–4.62)	<0.001
Male gender	1.26 (1.07–1.49)	0.005
Heart failure	2.71 (2.13–3.47)	<0.001
Hypertension	1.35 (1.14–1.61)	0.001
Diabetes mellitus	1.60 (1.31–1.95)	<0.001
Prior stroke or TIA	0.98 (0.80–1.20)	0.83
Hypercholesterolemia	0.83 (0.71–0.98)	0.03
Coronary artery disease	1.56 (1.29–1.89)	<0.001
Active malignancy	1.30 (0.85–1.98)	0.23
Chest pain	0.44 (0.36–0.54)	<0.001
ST depression on admission ECG*,†	3.06 (2.19–4.27)	<0.001
Ventricular rate ≥ 100 bpm at admission	1.37 (1.14–1.64)	0.001
AF at admission	1.79 (1.51–2.12)	<0.001
eGFR < 45 ml/min/1.73 m^2	6.40 (4.82–8.51)	<0.001
CRP ≥ 50 mg/L†	5.04 (3.46–7.35)	<0.001
Hemoglobin < 10.0 g/dL	6.19 (3.34–11.4)	<0.001

AF, atrial fibrillation; CI, confidence interval; CRP, C-reactive protein; ECG, electrocardiography. eGFR, estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration equation); TIA, transient ischemic attack. *≥1 mm ST depression in two adjacent leads. †The number of patients with missing data for CRP was n = 261 (9.0%) and for ST depression was n = 265 (9.1%).

In multivariate analysis, the strongest independent predictor of ACS was chest pain. Other independent predictors of statistical significance were eGFR <45 ml/min/1.73 m^2 and known CAD (Table 5). Only one patient with cTn elevation and non-ACS primary diagnosis was treated for ACS during the 30-day follow- up.

Table 5. Adjusted predictors of ACS among patients with AF and elevated cTn.

Multivariable	Odds Ratio (95% CI)	p-Value
Chest pain	8.29 (5.20–13.2)	<0.001
Coronary artery disease	2.33 (1.42–3.81)	0.001
eGFR <45 ml/min/1.73 m^2	1.65 (1.04–2.63)	0.035

CI, confidence interval; eGFR, estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

5.3 Prognostic effect of minor troponin T elevation in patients with atrial fibrillation presenting to the emergency department (Study III)

This observational study cohort comprised the same patients (n = 2911) as in Study II, divided into three groups according to maximum cTnT level (<15 ng/l, 15–50 ng/L, and 50–100 ng/L). Only 2% (n = 59) patients presented with cTnT levels below level of detection (<5 ng/L). 72.7% (n = 2116) of the patients had cTnT levels over UNL (≥15 ng/L), and over one third (n = 670) presented with a maximum cTnT 50–100 ng/L. The mean age of the study population was 77.1 years; the sexes were equally represented. Patients with cTnT >50 ng/L were older than in the normal cTnT group (80.7±9.6 years vs 71.0±10.3 years, p <0.001), and patients were predominantly male (55.5% vs 45.7%, p = 0.001). Comorbidities were significantly more common in groups with elevated cTnT, except for prior stroke/TIA and active malignancies (p = 0.65 and p = 0.48, respectively). Dyspnea was more common in patients with elevated cTn, but chest pain was twice as common in patients with normal cTnT in comparison to the group with cTnT >50 ng/L (27% vs. 13.3%). Anemia, elevated C-reactive protein, and deterioration of kidney function were significantly more common in patients with troponin elevation, and these patients also sought care at an ED more often with ECG changes indicative of myocardial ischemia (Table 6).

Table 6. Patient characteristics.

