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DISSERTATION

ASSOCIATION OF PRE-HOSPITAL CARE AND INVASIVE MANAGEMENT IN PATIENTS WITH MYOCARDIAL INFARCTION. A SINGLE CENTRE STUDY BASED ON THE BERLIN MYOCARDIAL INFARCTION REGISTRY

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Table of contents

Abbreviations

ACS	acute coronary syndrome
BMI	body-mass-index
BMIR	Berlin Myocardial Infarction Registry
CABG	coronary artery bypass graft
CCL	cardiac catheterization laboratory
CHD	coronary heart disease
CT	computed tomography
DTB	door to balloon
DTN	door to needle
ECG	electrocardiogram
ED	emergency department
ED bypass	emergency department bypass
EMS	emergency medical system
EMT	emergency medical technician
EP	emergency practitioner
FMC	first medical contact
ICU	intensive care unit
GP on call	general practitioner on call
LBBB	left bundle branch block
LDL	low density lipoprotein
LDL-C	low density lipoprotein cholesterol
HDL-C	high density lipoproteins cholesterol
NSTEMI	non-ST elevation myocardial infarction
MI	myocardial infarction

PCI	percutaneous coronary intervention
PTCA	percutaneous transluminal coronary angioplasty
RBBB	right bundle branch block
STEMI	ST elevation myocardial infarction
WHO	World Health Organization

Zusammenfassung

Hintergrund:

Leitlinien geben vor, dass bei STEMI Patienten das Herzkatheterlabor prähospital aktiviert und Patienten direkt im Herzkatheterlabor behandelt werden sollten. Dies beschleunigt die Patientenversorgung. Der Erfolg dieser Strategie hängt von einer schnellen und eindeutigen Frühdiagnose sowie einer präklinischen Triage ab.

Zielsetzung:

Zu Beginn der Studie stellten wir fest, dass bei vielen Herzinfarktpatienten mit ST-Streckenhebung im prähospitalem EKG explizit kein STEMI diagnostiziert wurde.

Wir haben den Zusammenhang zwischen einer eindeutigen, prähospitalen STEMI-Diagnose und der anschließenden Door to Balloon (DTB)-Zeit mit der DTB-Zeit für Patienten mit einer ST-Streckenhebung im EKG ohne explizit angegebene STEMI-Diagnose verglichen. Darüber hinaus haben wir den Anteil der Patienten mit präklinischer STEMI-Diagnose zu denjenigen mit retrospektiv diagnostizierter ST-Strecken-Hebung während und außerhalb der Arbeitszeit untersucht.

Methode:

Wir führten eine retrospektive monozentrische Studie im einem akademischen Lehrkrankenhaus in Berlin durch. Eingeschlossen wurden 474 Patienten, die von Januar 2008 bis Dezember 2011 wegen Typ-I-Myokardinfarkt (M) behandelt wurden. Wir konzentrierten uns auf Patienten mit STEMI-Diagnose bei Krankenhausentlassung und prähospitaler Behandlung von einem Arzt. Wir teilten die Studienpopulation in vier Gruppen: (1) Patienten mit prähospital diagnostiziertem STEMI, (2) Patienten mit prähospital erkannter ST-Streckenhebung im EKG, (3) Patienten mit prähospitaler MI- oder NSTEMI-Diagnose und (4) andere Patienten. In jeder Gruppe wurde unterschieden zwischen Patienten, die während der regulären Arbeitszeit und jenen die außerhalb der regulären Arbeitszeit stationär aufgenommen wurden. Untersucht wurden die DTB-Zeiten.

Ergebnisse:

Der Aufnahmezeitpunkt während der Arbeitszeit war in allen Gruppen mit einer kürzeren mittleren DTB verbunden. Die DTB-Zeit bei Patienten mit einer eindeutigen präklinischen STEMI-Diagnose betrug 50 Minuten (Median) und war 8 Minuten schneller als bei Patienten mit dokumentierter ST-Hebung im EKG ohne präklinische STEMI-Diagnose (während der Arbeitszeit 20 Minuten kürzer als außerhalb der Arbeitszeit). Die längste DTB-Zeiten wurden bei den Patienten beobachtet, die außerhalb der Arbeitszeit ohne MI- oder STEMI- oder NSTEMI-Diagnose und ohne dokumentierte ST-Streckenhebung im EKG aufgenommen wurden. Die Anzahl der präklinisch diagnostizierten Patienten mit STEMI war bei allen Patienten mit ST-Hebung im EKG außerhalb der Arbeitszeit signifikant niedriger als während der Arbeitszeit (p = 0,032).

Schlussfolgerung:

Wir beobachteten längere DTB-Zeiten bei STEMI-Patienten ohne eindeutige präklinische STEMI-Diagnose. Darüber hinaus war der Anteil der Patienten mit eindeutiger, präklinischer Diagnose „STEMI“ bei allen mit Diagnose STEMI entlassenen Patienten außerhalb der regulären Arbeitszeit signifikant niedriger. Unsere Daten legen nahe, dass die präklinische STEMI-Diagnose ein entscheidender Faktor für die in den Leitlinien geforderte schnelle Patientenversorgung ist.

Summary

Background:

There is strong evidence that pre-hospital cardiac catheterization laboratory activation and bypass of Emergency Departments reduces door to balloon time (DTB) in STEMI patients. The success of these strategies depends on definite and stable early diagnosis and pre-hospital triage for patients with STEMI.

Objective:

In preparation of the study protocol, we observed that many patients with ST elevation in the pre-hospital ECG protocol were not diagnosed as “STEMI”. We sought to determine the association of a clear pre-hospital STEMI diagnosis and the subsequent DTB time in comparison to patients with a ST segment elevation, but not an identified or explicitly stated diagnosis, who therefore had not been given the “label” STEMI. In addition, the proportion of pre-hospital STEMI diagnoses in patients with retrospectively diagnosed ST-segment elevation was evaluated according to presentation during regular working hours versus off-hours.

Methods:

We conducted a retrospective monocentric study in the hospital in Berlin. We collected the data of 474 consecutive patients admitted to our facility from January 2008 to December 2011, who had been treated for type I MI.

The data of the screening population had previously been assessed according to the dataset of the Berlin Myocardial Infarction Registry. We focused on patients with STEMI diagnosis on discharge protocol, treated pre-hospital by a physician. We divided the study population into four groups: patients with pre-hospital STEMI diagnosis, patients with pre-hospital ST-elevation, patients with pre-hospital MI or NSTEMI diagnosis and other patients. We compared DTB times between the groups according to in- and off-hours admission.

Results:

Admission during working hours was associated with shorter median DTB in all groups. DTB time in patients with a defined pre-hospital STEMI diagnosis was 50 min (median), 8 min shorter than in patients with ST-elevation but no pre-hospital diagnosis of STEMI during working-hours (20 min shorter during off-hours). The longest DTB time was observed in patients admitted during off-hours, without MI or STEMI, or NSTEMI diagnosis, and with no documented ST-segment elevation. Furthermore, the number of pre-hospital recognized STEMIs among all ST-segment elevation patients during off-hours was significantly lower than during working-hours (p=0.032).

Conclusions:

We observed longer DTB times among STEMI patients without definite pre-hospital STEMI diagnosis. Furthermore, the proportion of patients with correct and firm classification as “STEMI” in the pre-hospital setting to all STEMI-discharged patients was significantly lower during off-hours. These data suggest that pre-hospital definite STEMI diagnosis is a crucial factor for delivery of reperfusion therapy in a timely manner.

1. Introduction

1.1 Myocardial infarction

1.1.1 Definitions

1.1.1.1 Myocardial Infarction

”Myocardial infarction” (MI) denotes a myocardial necrosis caused by prolonged myocardial ischemia.[1] Since the 1970s, the main role in creating the universal definition of MI was played by the WHO. The first standardized myocardial infarction definition was published in 1971.[2] This first definition was based on three main characteristics: ECG changes (at that time consisting in “persistent Q or QS waves and evolving injury current”), elevated cardiac biomarker levels and typical clinical presentation with chest pain or its equivalent. In accordance with this definition, a myocardial infarction diagnosis could be made if two of these occurred. Further characteristics like autopsy findings in fatal cases and the findings of imaging techniques have become increasingly important in more recent definitions.[3] The late 80s and early 90s brought a better mechanistic understanding of myocardial necrosis pathophysiology, and new developments in laboratory diagnostics. The discovery in 1989, and the subsequent validation of assays based on new biomarkers specific to the myocardium[4] - the cardiac troponins – have resulted in an update to this first MI definition, published in 2000.[5] Since the year 2000 and the publication of “Myocardial Infarction Redefined – A Consensus Document”, the concept that any amount of myocardial necrosis caused by ischemia should be labeled as an MI was accepted. As troponins – highly specific cardiac markers - are able to identify even a small amount of myocardial necrosis, the troponins started to play the pivotal role in MI definition. For the first time, this provided a differentiation between STEMI, reflecting the MI with ST segment elevation, mostly due to complete coronary occlusion, and NSTEMI, indicating myocardial necrosis without ST segment elevation in the ECG.[6] The definitions of STEMI and NSTEMI are given below. The First Global Taskforce, who authored the above mentioned Consensus Document in the year 2000, classified any degree of myocardial necrosis due to cardiac ischemia as a MI. In 2007 the Second Global Taskforce updated the first MI definition and added 5 new classification categories due to MI pathophysiology.[7]

Table 1 Clinical classification of different types of myocardial infarction

Type 1	Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2	Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
Type 3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a	Myocardial infarction associated with PCI
Type 4b	Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5	Myocardial infarction associated with CABG

Figure 1. Clinical classification of different types of myocardial infarction[8]

It became clear that in many settings myocardial injury producing elevated troponin levels cannot be labeled as myocardial infarction. An elevated troponin level can also be associated with congestive heart failure, aortic dissection, apical ballooning syndrome, pulmonary embolism, sepsis, or shock and critical illness caused by various conditions.[9,10]

As the MI definition was updated while the study was in progress, we have not used the current MI definition. For the purposes of this work, we used the Second Universal MI Definition published in European Heart Journal in 2007. According to this document the MI definition is as follows: “Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following: symptoms of ischemia, ECG changes indicative of new ischemia (new ST-T changes or new LBBB), development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.”[11]

Only the patients suffering from a type 1 MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, or fissuring, were of interest for this study. The immediate diagnosis of this type of MI and the implementation of an effective therapy during the acute phase of type 1 MI has been very challenging for many years, and still is.

The third updated definition of MI was published by the Global Myocardial Infarction Task Force in October 2012. The most important changes refer to "the adoption of higher biomarker thresholds and more stringent criteria for revascularization-related MI". "The third global MI task force also differentiated between recurrent MI and reinfarction", "summarized the ECG abnormalities that mimic myocardial ischemia or MI" and "reduced the emphasis on the use of other cardiac biomarkers."[12]

The Third Universal MI Definition also added the new type 4c "PCI-associated Myocardial infarction related to restenosis" to the MI classification.[13]

The most recent fourth definition of MI published in 2018 distinguishes MI from myocardial injury, especially those after cardiac and non-cardiac procedures.[14]

It is important to note that the marked variation of MI definitions over the last two decades makes it difficult and sometimes even impossible to compare studies that used different definitions. Also longitudinal observations have their limitations due to the evolving MI definitions. This study relies on the Second Universal Definition of MI, published in 2007.

1.1.1.2 Acute Coronary Syndrome

Acute Coronary Syndrome is the common term first used in the 90s to describe life threatening disorders caused by acute myocardial ischemia.[15] It includes three entities: ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina. The pathological correlate at the myocardial level is, in the case of NSTEMI and STEMI, cardiomyocyte necrosis or myocardial ischemia without cellular disintegrity (unstable angina).[16]

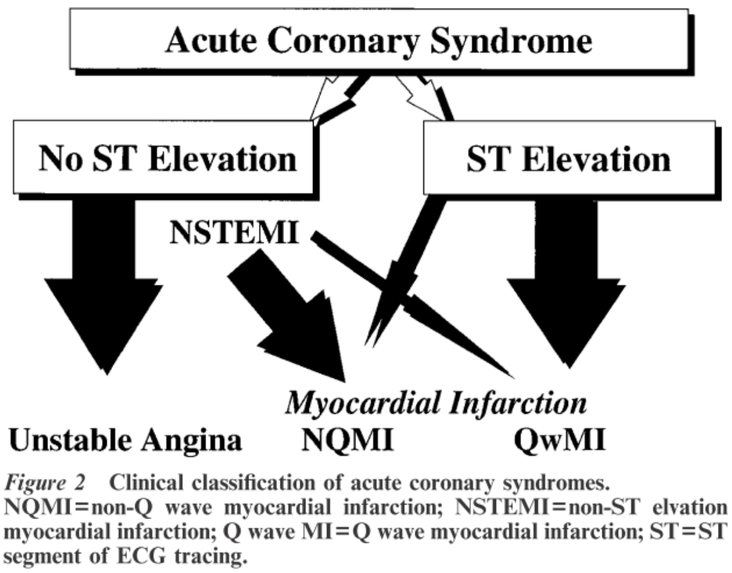
1.1.1.3 ST Segment Elevation Myocardial Infarction (STEMI)

ST Segment Elevation Myocardial Infarction (STEMI) is an acute coronary syndrome with persistent (>20 min) ST segment elevation in the ECG. The exact description of ECG changes labeled as “ST-Segment-elevation” is as follows: “New ST elevation at the J point in two contiguous leads with the cut-points: ≥ 0,1 mV in all leads other than leads V2-V3 where the following cut points apply: 0,2≥ mV in men ≥ 40 years; ≥ 0,25 mV in men <40 years, or ≥ 0,15mV in women.”[17] A STEMI is more uniform, as it is almost always associated with coronary occlusion[18] causing a large area of myocardial ischemia and subsequent necrosis. STEMI is typically a sudden and life threatening form of ACS. Therefore STEMI was separated as an entity demanding a different and particularly structured and fast reacting treatment strategy.[19]

1.1.1.4 Non-ST Segment Elevation Myocardial Infarction (NSTEMI)

The distinction between STEMI and NSTEMI, at the definition level, results from the differences in the ECG. All MIs not meeting the ST-segment elevation criteria (see above) are referred to as NSTEMI. Pathophysiologically, NSTEMI usually – but not always - reflects less severe MI, with incomplete coronary artery occlusion[20] leading to subendocardial necrosis.

The taxonomic relationship between MI, ACS, STEMI and NSTEMI is shown in the figure below.



[21]

Figure 2. Taxonomic relationship between MI, ACS, STEMI and NSTEMI

1.1.2 The pathophysiology of acute myocardial infarction

In most cases a regional acute myocardial infarction (MI) occurs as a result of coronary heart disease (CHD). CHD is a manifestation of coronary atherosclerosis.[22] Less common conditions leading to MI comprise coronary artery dissection, coronary vasospasm, coronary vasculitis, coronary embolism, and various other conditions leading to an imbalance of oxygen and energy supply and demand.[23] Atherosclerotic plaque erosion or plaque rupture is the typical starting point for the development of a MI. Recent decades have brought a better fundamental mechanistic understanding of atherosclerotic plaque formation.

There is significant evidence that atherosclerosis is at least in part an inflammatory disease.[24] Endothelial functional damage due to this inflammatory process results in an increased permeability of the vascular wall and the penetration of macrophages, lymphocytes and lipids.[25] There are many possible causes (cardiovascular risk factors) promoting endothelial dysfunction.

There are different stages and types of atherosclerotic plaques. At one extreme, there are stenotic plaques, containing a higher amount of fibrosis and calcification, with a thick cap, and without compensatory artery enlargement. On the other hand, there are lipid (large lipid core) rich non-stenotic lesions with a thin cap. In most cases, this second type is responsible for an ACS, while the first type often remains stable and can even be asymptomatic.[26,27]

With the progression of the atheromatous plaque, a fibrous cap and necrotic core develop. As a consequence of macrophages infiltration and inflammatory processes inside the plaque, apoptosis occurs.[28,29]. In this “mature” plaque we observe progressive thinning of the fibrous cap leading to vulnerability of its surface. This vulnerability is mainly determined by the composition of the plaque, and the rupture trigger is an extrinsic factor.[30] The ruptured plaque loses the integrity of the overlaying cap. Plaque rupture in most cases occurs when the predisposed plaque is exposed to tensile stress.[31] As a consequence, the necrotic plaque core is exposed to the blood and intraluminal thrombus formation occurs.[32]

While the process leading to plaque rupture is relatively well known, many questions related to pathophysiology and factors triggering plaque erosion remain unanswered.

Plaque erosion is the second most common mechanism inducing intraluminal thrombosis, and is responsible for 30-40% of STEMIs.[33] Erosion occurs when the endothelium overlying the plaque loses its integrity. In autopsy series, significantly lower inflammation marker levels were found in cases of plaque erosion compared to ruptured plaques.[34] In contrast to plaque rupture, in eroded plaques neutrophils are abundant instead of macrophages and lymphocytes.[35] Erosion of the plaque-lining endothelium allows blood contact with collagen. Subsequently, local activation of the coagulation system and intraluminal thrombus formation begins.

In this case, coronary thrombosis causes the blood demand-supply imbalance, and results in myocyte necrosis. The myocardial necrosis is not immediate. Until the first 30-40 minutes after the onset of ischemia, the changes are reversible.[36]

It is noteworthy that in an acute coronary event, it is not only thrombus formation at the culprit lesion that impairs the blood flow in the impacted artery. Additionally, as a result of local and systemic vasoactive mechanisms (increased systemic catecholamine activity, release of thrombin and other vasoconstrictors from coronary lesions), vasoconstriction has also been shown to contribute to compromised coronary flow. [37]

1.1.3 Cardiovascular risk factors

There is clear scientific evidence that atherosclerotic plaque progression is accelerated by several well defined risk factors. The relation between alimentary factors and atherosclerosis was already postulated in the early 1930s.[38] A rapidly increasing number of studies have been undertaken to evaluate possible promoters of cardiovascular diseases after the end of the World War II. It became clear in 1970 that CHD risk is related to cholesterol serum level, after this association had been evaluated in the population of seven countries.[39] The growing evidence pointing at the importance of several modifiable risk factors favouring CHD gave basis to the rationale to design the Framingham Heart study, which turned out to be the milestone study on cardiovascular prevention. The Framingham Heart study evaluated five candidate modifiable risk factors: arterial hypertension, diabetes mellitus, hypercholesterolemia, obesity and use of tobacco.[40] These five main risk factors together with psychosocial factors and lack of preventive lifestyle factors (regular physical activity, diet modification and alcohol) contribute to over 90% of an initial myocardial infarction risk.[41] Since the effect of potentially modifiable risk factors on CHD was known, rising awareness of the need to control risk factors led to a continuous decline of CHD prevalence in developed countries.[42]

Some authors suggest that the two most important risk factors are smoking and abnormal lipids, and a “poly-pill” containing a statin, an antihypertensive drug, and aspirin, combined with the avoidance of smoking could reduce the myocardial infarction risk by more than 80%.[43]

Hypertension:

The Framingham study results showed that systolic arterial hypertension is strongly related to the risk of developing cardiovascular disease.[44] Overall, the prevalence of arterial hypertension ranges between 30 and 45% and the probability of developing hypertension rises with aging.[45] Worldwide, 62% of strokes and nearly half of coronary heart disease cases can be attributed to high blood pressure, which has been estimated to result in over 7 million deaths per year.[46] A significant increase in the mean arterial blood pressure level has been observed in populations moving from rural to industrialized urban environments.[47]

Use of tobacco:

The first scientific data on the impact of smoking cigarettes on mortality from cardiovascular disease were obtained and published in the 1950s.[48] Not only the mere fact of smoking or non-smoking, but also the number of smoked cigarettes, correlate with cardiovascular risk.[49] According to Yusuf *et al.* “findings suggest that there is no safe level of smoking and that if quitting is not possible, the risk of myocardial infarction associated with smoking could be significantly reduced by a reduction in the numbers smoked.”[50]

The most often mentioned components of cigarette smoke that are directly responsible for the damage of the vascular endothelium, and thus the development of atherosclerosis, are nicotine, carbon monoxide and thiocyanates. These substances accelerate plaque development not just in smokers but also in cases of passive inhaling of cigarette smoke.[51]

Lipids:

Epidemiological studies confirmed a strong association between total serum cholesterol levels and cardiovascular risk.[52] The risk of developing CHD especially correlates with the serum concentration of low density lipoprotein (LDL) cholesterol.[53] Trapped in the arterial wall, LDL particles may undergo oxidation, which is an initial step in the development of atherosclerotic plaque.[54] Contrary to LDL-C, high density lipoprotein cholesterol (HDL-C) has been found to protect against cardiovascular disease. Experimental data have shown that HDL-C prevents LDL-C oxidation and plays a role in increasing hepatic LDL-C uptake, which in turn clears LDL from the blood. The resulting lower LDL-C levels potentially stabilize endothelial prostacyclin production, favour vasodilatation and inhibit platelet activation.[55]

Diabetes mellitus:

Diabetes mellitus is not only associated with an increased risk of cardiovascular diseases, but also raises the probability of developing triglicerydaemia and high blood pressure. Diabetes is strongly associated with obesity. [56] There are many reasons for increased CHD risk in diabetes patients. First, plaque composition in diabetics differs from that in non-diabetic patients, which results in a higher risk of plaque rupture and coronary thrombosis. Secondly, insulin resistance leads to hypercoagulability due to increased levels of procoagulatory proteins. Finally, there is a variety of endothelial functional abnormalities in diabetics including increased endothelial adhesiveness, impaired vasodilatation, increased coagulation activity, increased permeability, and increased tissue factor expression.[57]

Obesity:

According to the World Health Organization (WHO) obesity is defined as ”abnormal or excessive fat accumulation that may impair health”. For adults, the WHO defines weight limits as follows: “overweight is a BMI greater than or equal to 25; and obesity is a BMI greater than or equal to 30.” [58]

WHO publications state that “in 2016 worldwide, 40% of women and 39% of men aged 18 and over were overweight”. A widespread epidemic of obesity and overweight is being observed not only in adults but also in children.[59]

Obesity is not only an independent risk factor of all-cause mortality, but this metabolic condition is also often associated with additional CHD risk factors like arterial hypertension, dyslipidemia, or diabetes.[60,61]

Obesity and overweight is - after cigarette smoking - the second leading preventable death cause.[162]

Non-modifiable and novel risk factors:
The most important non-modifiable risk factors are male sex, advanced age, and a family history of premature CHD.
Apart from the above-mentioned classical risk factors, there are several additional promotors of atherosclerosis that have been referred to as novel risk factors by many authors. Among them there are elevated levels of homocysteine, C-reactive protein, and lipoprotein a.[63] As the association of these non-classical risk factors to CHD was discovered later, less related scientific information is available on them.