	All patients (*n*=2911)	TnT <15 ng/L (*n*=795)	TnT 15–50 ng/L (*n*=1446)	TnT 51–100 ng/L (*n*=670)	*p*-Value
Age, years	77.1 ± 10.5	71.0 ± 10.3	78.8 ± 9.6	80.7 ± 9.6	<0.001
Women	1457 (50.1)	432 (54.3)	728 (50.3)	298 (44.5)	0.001
Paroxysmal AF	1211 (41.6)	493 (62.0)	479 (33.1)	239 (35.7)	<0.001
New onset AF	305 (10.6)	34 (4.3)	201 (14.0)	70 (10.6)	<0.001
CHA_2DS_2-VASc	3.89 ± 1.76	3.3 ± 1.85	4.03 ± 1.68	4.29 ± 1.65	<0.0001
Comorbidities					
Heart failure	610 (21.0)	86 (10.8)	315 (21.8)	209 (31.2)	<0.001
Hypertension	1990 (68.4)	505 (63.5)	980 (67.8)	505 (75.4)	<0.001
Diabetes mellitus	745 (25.6)	155 (19.5)	377 (26.1)	213 (31.8)	<0.001
Coronary artery disease	869 (29.9)	186 (23.4)	444 (30.7)	239 (35.7)	<0.001
Prior myocardial infarction	449 (15.4)	99 (12.5)	223 (15.4)	127 (19.0)	0.003
Prior stroke or TIA	553 (19.0)	153 (19.2)	281 (19.4)	119 (17.8)	0.65
Peripheral artery disease	160 (5.5)	24 (3.0)	85 (5.9)	51 (7.6)	<0.001
Active malignancy	128 (4.4)	29 (3.6)	68 (4.7)	31 (4.6)	0.48
Main symptoms					
Dyspnea	823 (28.3)	132 (16.6)	438 (30.3)	253 (37.8)	<0.001
Chest pain	513 (17.6)	215 (27.0)	209 (14.5)	89 (13.3)	<0.001
Laboratory parameters					
cTnT, ng/L	27.0 [14.0–48.0]	10.0 [8.0–12.0]	29.0 [22.0–38.0]	68.0 [58.0–79.0]	<0.001
Hemoglobin, g/L	131 [118–144]	138 [128–148]	130 [117–143]	123 [111–138]	<0.001
eGFR, ml/min/1.73 m^2	60.0 [44.3–76.7]	71.0 [58.5–83.5]	58.3 [43.0–75.5]	47.8 [33.5–65.9]	<0.001
NT-proBNP, ng/L[a]	2930 [1230–5838]	1030 [457–2358]	3140 [1390–5630]	4949 [2115–9645]	<0.001
CRP, mg/L[b]	17.5 [4.0–70.0]	4.0 [2.0–14.5]	22.0 [6.0–79.3]	36.0 [10.0–106.0]	<0.001
Systolic blood pressure, mmHg[c]	141 [123–161]	144 [126–165]	142 [124–162]	136 [115–157]	<0.001
ST depression on admission ECG	220 (7.6)	20 (2.8)	139 (10.5)	61 (10.3)	<0.001

Values are n (%), mean ± standard deviation, median [inter-quartile range, 25th-75th percentiles]. AF, atrial fibrillation; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration equation); cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro brain natriuretic peptide; TIA, transient ischemic attack; [a]data missing on 1507 patients; [b]data missing on 261 patients, [c]data missing on 352 patients.

At 30 days, there were 7 (0.9%) deaths in the subgroup of patients with cTnT at or below the 99th percentile, 98 (6.8%) in the subgroup of patients with cTnT between 15–50 ng/L, and 91 (13.6%) in the subgroup of patients with cTnT of 50–100 ng/L. The respective mortality rates at 1 year were 5.4% (n = 43), 23.4% (n = 338), and 39.6% (n = 265), respectively (p <0.001). At 3 years, the respective mortality rates were 11.2% (n = 89), 39.8% (n = 575), and 59.3% (n = 397). Adjusted Cox survival curves for all patients and AF subgroups are shown in Figure 5. A log-rank test for cTnT subgroups was significant (p <0.001), and a similar pattern was observed for permanent and paroxysmal AF (log-rank <0.001). When compared with normal cTnT values (cTnT <15 ng/L), cTnT 15–50 ng/L was strongly associated with mortality at 30 days (HR 6.02, 95%CI 2.62–13.8), 1 year (HR 3.08, 95%CI 2.15–4.40) and 3 years (HR 5.33, 95%CI 4.11–6.92). For cTnT elevation of 51–100 ng/L, the hazard rations (HR) were 11.3 (95%CI 4.887–26.1) at 30 days, 5.07 (95%CI 3.49–7.35) at 1 year, and 3.21 at 3 years (95%CI 2.51–4.11), respectively. Other independent predictors of mortality at 30 days were active malignancy, ST depression on admission ECG, CRP >30mg/L, and heart failure. At 1 year, active malignancy, age >75 y, heart failure, anemia, ST depression on admission ECG, CRP > 30 mg/L, and AF detected on admission ECG were associated with increased mortality (Table 7).

Table 7. Adjusted hazard ratios for all-cause mortality.