Although in this section every single risk factor is represented separately, in the real world only a small population group has one risk factor alone. Thus, since 1994 recommendations on the prevention of CHD have focused on global or total cardio-vascular risk that is greater than the sum of its components.[64]

1.1.4 Epidemiological significance of myocardial infarction worldwide and in Germany

According to the WHO, cardiovascular diseases including coronary artery disease are the top cause of death worldwide. The global incidence in 2012 was 247 deaths per 100,000 per year.[65] Similarly in Germany, coronary heart disease was the main cause of death. It is noteworthy that the incidence has been higher for years in western industrialized countries.[66]

The yearly number of hospitalizations for MI in Germany reached 217,000 in 2011. According to data from the BHIR the in-hospital mortality in Berlin has declined rapidly in the last decade, starting out at more than 13% in 1999, and reaching a constantly low level of around 6.5% in the years 2013 and 2014.[67] Myocardial infarction caused 54,538 deaths in Germany in 2013.[68] The overall death rate due to acute myocardial infarction has decreased in Germany almost continuously since 1980; the mortality rate in men fell from 152.5 per 100,000 inhabitants (1980) to 71.2 (2011), corresponding to a reduction of 52%, and mortality in women dropped from 87.4/100,000 (1980) 56.4 (2011), a reduction of 35.5%.

It has been assumed that this clinically significant mortality reduction is at least in part a result of improved diagnostic and therapeutic measures, and may also be due to logistically optimized treatment processes.[69]

Nonetheless, the worldwide annual mortality from cardiovascular disorders is predicted to remain in first place among the causes of death in 2020.[70] Thus CHD and MI are not just individual diagnoses and life-changing clinical events, but are also of huge socioeconomic importance.

1.1.5 Myocardial infarction management

1.1.5.1 Pre-hospital and early hospital myocardial infarction care phases and time points.

In general, the evaluation and treatment of a patient suspected of having an acute MI is divided in three phases: the pre-hospital phase, the in-hospital phase and rehabilitation after being discharged from hospital. The first phase begins with the moment of coronary occlusion, which after a short, but variable period of latency, leads to the onset of symptoms. The first professional evaluation and treatment of a patient suspected of having MI is defined as the First Medical Contact (FMC). The time delay from that moment to the delivery of myocardial reperfusion therapy constitutes the system delay. In this initial period, the logistics and quality of emergency diagnostic and therapeutic processes are critically important, and at the same time challenging. Apart from assessing the specific patient history, the first and crucial diagnostic step in patients with suspected MI is the timely and valid interpretation of an immediately obtained ECG. The ECG as an integral part of the diagnostic work-up of patients with suspected MI should be acquired and interpreted promptly (i.e. a target of within 10 min) after clinical presentation.[71]

English National MI registry findings showed a significant survival advantage in MI patients when a pre-hospital ECG was obtained. The patient examination and acquisition of a pre-hospital ECG allows specific medications to be given prior to hospital admission, mandates continuous ECG and vital parameter monitoring, and allows the determining of which type of hospital should receive the patient. In addition, the pre-hospital ECG facilitates the activation of the cardiac catheter laboratory if indicated.[72]

The in-hospital phase starts at the moment of hospital admission. If the patient presents themselves to the hospital emergency department (ED) without using the pre-hospital emergency medical system, the FMC takes place in the ED.

1.1.5.2 Phases and time points in STEMI management

The general goal of pre-hospital and early in-hospital STEMI treatment is delivering timely pharmacologic and/or mechanical reperfusion therapy. “Percutaneous coronary intervention (PCI) has been shown to be superior to fibrinolysis in the treatment of acute myocardial infarction with ST-segment elevation in patients admitted to highly experienced angioplasty centers”, and if delivered in a timely manner.[73] If the reperfusion therapy cannot be delivered in a timely manner by an experienced team, thrombolysis should be considered.[74]

The time between symptom onset and reperfusion therapy is known as “Time to Treatment“. The door-to-balloon time (DTB) is a well-established benchmark of the quality of STEMI patient care in the early hospital phase and reflects the delay between admission to the hospital and delivering the PCI. In cases where thrombolysis is administered as reperfusion treatment, the door-to-needle time is used as a quality benchmark instead.

“Although the use of an EMS decreases the delay to treatment and is the preferred mode of initial care for patients with suspected STEMI, it is under-utilized in many countries and, not infrequently, patients self-present to the ED.”[75] If the STEMI patient comes via EMS, direct admission to the cardiac catheterization laboratory (CCL) is preferred. This so called “Emergency Department bypass” (ED bypass) of ST-segment elevation myocardial infarction patients identified with a pre-hospital ECG is associated with shorter reperfusion times, and has therefore been recommended as the preferred option.[76]

Informing and rehabilitating the patient, as well as the initiation of secondary prevention are the main goals of the late in-hospital phase. In addition, treatment of possible secondary complications (e.g. heart failure) has to be focused on before patient discharge.

This study is mainly focused on the pre-hospital and early in-hospital phase until PCI.

1.1.5.3 Relevance of care delays in primary STEMI patient care for survival, quality of life and their importance as a quality benchmark.

The time delay in the treatment of STEMI patients includes patient delay and system delay (including the pre-hospital component, and the in-hospital delay mainly characterized by DTB time or DTN time). Every single component of the total ischemic time is of major importance and should be optimized. Thus, the delay to treatment is an obvious and measurable quality index of care of STEMI patients.[77]

The prevention of unnecessary delays is crucial in STEMI for two reasons: first, the most critical time of an acute myocardial infarction is the early phase, during which the patient is threatened by cardiac arrest and sudden death; secondly, the early provision of coronary reperfusion therapy is of paramount importance for the technical and clinical effectiveness of STEMI treatment.[78] Longer treatment delays are associated with higher long-term mortality in patients undergoing PCI or receiving fibrinolytic therapy.[79]

Several approaches to shorten time delays between symptom onset and hospital admission have been proposed; as early as in the late 1960s to early 1970s, it became clear that a great number of deaths among the patients with MI occur before they reach hospital.[80] Twenty years later, the international MONICA Project has shown that approximately two-thirds of 28-day CHD deaths in men and women occurred before reaching the hospital.[81] Further investigations confirmed the importance of the first hours following symptom onset for patient outcome in myocardial infarction (see Figure 3).

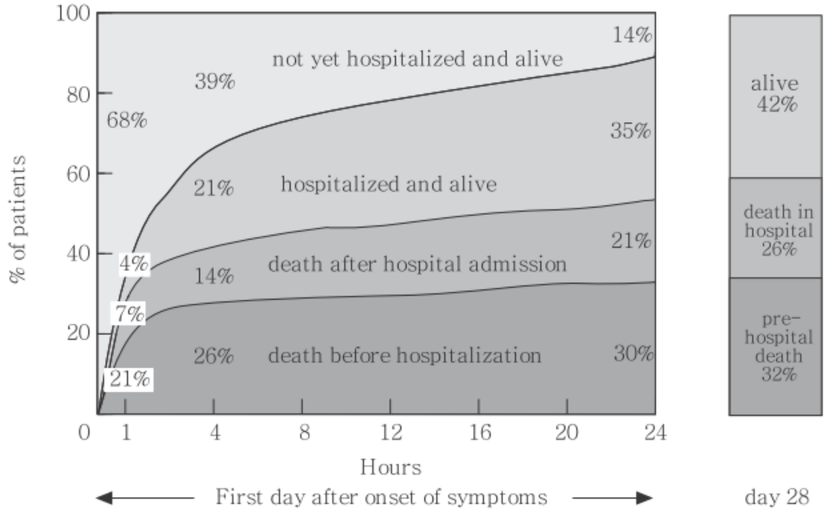


Figure 1 **Survival in the first day after acute myocardial infarction. Updated English version of Fig. 3 from Löwel *et al.*[5].**

82

Figure 3. Survival in the first day after acute myocardial infarction

The patient delay, constituting the first component of the pre-hospital delay can be shortened by the education of identified risk patients and by informing the general population. But nevertheless, women especially, despite improvements, continue to have significantly longer times to EMS alarm and FMC.[83]

"It might be useful to evaluate how patients (and their partners and family) make the decision to call for help before advocating interventions. It may also be appropriate to target education at high risk groups, including family members. However, there is a need to educate the public at large to call an ambulance if they witness what could be a MI."[84]

According to 2012 ESC guidelines, a good index of the quality of care in the early pre-hospital phase is the time taken to record and validate the first ECG. In an EMS participating in the care of STEMI patients, the guideline-specified goal is to reduce this delay to 10 min or less.[85]

As regards the in-hospital component of the System Delay, DTB time is the most frequently used indicator of the quality of STEMI care. The timeline set by the 2012 ESC STEMI guidelines for this delay was 90 min or less if the patient is admitted to a non-PCI hospital, and 60 min or less if the patient is directly admitted to a PCI-capable center.[86] The impact of DTB time on mortality has specifically been evaluated. There is strong evidence that reduction of the DTB time from 90 to 60 min, and also from 60 to 30 min, is associated with lower mortality rates.[87] Other authors even suggest that the relationship between time to treatment and 1-year mortality is a continuous function, in the sense that every minute of delay in primary angioplasty for STEMI affects 1-year mortality. Therefore, all efforts should be made to shorten the total ischemic time.[88]

Efforts should be undertaken to make the time to treatment as short as possible, not only because of the increased mortality during the early phase of MI. Additional benefits from prompt treatment of STEMI are shorter hospitalization time, better quality of life, lower probability of subsequent heart failure, and improved late outcome. Mikkel and colleagues state in their related publication that: “In patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention, reperfusion delay predicts the extent of salvaged myocardium, final myocardial infarct size, chronic heart failure and long term mortality.”[89]

In settings when fibrinolysis has been chosen as the therapy of choice, the fibrinolytic therapy should be delivered within 30 min of FMC. For patients arriving at the hospital a realistic aim is fibrinolysis administration within 30 min.[90]

Total mortality rates from MI in different developed regions have been decreasing over the last few decades. This success can partly be attributed to more efficient pre-hospital patient care and early reperfusion, but important regional disparities appear to persist.[91]

1.1.5.4 What influences the "time to reperfusion"?

Unnecessary delays can occur in every single phase from symptom onset to reperfusion. Thus, many different factors can influence the time to reperfusion. Obtaining a pre-hospital ECG is the key to prompt MI diagnosis and thus allows field triage and directing the patient to the nearest PCI-capable hospital. As a consequence of this pre-hospital diagnosis the fast route directly to CCL bypassing ED can be activated.[92] Better patient education focused on symptom recognition, and on the importance of immediate contact with the EMS in cases where symptoms suggesting MI occur, prevents delays in the earliest phase of infarction.

Probably the biggest effort has been made to identify factors affecting DTB, and to develop strategies to shorten this time delay. Lubovich *et al.* stated that: “there is significant reduction of the door-to-balloon time in the direct ICU (bypassing the ED) admission strategy. This reduction translates into improvement in clinical outcome of patients.”[93] A prerequisite for this strategy is optimal field triage by the EMS.

Whether current guideline-suggested time limits can be achieved depends on different factors including infrastructure limitations, the mode of cooperation between EMS, hospital and other outpatient medical care facilities, logistics, and the education of risk patients.

In a systematic review, Peterson *et al.* categorized predictors of DTB as follows: patient characteristics, hospital characteristics, health care practices, and a limited number of “other” characteristics.[94] They assigned various factors to the different groups and classified them according to the strength of evidence.

Health care practices

The health care practice with the strongest evidence for reducing the DTB is bypassing the patient from the ED directly to the CCL, instead of initially admitting them to the Cardiac Care Unit. As delay-reducing factors with moderate evidence, they mention CCL activation by an EMS physician, a single call to central page to activate the CCL, and obtaining a pre-hospital ECG. As strategies with low supporting evidence, they mention the continued presence of cardiologists on site, or staff arriving at the CCL within 20 min from activation.

Hospital related factors

A higher level of PCI-related specialization and a higher procedural PCI volume of a hospital are mentioned as the main hospital-related factors influencing DTB time. The strength of evidence is classified as moderate regarding these hospital factors.

Patient characteristics

There is also moderate evidence that patient-related factors like longer pre-hospital delay and cerebrovascular disease or prior stroke prolong DTB time. Other patient characteristics delaying DTB time have been reported to be: no chest pain on presentation, lower sum ST segment elevation, age “younger and older”, LBBB in the ECG and KILLIP Class ≥3 (necessitating time for broader emergency treatment like endotracheal intubation and respirator therapy, pharmacological circulatory support, external pacing, or cardiopulmonary resuscitation)

Other characteristics

Two factors are mentioned that are not directly associated with patient characteristics or behaviour, and hospital or healthcare practice, and that are known, however, to predict shorter DTB times: firstly, presentation to the EMS during working-hours, and secondly, treatment of a patient's MI in a more recent year. Evidence regarding the influence of these factors on DTB is moderate.

Compared to the multiple approaches to shortening the DTB delay, less attention has been paid to the pre-hospital component of time to reperfusion. It is worth noting, that in many patients efficient and timely early in-hospital care is the result of proper pre-hospital processes, including valid field triage, diagnosis and CCL activation by the EMS.

1.1.5.5 Importance of early STEMI-diagnosis and CCL activation

The solid pre-hospital diagnosis of STEMI patients is important for several reasons. First, not all hospitals are able to offer emergency PCI treatment to STEMI patients, and only the early diagnosis enables selecting the right hospital for the patient. Secondly, only after valid identification of a STEMI ECG is the CCL activation by EMS units reasonable. Pre-hospital ("field") CCL activation then gives the CCL staff the necessary time to prepare the catheterization laboratory to receive the STEMI patient. If the interventional cardiologist is not present at the hospital, field CCL activation allows them to arrive at the hospital in due time. This is particularly important during off-hours. Finally, a proper ECG-derived STEMI diagnosis guides the pre-hospital treatment, and monitoring strategy, and can trigger direct admission to the CCL (ED bypass).

1.1.5.6 Myocardial infarction care in Germany and in Berlin.

1.1.5.7 German and local Berlin setting.

Berlin, with a population of 3.5 million inhabitants, is the seventh most populous urban area in the European Union.[95] Health insurance is mandatory in Germany. Between city districts there are significant social and demographic differences. Berlin has a dense network of PCI-capable hospital departments offering 24h/7d emergency PCI services. Patients with an acute MI reach the hospital by different ways. Optimally, after symptom onset, patients call an EMS, others seek help via family doctors, or general practitioners (GP) on call, or they arrive directly at the hospital ED as self-presenters. If the FMC is made by a family doctor or GP on call, they call for an ambulance and an accompanying emergency physician to escort the patient to the hospital.

1.1.5.8 The Emergency Medical System in Berlin.

In contrast to the Anglo-American EMS model that is based around the "scoop and run" or the ”load and go” philosophy, the traditional Franco-German EMS-model favours a “stay and stabilize” or ”delay and treat” strategy. This implies more procedures being executed in pre-hospital environment.[96] The focus on pre-hospital stabilization in Germany explains why primarily physicians were entrusted with emergency medicine duties in Germany. EMS in Germany is invariably contacted via one universal telephone number: 112. After the dispatcher collects the necessary data, the decision whether or not to send an ambulance is made. There are two main types of ambulances: physician staffed ambulances (called “NEF” or “NAW”) and an emergency medical technician (EMT –“Notfallsanitäter”) or a paramedic-only staffed ambulances (mainly called “RTW”). According to standard dispatch criteria, in cases where a myocardial infarction is suspected, an ambulance staffed with a physician must be sent. If the EMT/paramedic-only ambulance arrives to the patient first, it is their decision whether to call for an additional physician-staffed ambulance, or not. Only physicians are expected to document a diagnosis and the ECG findings in pre-hospital protocols. As prompt ECG interpretation and an early accurate diagnosis is mandatory for triage, field CCL activation and ED-bypass, physician-escorted patients have a better chance of taking advantage of these DTB-shortening strategies.[97,98] The physician-escorted ambulance is the standard EMS transportation mode for patients with suspected MI. ECG teletransmission systems are used in some areas, but have no widespread application yet.

1.1.5.9 Cardiac catheterization laboratories and their activation in Berlin.

Having an attending interventional cardiologist always on site is one of the DTB-reducing strategies,[99] but Berlin PCI-capable hospitals are not equipped with an interventional cardiologist 24h seven days a week. Instead, the interventional cardiologist is called from home during the off-hours in the case of a STEMI or an unstable NSTEMI ACS.

In cases when the STEMI patient is admitted on a weekend, holiday or after hours, field CCL activation may provide the required time for the CCL staff to arrive to the hospital.

Optimally, the ambulance staff contacts the ICU or other hospital units responsible for primary care of MI patients, or even the interventional cardiologist directly, to activate the CCL team in the target hospital. In addition, this system enables the emergency physician to discuss the patients' findings and ECG with the interventional cardiologist, the ED or the ICU physician. At the time of the present study, there was no standardized and approved way of transferring ECG data. If the ambulance staff alert a hospital physician, a subsequent call is needed to activate the on call interventional cardiologist. While in most cases ED physicians and ICU physicians have experience in internal medicine or cardiology, the ambulance emergency physicians have a different background. Besides internists and cardiologists among them are many anesthetists, trauma surgeons and others. The emergency physician on the ambulance leads the situation, but the hospital physician or the interventional cardiologist on call can influence decision making, if they are involved.

1.1.5.10 Role of the myocardial infarction registries and STEMI networks in the improvement of care of the myocardial infarction patients.

In order to improve the care of patients with MI, hospitals and emergency medical systems organize networks that help them to cooperate. According to Huber *et al.* "essential components of networks are a single telephone emergency number for entry into the respective emergency system, ambulance vehicles or helicopters depending on the geographical situation of networks that are equipped with 12-lead ECGs and defibrillators, a system to obtain and interpret pre-hospital ECGs for accurate diagnosis of STEMI, ability to call a single number to activate the catheterization laboratory at the time diagnosis is made, ambulances staffed with physicians and/or paramedics trained for basic and advanced life support, and initiation of fibrinolytic therapy in case of long distances or expected time delays. Further requirements are a clear definition of hospital capabilities and protocols to guide standardized care for emergency medical services (EMS), for hospitals without PCI capability including transfer protocols, and for PCI centers."[100] The general goal of these networks is to provide optimal care, while minimizing delays.[101] Myocardial infarction registries accompany the MI networks, and give insights into the trends and characteristics of quality of MI patient care. Thereby they stimulate professional dialogue and discussion between different hospitals, and frequently registry results are able to initiate procedural change and optimization.

1.2 Place of the study.

The study hospital is a tertiary care academic teaching hospital located in the German capital Berlin. The hospital provides 24/7 PCI service. The studied hospital is equipped with one cardiac catheterization laboratory, performing elective procedures during working hours. In this setting, pre-hospital CCL activation allows the CCL to be kept vacant, if the admission of a STEMI patient is expected. During off-hours there are no CCL staff at the hospital. Usually the CCL is activated by the ICU physician, who in turn is informed by the EMS staff.

1.3 Aim of the study.

The purpose of this study was to identify options to optimize pre-hospital and early in-hospital MI care. Our attention was focused on the association between pre-hospital diagnosis, pre-hospital ECG findings and time delays in early STEMI care. We sought to determine the association of a clear pre-hospital STEMI diagnosis and the subsequent DTB time in comparison to patients with an existing ST segment elevation, but not explicitly stated diagnosis, who therefore had not been given the "label" STEMI. In addition, the proportion of pre-hospital STEMI diagnoses in patients with retrospectively diagnosed ST-segment elevation has been evaluated according to presentation during regular working hours versus off-hours.

2. Methods.

2.1 Introduction.

This retrospective study was performed at a single urban academic hospital in Berlin. We collected data of 474 consecutive patients admitted to our department from January 2008 to December 2011, who have been treated for type I MI. All patients with an interval from symptom onset to hospital admission shorter than 24 h, and a discharge diagnosis of type I myocardial infarction, were screened for inclusion.

The data of the screening population were assessed according to the dataset of the Berlin Myocardial Infarction Registry (BMIR) that collects data from participating hospitals in the metropolitan area of Berlin. The BMIR questionnaire is mainly focused on information about the in-hospital phase of MI care. As this study aims at extending perceptions of MI care, we additionally evaluated the pre-hospital phase of enrolled MI cases. Part of the information on patient characteristics and in-hospital processes within this study was already incorporated in the BMIR database. The BMIR data collection sheet is shown in the Appendix.