Study interval		HR (95%CI)	*p*-value
30-day			
	cTnT levels		
	cTnT 51–100 ng/L	11.28 (4.87–26.12)	<0.001
	cTnT 15–50 ng/L	6.02 (2.62–13.83)	<0.001
	Active malignancy	2.86 (1.82–4.49)	<0.001
	ST depression	1.83 (1.23–2.74)	0.003
	CRP >30 mg/L	1.52 (1.11–2.07)	0.008
	Heart failure	1.37 (0.99–1.89)	0.06
1-year			
	cTnT levels		
	cTnT 51–100 ng/L	5.07 (3.49–7.35)	<0.001
	cTnT 15–50 ng/L	3.08 (2.15–4.40)	<0.001
	Active malignancy	2.56 (1.93–3.39)	<0.001
	Age >75 years	1.79 (1.44–2.22)	<0.001
	Heart failure	1.45 (1.21–1.74)	<0.001
	Anemia[a]	1.34 (1.13–1.59)	0.001
	ST depression on admission ECG	1.31 (1.01–1.69)	0.039
	CRP >30 mg/L	1.29 (1.01–1.54)	0.006
	AF on admission	1.26 (1.01–1.56)	0.04
	Chest pain	0.69 (0.53–0.91)	0.009
3-year			
	cTnT levels		
	cTnT 51–100 ng/L	5.33 (4.11–6.92)	<0.001
	cTnT 15–50 ng/L	3.21 (2.51–4.11)	<0.001
	Active malignancy	2.31 (1.80–2.97)	0.001
	Age >75 years	1.68 (1.43–1.98)	<0.001
	Heart failure	1.53 (1.32–1.77)	<0.001
	Prior stroke or transient ischemic attack	1.36 (1.12–1.58)	<0.001
	Anemia[a]	1.35 (1.18–1.54)	<0.001
	Prior myocardial infarction	1.28 (1.08–1.52)	0.004

HR, Hazard ratio; CI, confidence interval; AF, atrial fibrillation; CRP, C-reactive protein; TnT, high-sensitivity cardiac troponin T. [a]Hemoglobin level below 120 g/L in females and 130 g/L in males.

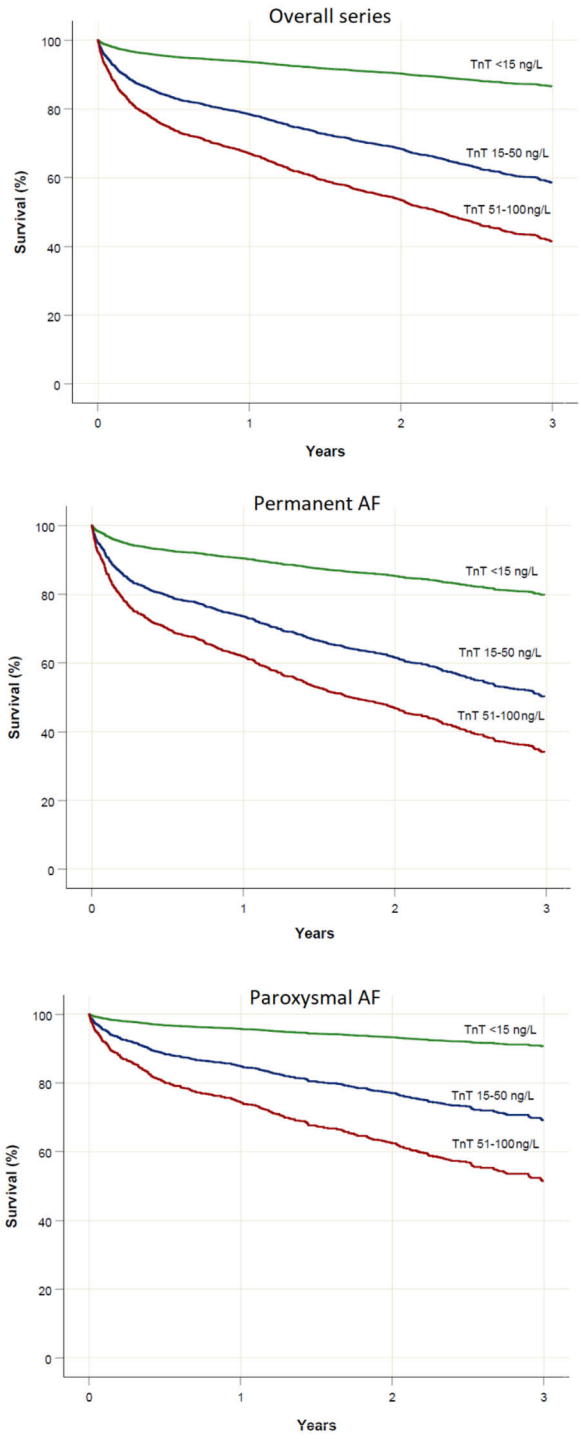

Figure 5. Cox adjusted survival curves for all AF patients (upper panel), patients with permanent AF (middle panel), and patients with paroxysmal AF (lower panel).

At 30 days, MI was a rare occurrence, with an incidence of 0.2%. No relation to cTnT levels was observed. At 1 year, incremental rates of AMI were seen in patients with normal TnT (0.6%) as well as in patients with TnT 15–50 ng/L and TnT 50–100 ng/L (1.7% and 2.8%, p = 0.004). The association between TnT levels and mortality was similar irrespective of the discharge diagnosis (Figure 6).