Berlin Myocardial Infarction Registry (BMIR)

The Berlin Myocardial Infarction Registry (BMIR) was founded in 1999 to voluntarily assess, confidentially compare, and consistently improve the care of patients with MI in Berlin. Since 1999 an increasing number of hospitals have decided to join the registry. In 2015 MI patient data from 23 hospitals were collected by the BMIR. Data are validated by regular peer monitoring. Stored data were the starting point for multiple studies and publications. Outcome data showed a dramatic decrease of hospital mortality following an MI.[102] The BMIR dataset related to the in-hospital phase of MI treatment. In recent years, scientific interest has evolved towards also comprising the pre-hospital phase of MI care. Until 2012, data of about 30,000 patients were entered into the BMIR database.[103]

2.2 Data collection.

Data related to the pre-hospital period of MI care were obtained from the EMS, GP on call and family doctor protocols. In case a patient had been transferred, we analyzed the ED protocol of referring facilities. We collected data related to admission mode and time, primary diagnosis, chief complaints, first ECG findings, medical history, cardiovascular risk factors, comorbidity, as well as heart rate, blood pressure and the starting point, time of symptom onset and time of EMS call that allowed for analyzing the subsequent pre-hospital care delays.

Data related to the hospital phase of MI care were retrospectively collected for the BMIR. These data were usually obtained from electronic patient records or patient charts. These data had previously been entered by the responsible physicians into the standardized data collection forms (see Appendix, Figure 7). In order to achieve pseudonymization, a specific coding number was assigned to each patient. For all patients' information regarding demographics, clinical history, risk factors, ECG findings, therapy, discharge diagnosis and medication was obtained. The form also included time and mode of admission and discharge, as well as time of first balloon inflation, if the patient was treated by PCI. These data were collected by physicians with at least 3 years of experience at a cardiology department. Subsequently, the dataset was converted to SPSS spreadsheets by BMIR data experts.

2.3 Study population

2.3.1 Inclusion criteria

The study included all patients who were discharged from hospital or died after a final diagnosis of a Type I MI had been established. Patients were only included if the time from symptom onset to hospital admission did not exceed 24 h. The universal definition of MI published in 2007 states that a Type I MI is diagnosed in case of “Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit together with evidence of myocardial ischemia with at least one of the following:

-symptoms of ischemia

-ECG changes indicative of new ischemia (new ST-T changes or new LBBB)

-development of pathological Q waves in the ECG

-imaging evidence of new loss of viable myocardium or new regional wall motion abnormality”. [104]

Clinical classification of type I can be recognized if the spontaneous myocardial infarction is related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection.[105]

2.3.2 Exclusion criteria

We excluded patients aged younger than 18 and older than 95. Furthermore, we excluded unstable patients and cases with missing documentation. As unstable patients, we defined those with systolic blood pressure RR <100 mmHg or not measurable, as well as resuscitated, defibrillated, or mechanically ventilated patients.

A flow diagram on patient enrollment is represented in Figure 4.

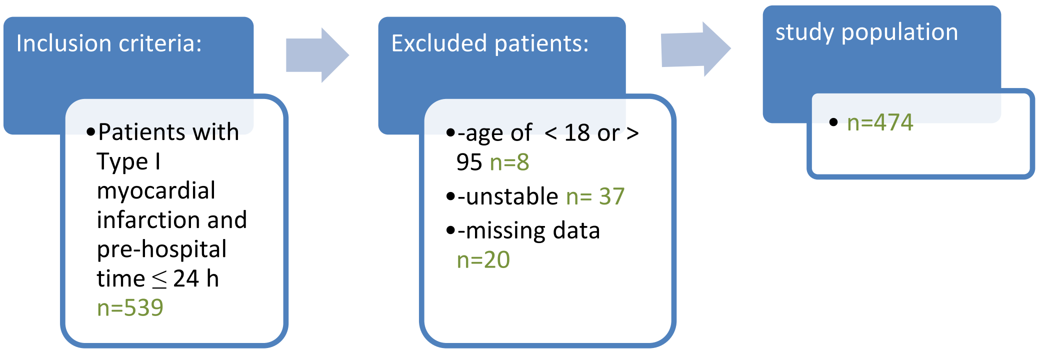


Figure 4. Enrollment flow diagram.

2.3.3 Patients excluded from time relations analysis

If the recorded time intervals suggested documentation bias (extreme long or unrealistic short time intervals) we did not include these patients into time intervals analysis (patient delay, pre-hospital system delay, DTB time and time of admission - in-/off-hours). From the time relations analysis, we also excluded patients with DTB ≥ 1,440 minutes, as presumably the PCI in these cases was not the primary treatment strategy. As the city of Berlin is covered by a dense EMS network, the pre-hospital system delay is rarely longer than one hour. Patients with a pre-hospital system delay of ≥ 180 minutes were excluded, because a pre-hospital system delay over three hours suggested documentation bias.

Patients excluded from time relations analysis:

- Patients with “patient delay” ≥ 1,440 minutes, ≤ 0 minutes

- Patients with "pre-hospital system delay“ ≥ 180 minutes, ≤ 0 minutes

- Patients with "door to balloon time“, ≤0 minutes, ≥ 1,440 minutes

Over the enrollment period we included 474 patients into the study.

2.4 Analyzed variables

Baseline characteristic and demographic variables

Data regarding sex, age and BMI were obtained from the BMIR database. Age and BMI are displayed as means and standard deviation. The age distribution is presented separately for males, females, and all patients.

Cardiovascular risk factors and comorbidity

Data on cardiovascular risk factors and comorbidity were obtained from discharge summaries and from the patients’ hospital charts. These data were also part of the BMIR dataset and included history of smoking, diabetes mellitus, arterial hypertension, hypercholesterolemia, past myocardial infarction, prior PCI or CABG, a history of stroke, heart failure, or renal failure. Renal failure was defined, if creatinine levels were over 2 mg/dl, or if the patient underwent chronic hemodialysis or had a history of renal transplantation. Hypercholesterolemia was assumed, if total cholesterol levels of over 200 mg/dl were recorded. The variable “smoker” comprised current as well as former smokers.

Admission mode

There were 6 possible units involved in primary MI care: hospital exclusive ED in case of intra-hospital myocardial infarctions, physician-staffed ambulance, paramedic-staffed ambulance, ED in case of self-presenters, GPs on call and family doctors. It was not possible to determine the units involved in primary care of transferred patients as we did not study the complete documentation of the transferring facilities.

We distinguished 7 modes of admission, although the route from symptom onset to hospital arrival can be more complicated and involve more than one of the above mentioned units. Two principal questions guided our considerations: “who primarily diagnosed and/or treated the patient?” and “who most importantly influenced the primary diagnosis and the appraisal of the findings in a specific patient?”.

If more than one unit was involved in the primary treatment only the one “dominant” unit was of interest. These units were grouped in the following order (from dominant to subordinate): intra-hospital or transferred -> GP on call -> family physician -> physician-staffed ambulance -> paramedic-staffed ambulance -> ED (self-presenter)

For example, if the patient was transferred from another medical facility after diagnosing an MI, this was described as “transfer”, regardless of means of transport (physician-staffed ambulance or paramedic-staffed ambulance). Patients primarily seeking care by their family physician or by the GP on call were mainly transferred via physician-staffed ambulance or paramedic-staffed ambulance and were treated in the ED, but we define it as “family-physician” or “GP on call” admission mode. In the majority of cases the unit contacted at FMC also referred the patient to the hospital. One additional exception was the situation when FMC had been established by a paramedic-staffed ambulance, but pre-hospital MI care had subsequently been supported by a physician-staffed ambulance. In that case, although FMC had been with the paramedic-staffed ambulance, we grouped the patient to “physician-staffed ambulance admission mode”, as the ambulance (incorporating the emergency physician) in Germany takes the responsibility for diagnosis, triage, and treatment. As physician escorted EMS admission mode, we defined all cases where a physician-staffed ambulance was in any way involved, apart from intra-hospital MIs and patients, who had been transferred from another hospital.

FMC:

FMC is defined according to the current guidelines as the point at which the patient was initially assessed by a paramedic or by a physician, or by other medical personnel in the pre-hospital setting. For self-presenting MI patients, the time of arrival at the hospital ED has been defined as FMC.[106]

Pre-hospital physician contact:

Three different ways of pre-hospital physician contact occurred. The patient could first have been seen by an emergency physician on the ambulance (either physician-staffed ambulance, or paramedic-staffed ambulance subsequently complemented by an emergency physician). Alternatively, the first physician involved in the pre-hospital phase could have been the GP on call, and finally a patient’s family physician could be the first physician involved prior to hospital admission.

MI-discharged, STEMI-discharged patients:

These diagnoses were determined if a patient was diagnosed with confirmed MI or STEMI at hospital discharge, and if this was confirmed in the discharge summary. This diagnosis was of major importance for the enrollment process as well as inclusion to one of analyzed groups and subgroups of patients.

Primary symptoms:

We gathered detailed data about chief complaints, but the main focus was on the documentation of chest pain. We did not distinguish typical and atypical angina pectoris. Chest pain was defined as a categorical variable with the following classifications: chest pain present, no chest pain, and missing data / data not legible.

First diagnosis, Pre-hospital diagnosis

As first diagnosis, we defined the diagnosis first recorded in physicians’ protocols. In rare cases the diagnoses were also found in paramedics' protocols. The following categories of this variable were distinguished: STEMI, NSTEMI, ACS, myocardial infarction, chest pain, primary arrhythmia, other diagnosis, and no diagnosis or diagnosis not legible. More than one diagnosis for one patient was possible.

The pre-hospital diagnosis was the first diagnosis given by the emergency physician on the ambulance, the GP on call, or the family doctor.

First ECG findings, Pre-hospital ECG findings

Similarly to first diagnosis, we divided the first recorded ECG protocol findings in different categories. If more than one finding existed, only the one “dominant” ECG finding was of interest. ECG finding categories were grouped in the following order (from dominant to subordinate): no protocol -> ST-segment elevation -> pacemaker ECG -> LBBB -> RBBB -> other signs of ischemia (T-wave inversion, ST-segment-depression) -> no signs of ischemia. For example: if in one patient ST-segment-elevation, and, in addition, other ischemic signs were documented, the patient’s dominant ECG finding was the ST-segment elevation. We did not interpret ECGs, but we recorded the interpretation that had been documented by physicians in protocols.

Pre-hospital ECG findings were defined as the first ECG findings recorded by the emergency physician on the ambulance, by the GP on call, or by the family physician.

In- /off-hours admission:

There were two possible categories of this variable: In-hour cases were defined as having their admission on Monday to Friday from 7.30 a.m. to 4 p.m. Off-hours were defined as weekdays from 4 p.m. to 7.30 a.m., Saturdays, and Sundays. Our goal was to differentiate admissions with the CCL staff residing in hospital from those where patients were admitted at times when the CCL staff had to be called from home. The accuracy of our distinction is limited by the fact that we did not include holidays into the off-hour periods.

Although initially we also identified patients with intra-hospital MI and transferred patients with MI, we did not include these subjects into the time intervals analysis and analysis of in-/off-hours admission. Furthermore, we excluded patients with missing data regarding the admission mode from this analysis.

2.5 Time points and time intervals

Time-related data were collected from the electronic data storage system of the hospital, patients' documentation in paper form as well as EMS, and family physicians' or GP on call protocols. The clocks used to record admission time, EMS alarm and the moment of coronary reperfusion were not synchronized. As mentioned above (section 2.3.3) patients with incomplete or implausible time data were excluded from the analysis of time-intervals. The following information on points in time and time intervals were collected.

2.5.1 Time points

Symptom onset:

Symptom onset has been defined as the starting time point of symptoms suggesting an acute MI. In some patients this information was contained in the EMS record, whereas in other cases the time of symptom onset has been derived from the patient history, as reflected in hospital files and discharge summaries. Retrospectively assessing symptom onset posed considerable difficulties, because the respective information had to rely on the patients' recollection, and hence necessarily contained an inevitable portion of subjective estimation.

EMS alarm:

EMS-alarm was defined as the moment at which the patient called the EMS. This time is always recorded on EMS protocols.

Time of hospital admission ("Door"):

The time of hospital admission (Door) has been defined as the point in time when the patient had first been primarily ascertained by the hospital's dispatcher who registered the case to the hospital's data processing system. This moment is always well documented and can easily be found in the patients' electronic documentation.

Balloon time:

As the time of wire passage into the culprit artery during primary PCI was not routinely documented, for this study, we used the time of inflation of the first balloon within the culprit lesion. This point in time has been named "balloon time" and is always well documented in the coronary catheterization protocol. In the study subjects, reperfusion time always is reflected by this time, because none of the patients has been treated by thrombolysis. Therefore the terms reperfusion time and balloon time are used as synonyms.

2.5.2 Time intervals

Patient delay:

The patient delay according to the ESC guidelines "is the delay between symptom onset and FMC"[107]. Since FMC was only rarely recorded specifically in the EMS protocols, and symptom onset was instead part of the routine dataset of the BMIR, we modified the definition of patient delay, and defined this time interval as the time from symptom onset to EMS call. We did not include patients into the patient delay analysis who had previously been treated by the GP on call or by family doctors, as for these patients, neither an EMS call by the patient, nor the FMC time could be defined.

Pre-hospital system delay:

Most authors define the pre-hospital system delay as the time between FMC and hospital admission or "door" time.

As for most patients the EMS personnel did not record the time of FMC, we used the EMS alarm time as the starting point for the calculation of the pre-hospital system delay. The terminating point of the pre-hospital system delay was the time of admission to the hospital. The pre-hospital system delay is considered to be a relevant indicator of pre-hospital care of the MI patient. As mentioned for the assessment of the patient delay, patients who had primarily been seen by the GP on call or family doctors could not been included in the pre-hospital system delay analysis, because either no EMS alarm time had been recorded, or the recorded EMS alarm time had already been preceded by a period of contact to the medical system and could therefore not be taken as the starting point of the pre-hospital delay.

Door to balloon (DTB):

Door to balloon has been defined to be the time from hospital admission to the first balloon inflation within the culprit coronary artery lesion during primary PCI.

Time to treatment:

Time to treatment has been defined as the time interval from symptom onset to the first balloon inflation at the culprit coronary artery lesion during primary PCI. In the patients enrolled in this study this delay also reflects the reperfusion time, as none of the patients underwent thrombolytic therapy.

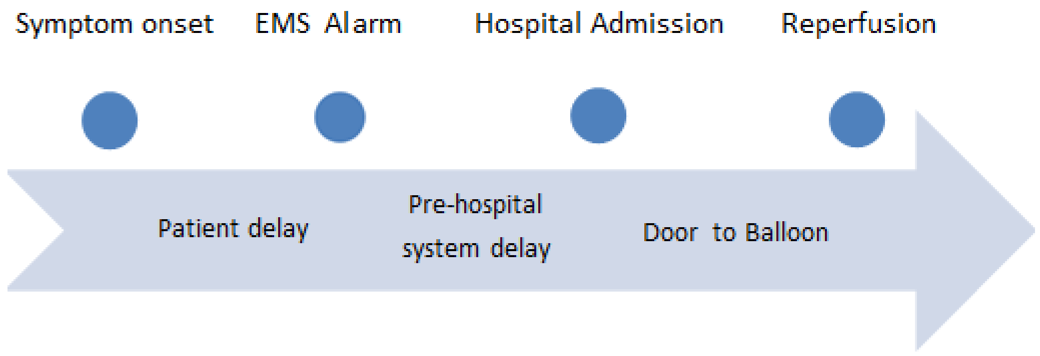


Figure 5. Time points and intervals

2.6 Statistics

Categorical variables are presented as absolute values and percentages. Continuous variables are represented as mean values ± standard deviation. Median values with interquartiles (25th and 75th percentile) were used to describe time intervals.

Statistical testing was performed using the Statistical Package of the Social Scientist software (SPSS Inc, Chicago, IL Version 25 2017).

A Kruskal-Wallis non-parametric test was performed for comparison between 4 developed groups of patients. We analyzed non-parametric data between two groups with the Mann-Whitney U test. Statistical significance was defined as $p<0.05$.

3. Results

3.1 Overview

The following flow diagram (Figure 6) provides an overview of the total group of enrolled patients and relevant subgroups according to NSTEMI versus STEMI discharge diagnosis and according to type of hospital admission.

Baseline data, admission mode, initial diagnosis and initial ECG interpretation of all MI patients are presented in section 3.2, and the groups with a STEMI diagnosis at discharge are presented in the following section 3.3. Finally, the main focus of the analyses lies on the subgroup of STEMI discharged patients, who were primarily seen by a physician in the pre-hospital setting (either by an emergency physician-staffed EMS team, or by the family doctor, or by the GP on call). This subgroup comprised almost a quarter of the initial study population.

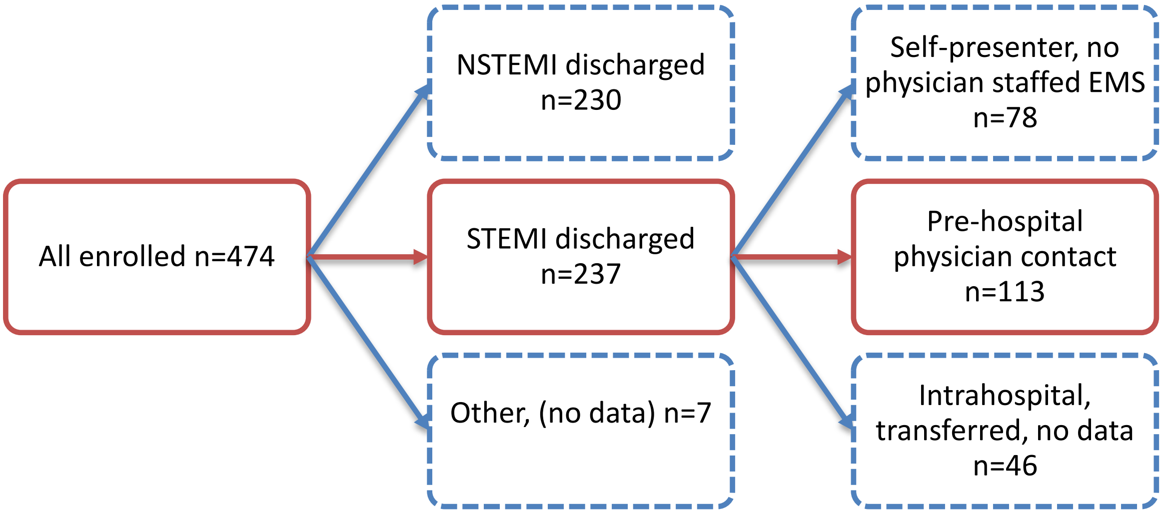


Figure 6. Enrolled patients and subgroups according to NSTEMI versus STEMI discharge diagnoses and according to type of hospital admission.

3.2 All enrolled patients

3.2.1 Baseline characteristics of all enrolled patients

STUDY POPULATION (n)	474	
STEMI (n;%)	237	50.7
NSTEMI (n;%)	230	49.3
no data (n)	7	
SEX		
female (n;%)	141	30.4
male (n;%)	323	69.6
no data (n)	10	
AGE		
all patients (mean; SD)	66.6	13.47
female (mean;SD)	72.4	12.9
male (mean;SD)	64.0	12.9
no data	12	
ON-/OFF-HOURS ADMISSION*		
on-hours (n;%)	135	35.4
off-hours (n;%)	246	64.6
no data (n)	93	
CHEST PAIN		
present (n;%)	280	81.9
no chest pain (n;%)	62	18.1
no data (n)	132	
BMI in kg/m2 (mean; SD)	27.3	5.3
no data (n)	109	

Table 1. Baseline characteristics of all enrolled patients

* We did not include into the analysis of working-hours versus off-hours patients: intra-hospital MI patients, patients transferred from another hospital (n=92), and patients with data lacking regarding the admission mode (n=1).

The baseline characteristics of all enrolled MI patients are presented in Table 1. During the period from 01.01.2008 to 31.12.2011, a total of 474 patients were included in the study. In half of the study population (n=237) STEMI was the discharge diagnosis. Nearly one third of the patients were female (n=141, 30.4%). The mean age of the study population was 66.6 years. Women were on average older by 8.4 years compared to male patients. Patients were more commonly admitted during off-hours than during working hours (n = 246 versus n = 135, respectively). The vast majority of patients presented with chest pain (n = 280, 81.9%). The mean BMI was 27.3 kg/m^2.

3.2.2 Comorbidity of all enrolled patients

	n	%
study population (n)	474	
smoking	253	61.0
diabetes	134	30.3
hypertension	326	71.6
hypercholesterolemia	165	42.5
past myocradial infarction	85	19.1
history of PTCA	86	19
history of CABG	24	5.3
history of stroke	34	7.6
history of heart failure	60	13.4
renal failure	79	17.0

Table 2. Comorbidity of all enrolled patients

Cardiovascular risk factors and comorbidities of the entire study group are shown in Table 2. The most common risk factors among the study population included hypertension (71.6%) and smoking (61%). Hypercholesterolemia and diabetes were prevalent in 42.5% and 30.3% of cases, respectively. In 86 patients data on their history of hypercholesterolemia were missing. A subgroup of 19.1% of the patients had a history of prior myocardial infarction and 13.4% had a history of heart failure. A prior PCI had been performed in 19% of the population and 5.3% had previous CABG surgery. Renal impairment was prevalent in 17%, and 7.6% had a history of stroke.