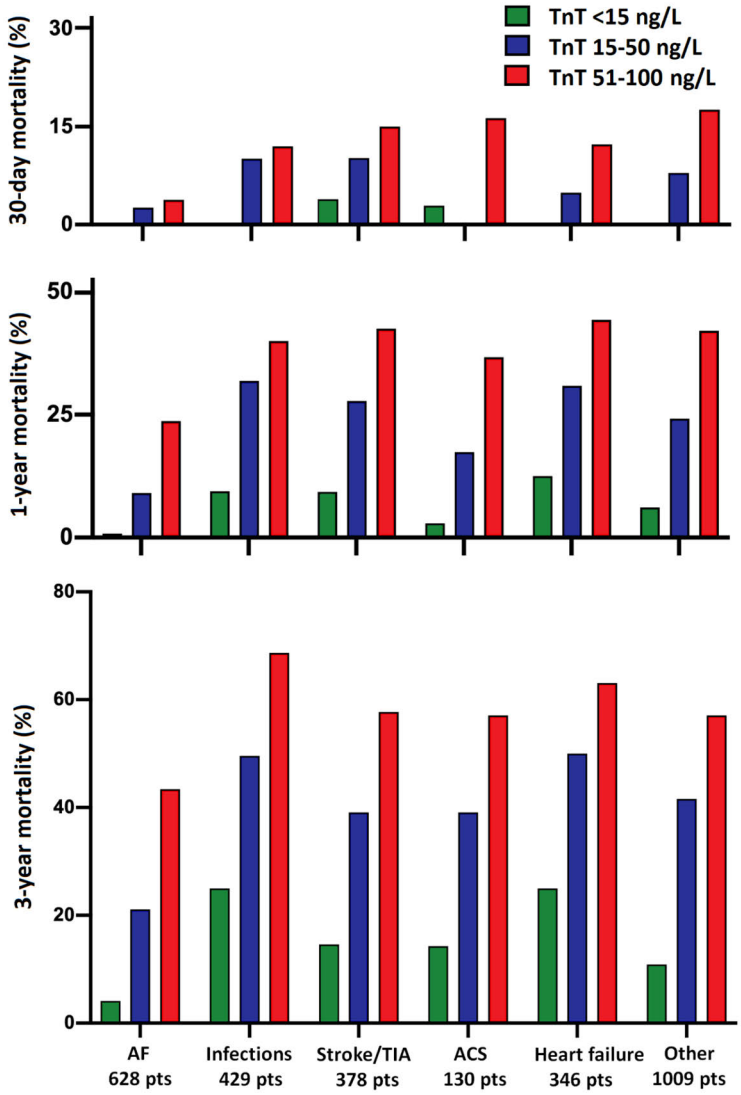

Figure 6. 30-day (upper panel), 1-year (middle panel), and 3-year mortality rates according to primary discharge diagnosis. AF, atrial fibrillation; ACS, acute coronary syndrome; TIA, transient ischemic attack.

6 Discussion

6.1 Study I

"Hail, we are the victors!" announced Pheidippides, the courier who brought news of the Greek victory over Persia in the battle of Marathon (490 BC) and then dropped and died on the spot (Lucas, 1976). Despite this abysmal end to the "first marathon," the protective effects of physical activity in terms of cardiovascular mortality and diseases is well established (Lear et al., 2017). Ancient tales do not elaborate on Pheidippedes' possible comorbidities or symptoms, let alone his cTn levels, but in light of studies conducted during recent decades, we know that cTn elevation is common after strenuous physical exercise (Shave et al., 2007). Our results confirm this finding, as in our study almost all the participants (95%, n = 38/40) had cTnT levels >UNL post-race, i.e., above the rule-in criteria for the diagnosis of acute myocardial injury (Morrow, 2020). Current evidence indicates troponin elevations occur shortly after commencement of strenuous exercise and remain elevated for at least 1 hour after exercise, with a secondary peak within 24 hours (Middleton et al., 2008). This elevation is assumed to be mostly physiological, as post-race echocardiography or magnetic resonance imaging have not been able to detect evidence of myocardial necrosis (Scharhag et al., 2006). Prolonged elevation (beyond 24 h) of cTn levels after exercise have been shown to be associated with obstructive CAD (Kleiven et al., 2020). Furthermore, recent studies have suggested the cTn forms released after exercise are secondary, smaller fragments identical to those found in patients with end-stage renal disease and differ in size from those of patients with AMI (Vroemen et al., 2019).

CAC is a highly specific, consistent feature of coronary atherosclerosis exhibiting a strong association with major cardiovascular outcomes in asymptomatic people (Greenland et al., 2018). High levels of physical activity have been associated with increasing CAC levels (Aengevaeren et al., 2017). 53.6% of the middle-aged participants in the MARACAT study presented with CAC (median score 2.0[IQR80]) on a CT scan. The positive association between physical activity and CAC has been established (Aengevaeren et al., 2017; Sung et al., 2021). As high cardiorespiratory fitness is associated with increasing CAC levels, it is also inversely associated with lower cardiovascular mortality irrespective of CAC score (Radford