3.2.3 Admission mode of all enrolled patients

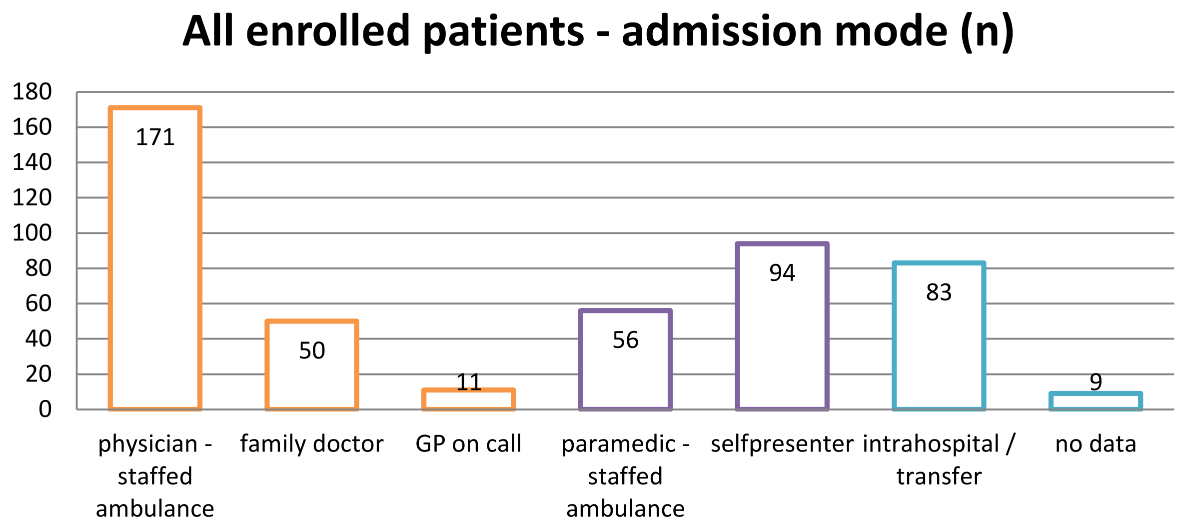


Chart 1. All enrolled patients – admission mode

Chart 1 demonstrates the mode of admission. Only one mode of admission per patient was possible. More than a third of the study group were treated in the pre-hospital setting by an emergency physician-staffed ambulance (171 cases, 36%). In 56 MI patients the paramedic-staffed ambulance was responsible for initial treatment. A fifth (n=94) of the study population directly presented themselves to the hospital. Fifty patients (10.5%) initially contacted their family doctor. Only a very small number of patients were initially seen by the GP on call (n=11 - 2.3%). In 9 cases, data on the admission mode were missing due to incomplete documentation. Eighty-three patients (17.5%) suffered an intra-hospital MI, or were transferred from another hospital.

3.2.4 First diagnosis of all enrolled patients

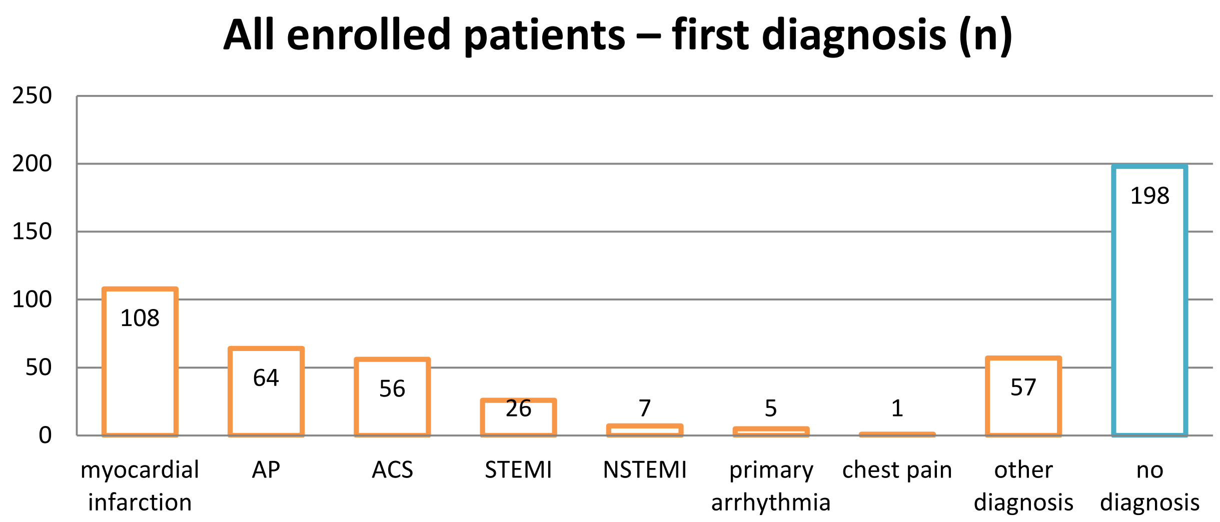


Chart 2. All enrolled patients – first diagnosis

The distribution of the first EMS diagnoses is represented in Chart 2. In many protocols, we noticed more than one primary diagnosis. In 39 cases we identified 2, and in 3 patients three different diagnoses in one protocol. One patient had 4 diagnoses documented.

The ambulance paramedics team is not obliged to document a specific diagnosis in the EMS protocol in the absence of an emergency physician. This contributes to a large number of cases, where “no diagnosis” has been recorded. In only 26 patients was “STEMI” recognized and explicitly documented as the EMS diagnosis. The most common diagnosis on the EMS protocols was “myocardial infarction”. In 57 cases, the first diagnosis suggested by the EMS did not relate to myocardial ischaemia.

3.2.5 First ECG findings of all enrolled patients

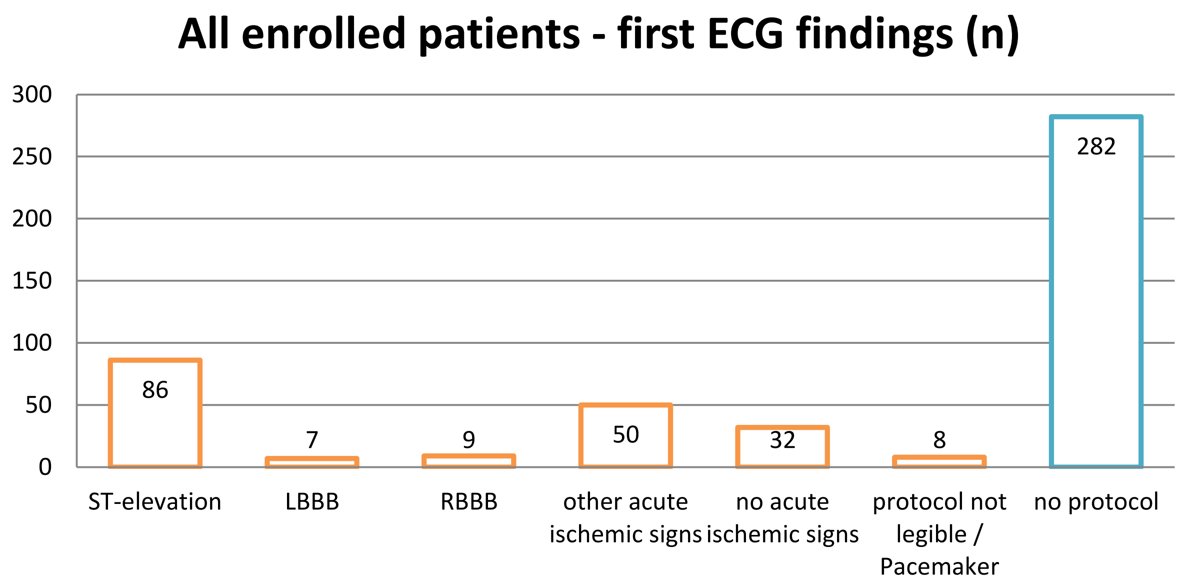


Chart 3. All enrolled patients – first ECG findings.

In contrast to the documentation of the first clinical diagnosis, only one ECG diagnosis per patient was possible. In cases of hospital-diagnosed MIs, primary ECG diagnoses have rarely been found to be documented in the initial phase. Most ECGs have only been formally adjudicated at discharge. In addition, the paramedic ambulance staff are not obliged to record and judge ECG findings in the EMS protocol. This contributes to a large number of cases where the ECG description is missing. For only 86 patients was the ST-elevation recognized and explicitly documented. In 32 patients with an ECG protocol, no acute ischemic signs were mentioned.

3.3 STEMI discharged patients

3.3.1 Baseline characteristics of STEMI discharged patients

STEMI DISCHARGED POPULATION (n)	237	
SEX		
female (n;%)	69	29.5
male (n;%)	165	70.5
no data (n)	3	
AGE		
all patients (mean; SD)	64.0	13.7
female (mean;SD)	70.3	14.1
male (mean;SD)	61.3	12.8
no data	4	
ON-/OFF-HOURS ADMISSION		
on-hours (n;%)	69	36.1
off-hours (n;%)	122	63.9
no data (n)	46*	
CHEST PAIN		
present (n;%)	144	84.2
no chest pain (n;%)	27	15.8
no data (n)	66	
BMI in kg/m2 (mean; SD)	26.9	5.2
no data (n)	62	

Table 3. Baseline characteristics of STEMI discharged patients

* We did not include into the analysis of working-hours versus off-hours: patients with an intra-hospital MI and patients transferred from another hospital (n=46). Patients with data lacking regarding the admission mode were also excluded from this analysis, but in all STEMI discharged information on the admission mode was available.

Similarly to the gender distribution in the total study group, about a third of the STEMI patients were female (29.5%, n=69). The mean age of STEMI patients was slightly lower on average than in the entire population (64 y). Women with a STEMI discharge diagnosis were older on average by 9 years compared to men. Similarly to the admission mode in the total study group, patients were more commonly admitted during off-hours than during working-hours (n = 122 versus n = 69, respectively). The vast majority of STEMI patients (n = 144, 84.2%) presented with chest pain, similar to the entire study group. The mean BMI of STEMI patients was 26.9 kg/m^2.

3.3.2 Comorbidity of STEMI discharged patients

	n	%
STEMI discharged population	237	
smoking	147	69.4
diabetes	54	24.4
hypertension	141	62.9
hypercholesterolemia	72	37.5
past myocardial infarction	32	14.4
history of PTCA	34	15.0
history of CABG	6	2.6
history of stroke	20	8.8
history of heart failure	21	9.3
renal failure	26	11.2

Table 4. Comorbidity of STEMI discharged patients.

Cardiovascular risk factors and comorbidities of STEMI patients are shown in Table 4. The most common risk factors among the study population comprised cigarette smoking (69.4%) and hypertension (62.9%). Hypercholesterolemia and diabetes were prevalent in 37.5% and 24.4% of cases, respectively. STEMI discharged patients were thus somewhat less likely to be diabetic, and had a lower percentage of previous MI (14.4%), prior coronary revascularization (PCI 15%, CABG 2.6%), and heart failure (11.2%). Out of the STEMI population 11.2% were suffering from renal failure, and 8,8% had a history of stroke.