et al., 2018). Our study found no correlation between CAC and post-race TnT level (r_s = -0.013, p = 0.95). The clinical significance of this finding seems even more equivocal, as the diagnostic value of CAC in diagnosing obstructive CAD in patients <60 years of age seems limited (Mortensen et al., 2021). The finding is also supported by Kleiven et al., who studied recreational cyclists with elevated cTn and found no significant difference in CAC score whether or not they had CAD (Kleiven et al., 2020). CAC is associated with elevated levels of pregnancy-associated plasma protein A (PAPP-A) (Güven et al., 2013), a marker with a correlation to a poor outcome in patients with ACS (Lund et al., 2010) and stable CAD (Cosin-Sales et al., 2005) and produced in high quantities in vulnerable plaques (Bayes-Genis et al., 2001). fPAPP-A levels were significantly elevated post-race in our study, but no correlation with post-race cTnT levels or CAC score was apparent (r_s = -0.26, p = 0.11 and r_s = -0.23, p = 0.24, respectively). To our knowledge, this was the first study to evaluate fPAPP-A after physical exercise, and the significance of this finding remains elusive. Interpretation of this finding is hampered by the low number of study participants, relatively low CAC scores, and lack of sufficient long-term follow-up.

Skeletal muscle injury associated with physical exercise has been hypothesized to be associated with elevated cTn levels, not unlike the skeletal muscle injury observed in patients with skeletal myopathies (Schmid et al., 2018). The mechanisms are assumed to be either cross-reactivity between assays or possible cTn re-expression in the skeletal muscle, with the former possibility more likely (Giannitsis, Mueller & Katus, 2019). In our study, a novel skTnI assay (Bamberg et al., 2020) was used to evaluate skeletal muscle injury and a 10.7-fold increase was observed, but without correlation to post-race cTnT (r_s = 0.292, p = 0.068).

The only independent predictor of post-race cTn elevation in our study was younger age, a finding in line with previous reports (Fortescue et al., 2007; Eijsvogels et al., 2015). The causes of this finding remain unclear, but it can be hypothesized that higher intensity (Serrano-Ostáriz et al., 2011), higher maximum heart rate, or less training experience (Mehta et al., 2012) in younger runners may contribute. In our study, only a limited number of maximum heart rate values were recorded. The maximum heart rate correlated only moderately with cTn elevation, thus rendering the value of this finding questionable. Findings from other studies suggest that the magnitude of cTn release is more likely to be affected by intensity of exercise and recorded maximum heart rate than duration of exercise (Marshall et al., 2019; Eijsvogels et al., 2013). There is also evidence of individual variability in cTn response to exercise (Bjørkavoll-Bergseth et al., 2021). The exact mechanisms by which troponin is released from myocytes in response to physical exercise are not known. Most of the troponin isoforms are attached to the myofibrils, but 3–6% of the cTn isoforms exist in free form in the cytosol; most likely, increased cell

membrane permeability results in increased post-exercise cTn values, as unbound isoforms are released into the circulation. This hypothesis is supported by relatively low levels of circulating troponins post-exercise and a return to baseline levels within 24–48 hours (Middleton et al., 2008), as opposed to patients with AMI, in whom cTn levels usually are significantly higher and stay elevated for longer periods of time.

6.2 Studies II and III

6.2.1 Etiology

cTn is the preferred biomarker for diagnosing MI or injury, and current guidelines recommend the use of high-sensitivity assays to detect cTn levels (Collet et al., 2021). Fourth-generation "sensitive" assays were able to detect cTn in 20–50% of healthy populations, as opposed to current high-sensitivity tests, which detect cTn in over 50% of healthy individuals. The High-STEACS study conducted in 2018 showed that implementing high-sensitivity assays led to a reclassification of 1 in 6 patients with chest pain but showed no benefit in reducing MI or death from cardiovascular causes at 1-year follow-up (Shah et al., 2018). This increased sensitivity in the detection of MI accompanied by decreased specificity leads to a situation where hs-cTn tests should be used in conjunction with rigorous clinical assessment. These studies present a true clinical challenge, as these minor cTn elevations represent a wide variety of possible diagnoses (Apple & Morrow, 2010; Jaakkola et al., 2019), and the positive predictive value (PPV) of minor cTn elevation for MI is only 50% (Boeddinghaus et al., 2017), and when patients seek care at an ED with non-typical symptoms, the PPV is even lower.

It is estimated that cTn levels are tested for 17% of patients seeking care at an ED, and subsequently over 8% of tests are conducted in patients presenting without symptoms suggestive of ACS (Makam & Nguyen, 2015). In a patient cohort without suspicion of ACS, elevated cTn occurs in more than 12% of the cohort, with most of the patients presenting with myocardial injury (Lee et al., 2019). When AF patients are considered, a RE-LY substudy found 57.1% of the patients having detectable levels of TnI and 24.6% with values over URL (Hijazi et al., 2012). The ARISTOTLE trial used a high-sensitivity test (Hijazi et al., 2014), and the authors found that 93.5% of the patients had detectable levels of cTnT, with median values of 11.0 (IQR7.5–16.7) ng/L, and 1 in 4 patients had cTnT levels above 16.7 ng/L. Furthermore, in a study by Roldan et al., a high-sensitivity test was used, and 82.8% of the patients had detectable levels of cTn, whilst 31% had cTn elevations above URL (Roldán et al., 2012), with variations in cTn levels most likely reflecting differences in study populations and the assays used.

In our study, patients who sought care at an ED were evaluated. High-sensitivity cTn assays found detectable levels of cTn in almost all the patients, and over 70% had levels ≥URL. This finding is in line with a study by Stoyanov et al. that relied on the same assay, where the respective percentages were 88.3% and 56.4% (Stoyanov et al., 2018). When using the previous generation cTnI assays, troponin elevations are seen in under 20% of patients (van den Bos et al., 2011). In the present study, the most common discharge diagnosis in the normal cTn group was AF with a 1.7-fold prevalence compared to the group with elevated troponin. In the group with elevated cTn, the proportion of AF as the principal diagnosis was significantly lower, and the most common discharge diagnoses were infections and heart failure. The strongest predictors of cTnT elevation in our study were age, anemia, worsening kidney function, and infections. When age ≥75 years was combined with elevated CRP or low eGFR, virtually all patients in our study presented with elevated cTnT. The role of increasing age thus seems to be of marked significance. Other authors have suggested the use of age-specific cutoff values when cTnT is used. Data from three population studies—the Dallas heart study (DHS), the atherosclerosis risk in communities (ARIC), and the cardiovascular health study (CHD)—advocate increasing the cutoff value in male patients >65 years of age to 31 ng/L (Gore et al., 2014), and even higher cutoff values (54 ng/L) have been proposed in patients >70 years (Reiter et al., 2011).

HF and AF frequently coexist, and both are associated with elevated levels of cTn and NT-proBNP, a neurohormone secreted from the myocytes usually in response to volume or pressure overload. Elevated NT-proBNP levels predict increased risk of AF independent of other risk factors (Patton et al., 2009). In anticoagulated AF patients, elevated NT-proBNP has been found to be independently related to increased risk of stroke and mortality (Hijazi et al., 2012). Accordingly, patients with elevated cTn had higher NT-proBNP levels than patients with normal cTn, albeit the correlation was not strong ($r_s = 0.476$, $p < 0.001$). The multitude of discharge diagnoses and large quantity of missing NT-proBNP analyses preclude the drawing of further conclusions from our study. ACS is a rare diagnosis in AF patients seeking care at an ED. In our study, under 5% of patients were considered to have ACS irrespective of TnT elevation. A similar (5.0%) prevalence of ACS in AF patients seeking care at an ED has been reported by Stoyanov et al (Stoyanov et al., 2018). In our study population, coronary angiography was performed on very few patients and only a quarter of patients with an ACS diagnosis. Angiographically significant disease was found in almost all the patients, but only 1 in 5 patients had coronary revascularization. Independent predictors of ACS in our study population were chest pain (of note: chest pain was twice as common in patients without a final diagnosis of ACS), known CAD, and declining renal function. Again, these findings are in line with those of Lee et al., who investigated

patients suspected to have ACS (MI ruled out) and found patients three times more likely to have CAD, even with "high normal" cTn values (below URL) in comparison to "low normal" values (42% non-obstructive CAD and 30% obstructive disease) (Lee et al., 2021). The benefit of CAD diagnosis and accompanying treatment optimization in patients without MI and known CAD may appear plausible, but data on morbidity and mortality in this scenario is lacking. At present, the consensus is that aggressive antithrombotic treatment and invasive investigations in patients with type 2 MI or myocardial injury are not beneficial, but more clinical trials are needed on this topic.

6.2.2 Mortality

In Study III, the same patient cohort as in Study II was analyzed to evaluate the short- and long-term mortality in AF patients presenting to the ED. We divided the patients into three groups according to maximum cTnT levels. Almost half of the patients had cTnT 51–100 ng/l, with only 2% presenting with normal cTnT. The association of troponin level and mortality has been established across all age groups, with a direct relation in patients without ACS. Even minor troponin elevations lead to approximately 15% higher 3-year mortality rates (Kaura et al., 2019). In the present study, 30-day mortality risk was 6-fold in the group with cTnT 15–51 ng/L and 11-fold in the group with cTnT 51–100 ng/L, when compared to patients presenting with cTnT <UNL. At 1 year and 3 years, mortality rates in the 51–100 ng/L group were 5-fold compared to the group with normal cTnT. Similar short-term mortality risk rates have been found in other studies (Kaura et al., 2019), as have similar overall mortality rates (Stoyanov et al., 2018). These findings emphasize the importance of cTnT in the prognosis of the patient, as increased mortality was observed regardless of the discharge diagnosis.

One important finding in our study was the association between "high normal" cTnT levels and mortality. When patients with normal cTnT (<15 ng/L) were dichotomized according to the median cTnT value (10 ng/L), levels of 10–14 ng/L (minute cTnT elevation) were associated with increased risk of 1-year mortality (HR 2.51, 95%CI 1.09–5.74, p = 0.03), but no increase in 30-day mortality was observed (HR 1.41, 95%CI 0.26–7.72, p = 0.69) (Figure 7). Similarly, using the same high-sensitivity assay Stoyanov et. al. showed that even detectable levels of cTn increase mortality in AF patients (Stoyanov et al., 2018).

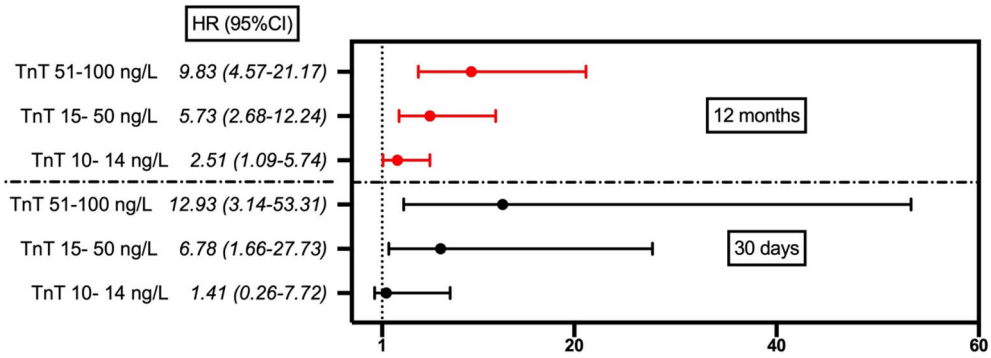

Figure 7. Adjusted hazard ratios for minute, minor and moderate TnT elevation in comparison to TnT level <10ng/L to predict all-cause mortality.

As most of our patients presented with non-ACS causes of elevated troponin levels, it seems reasonable to presume an overall burden of comorbidities or diminished organ level reserves play a large role in the elevated troponin, as opposed to it being an indicator of unstable CAD. In accordance with this finding, retrospective analysis found the cause of death in the non-ACS population to be obstructive coronary disease in only 3% of patients (Campbell et al., 2018).

In our study, survival rates were highest in the patients with a primary diagnosis of AF. Even so, the deleterious effect of cTnT elevation on mortality was seen in all types of AF, and increased mortality associated with minor cTn elevation is apparent in patients with short-lasting AF (<48 h) (Conti et al., 2013), while the first episode of AF with cTn elevation leads to a 2-fold mortality risk (Naffaa et al., 2017).

6.2.3 Possible limitations and strengths of the study

Study I was primarily limited by the small size and and heterogeneous nature of the cohort, which might not be representative of typical marathon runners, especially as only male subjects were included in the study. Studies II and III were retrospective and observational by nature. Treatment and diagnostic workup were based on the judgment of a heterogeneous group of emergency physicians without strict institutional protocol. Thorough data collection from patient records and complete follow-up can be seen as the main strengths of Studies II and III.

6.2.4 Clinical implications and future research needs

The individual studies comprising this dissertation emphasize the considerable sensitivity of current cTn tests in detecting myocardial injury and infarction. Even minor cTn elevation, which suggests myocardial injury, is associated with impaired

prognosis. Dynamic cTn elevations are considered a more specific marker of ACS, but in our study population, it did not have additional predictive power in the diagnosis of ACS, as most of the patients presented with acute illnesses known to cause temporary cTn elevations. Hence, imprudent use of cTn testing should be avoided in order to avoid clinical pitfalls leading to false diagnosis, futile tests, and possibly erroneous treatment. Extensive research is required to establish suitable treatment in these patients, as contemporary guidelines are targeted at treating MI. The caveat at the present time lies in distinguishing pathological cTn elevations from apparently normal physical variation in cTn levels. Recently published articles have elaborated on the possibility that cTn fragments found in circulation after vigorous exercise are smaller in size compared to the forms found in patients with ACS. Assays targeting the various forms of cTn in circulation might provide a more precise tool for differentiating between pathological and physiological cTn variations.

7 Conclusions

1. Elevated cTn levels are exceedingly common after strenuous physical exercise, such as a marathon, with no apparent association to skeletal muscle injury or markers of coronary atherosclerosis.
2. Minor cTn elevation is very common in AF patients presenting to the ED irrespective of primary discharge diagnosis.
3. Minor cTn elevations in AF patients presenting to the ED are rarely caused by ACS.
4. Even minor cTn elevations detected during care at an ED were associated with increased short- and long-term mortality in AF patients, regardless of the discharge diagnoses and type of AF.

Acknowledgements

This dissertation was conducted at the Heart Center, Turku University Hospital and University of Turku; Doctoral Programme in Clinical Research, Finland during 2019–2022.

I would like to express my sincerest and warmest gratitude to my dissertation supervisor, Professor Juhani Airaksinen, MD, PhD. As the establisher of the Heart Center, you brought modern cardiology to Turku, and we are hard-pressed to follow your standards of quality. Your outstanding scientific and clinical skills have made you a role model for all cardiologistst who have been fortunate enough to work with you. Throughout this project, you have always made time to help me and offer sound advice. Thank you for your patience.

I also wish to express my gratitude to my second supervisor, Samuli Jaakkola, MD, PhD. We embarked on our adventures in the world of cardiology in Pori and have continued to do so in Turku. Your support and assistance during this project have been invaluable. You more than anyone have been at the receiving end of my frustration and cursing over these years. I truly am grateful for your friendship.

I am deeply honoured that docent Olli Anttonen agreed to serve as my opponent. In addition to your skills as a clinician, your achievements as a teacher, an academic and a pioneer of electrophysiology in Finland speak for themselves. I also wish to express my deepest gratitude to my reviewers, docents Vesa Virtanen and Heikki Mäkynen, whose expertise and advice greatly improved this dissertation. I am also grateful to docents Vesa Anttila and Antti Ylitalo for being members of my supervisory committee. Your support has been invaluable.

A special thank you to Antti: you are the main reason I am a cardiologist today. Some people simply have a gift, an ability to make everything in cardiology seem simple and easy. Since the beginning of my career at Satakunta Central Hospital, you have inspired me as a collegue, mentor and friend.

Going back to my first years as a cardiologist, I want to thank my Satakunta Heart Center colleagues Pasi Karjalainen, Jussi Mikkelsson and Olli Kajander. We had a lot of fun and even more work to do. Your guidance and friendship were and still is greatly appreciated.

I wish to express my sincere gratitude to all co-authors for your contribution: Katriina Bamberg, Antti Saraste, Emilia Tuunainen, Saara Wittfooth, Petri Kallio, Juhani Knuuti, Kim Pettersson, Ilpo Nuotio, Tuomas Kiviniemi, Jussi-Pekka Pouru, Pekka Porela, Fausto Biancari and especially Tuija Vasankari for taking care of basically everything imaginable.

My deep gratitude goes to the hard working staff at Turku Heart Center. Juhani Airaksinen, Samuli Jaakkola, Antti Ylitalo, Heikki Ukkonen, Mikko Pietilä, Antti Saraste, Juha Lund, Pekka Porela, Mikko Savontaus, Raine Virtanen, Riikka Lautamäki, Teemu Ahola, Nea Kalleinen, Tuomas Kiviniemi, Petri Korkeila, Ville Kytö, Sanna Laurila, Tuomas Lehtinen-Svahn, Heidi Lehtola, Ilpo Nuotio, Rami Nylund, Jouni Pykäri, Tiina Salo, Helena Tuunanen, Tapani Vihinen, Toni Grönberg, Joonas Lehto, Joel Nuotio, Joonas Ottela, Jani Salminen, Iida Stenström, Vesa Anttila, Markus Malmberg, Vesa Vilkki, Maina Jalava, Gennadi Skvortsov and Kristiina Pälve. I am privileged to work with you, and as unplausible as it may sound, I am always eager to dig into a new day of work at our hospital. I'd like to thank Esa Joutsiniemi for his friendship, sparring and interest in this work.

I want to take this opportunity to thank late Professor Juhani Koistinen. He taught the importance of listening to the patient. His combination of intelligence, knowledge, skill and humour was unforgettable.

There is more to life besides work. **CHC**, you know who you are. Thank you for being my accomplice in enjoying the finer, and sometimes decadent, things in life.

I want to express my gratitude also to my family members: Hannu, Ville, Alexandra, Antti, Kerstin, Marita, Kerttu and Antti. My in-laws Maiju and Risto have been most supportive, as have been my wife's siblings Aleksi and Kaisa and their spouses Mari and Ville. Special commendation to my finnish teacher, Kaisa. I thought I knew how to write in finnish and was proven wrong!

My mother, Maija-Leena, has always provided me with unconditional support and love. For that, I cannot thank you enough.

Finally, I want to thank the love of my life, Anna, for your support throughout the years. This work and many other wonderful things in my life would not have been possible or worthwile without you. Everything I have achieved is the result of our partnership and love. As wonderful as this dissertation is, our greatest achievement is our family and children, Ilona, Veikko, and Fanni. I love you more than anything, and you give me all the joy I need in the world.

The work presented here was financially supported by the State Clinical Research Fund of Turku University Hospital, the Finnish Foundation for Cardiovascular Research and Turunmaa Duodecim Society.

Tuomas Paana

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TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

Painosalama, Turku, Finland 2022

ISBN 978-951-29-8828-0 (PRINT)
ISBN 978-951-29-8829-7 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)