3.3.3 Admission mode of STEMI discharged patients

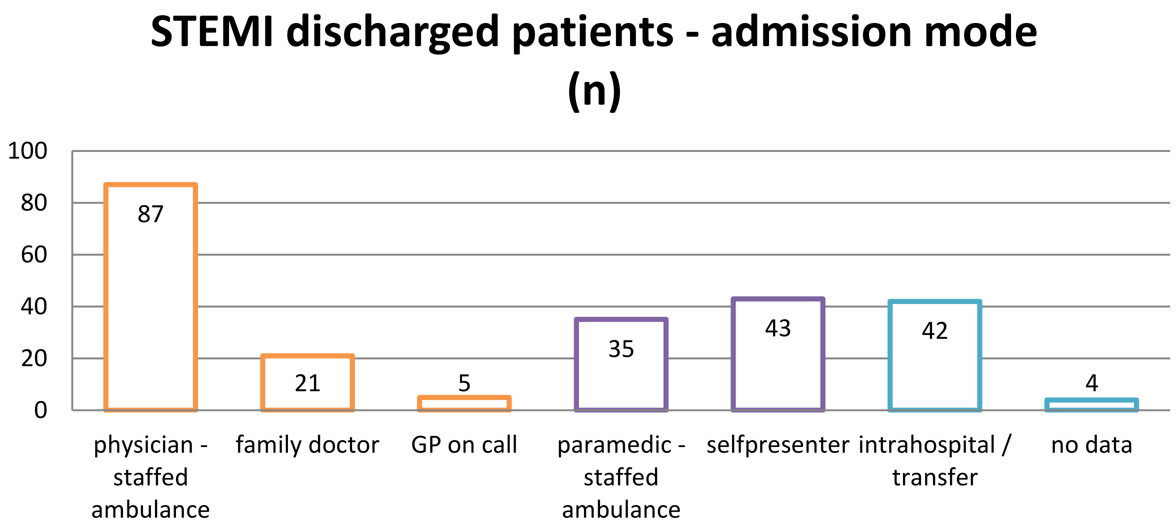


Chart 4. STEMI discharged patients admission mode.

Chart 4 displays the distribution of admission modes of STEMI discharged patients. The proportion of different modes of admission was similar for the overall MI population and STEMI-discharged patients. The number of self-presenters (n=43, 18%) was similar to that among all MI patients (20%). In 87 cases (37%), STEMI patients were primarily treated by a physician-staffed ambulance. This proportion was similar to that of the entire MI group (36%).

3.3.4 First diagnosis of STEMI discharged patients

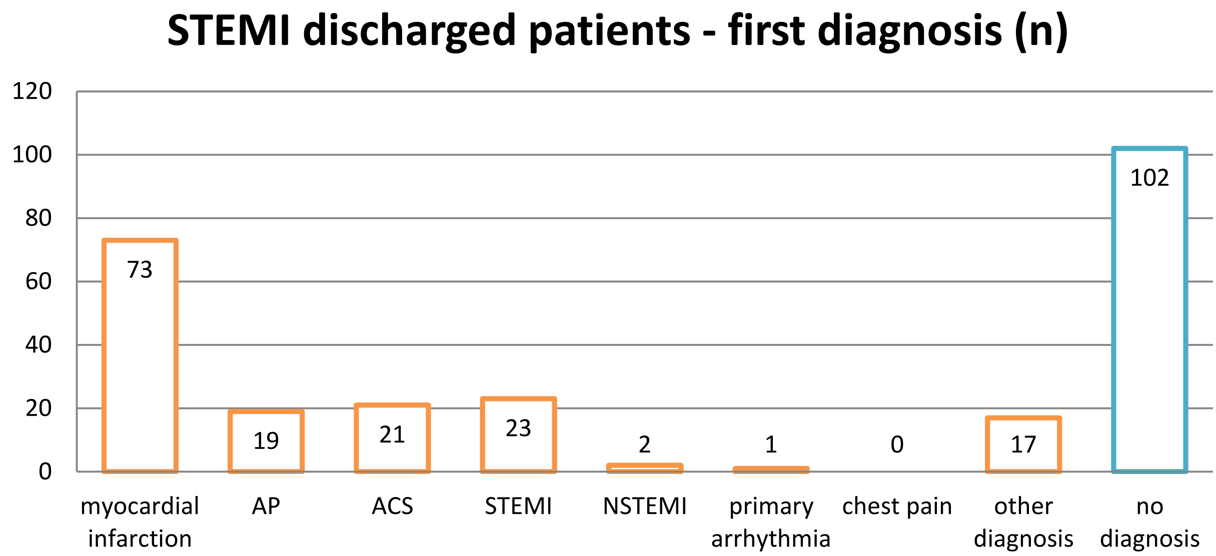


Chart 5. STEMI discharged patients – first diagnosis.

The most common diagnosis that was documented in STEMI discharged patients at FMC was myocardial infarction. The specifications STEMI and NSTEMI were used much less frequently. An explicit STEMI diagnosis was specified in 23 patients, and in 2 an NSTEMI was recorded. ACS was named as the diagnosis in 21 patients, and angina pectoris in 19. One patient received the diagnosis of a primary arrhythmia. In 17 cases, the suggested primary diagnosis was unrelated to myocardial ischaemia. The reason for the huge percentage of missing data is again that EMS paramedic staff are not required to document a clinical diagnosis on the EMS protocol.

3.3.5 First ECG findings of STEMI discharged patients

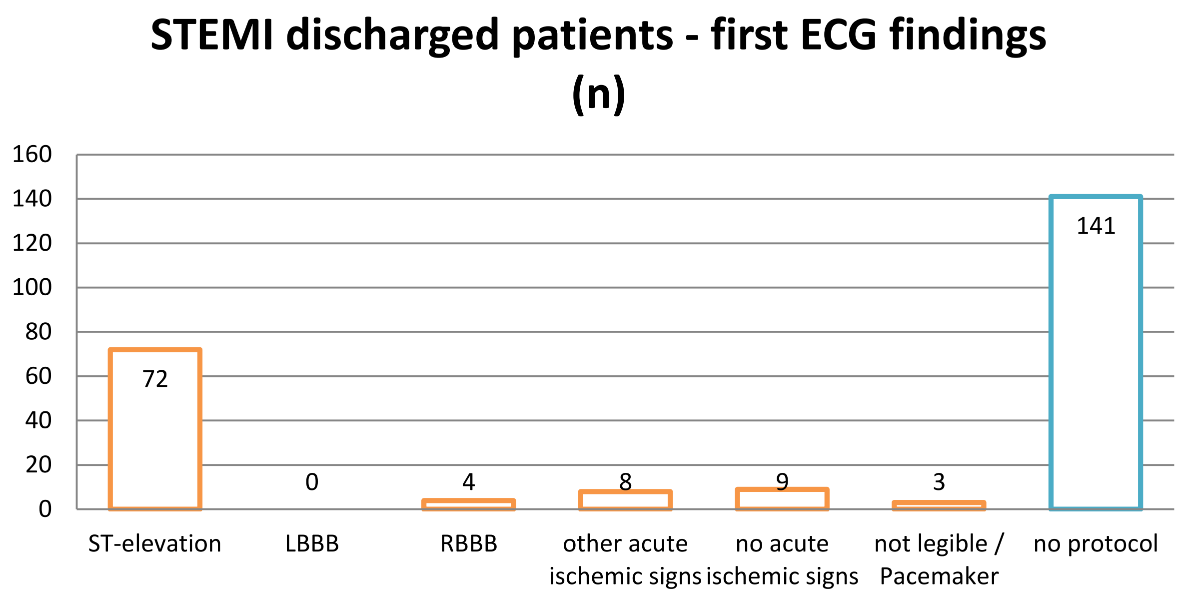


Chart 6. STEMI discharged patients – first ECG findings.

For many primary ECGs no written adjudication was available. Again, this is due to the fact that paramedic ambulance staff are not obliged to document or to adjudicate ECG findings. In the records of patients with an in-hospital diagnosis of MI, written ECG adjudications were also rarely documented in the treatment protocols of the initial phase. Therefore, the huge number of patients with a missing ECG adjudication in Chart 5 does not validly reflect the actual number of unrecognized ST-elevations. An ST segment elevation was explicitly documented in 72 patients, mainly in those admitted by the emergency physician-staffed ambulance. In 9 patients, who were discharged with a STEMI diagnosis, the initial ECG description did not mention the acute ischemic signs.

3.4 STEMI discharged patients with pre-hospital physician contact

3.4.1 Baseline characteristics of STEMI discharged patients with pre-hospital physician contact

STEMI DISCHARGED , PRE-HOSPITAL PHYSICIAN CONTACT POPULATION (n)	113	
SEX		
female (n;%)	32	28.6
male (n;%)	80	71.4
no data (n)	1	
AGE		
all patients (mean; SD)	64.7	13.0
female (mean;SD)	68.8	13.5
male (mean;SD)	63	12.5
no data	2	
ON-/OFF-HOURS ADMISSION		
on-hours (n;%)	47	41.6
off-hours (n;%)	66	58.4
no data (n)	0	
CHEST PAIN		
present (n;%)	96	91.4
no chest pain (n;%)	9	8.6
no data (n)	8	
BMI in kg/m2 (mean; SD)	27.5	5.0
no data (n)	27	

Table 5. Baseline characteristics of STEMI discharged patients with pre-hospital physician contact.

Nearly a third were women (28.6% n=32). The average age of the STEMI discharged study population with primary pre-hospital physician contact was 64.7 years. Women tended to be on average nearly 6 years older than men. As in the entire MI group, and in the group of all STEMI discharged patients admission during off-hours was more common compared to admission during working-hours, but the difference was less pronounced compared to all STEMI discharged patients or all enrolled MI patients. In 96 (91.4%) patients, a chest pain was documented as the chief complaint. The mean BMI was 27.5 kg/m2.

3.4.2 Comorbidity of STEMI discharged patients with pre-hospital physician contact

	n	%
STEMI discharged , Pre-hospital physician contact patients	113	
Smoking	70	70.7
Diabetes	25	23.4
Hypertension	73	67.6
Hypercholesterolemia	39	41.9
past myocardial infarction	17	16.0
history of PTCA	19	17.4
history of CABG	4	3.6
history of stroke	9	8.4
history of heart failure	7	6.4
renal failure	8	7.1

Table 6. Comorbidity of STEMI discharged patients with pre-hospital physician contact.

The important risk factors and comorbidities are shown in Table 6. The most common risk factors among the study population were similar to those of all STEMI patients. Smoking (70.7%) and hypertension (67.6%) were very common. Hypercholesterolemia and diabetes were prevalent in 41.9% and 23.4% of cases respectively. In 20 patients data regarding their history of hypercholesterolemia were missing. Sixteen percent of patients had a history of myocardial infarction, and 6.4% had prior heart failure. 17.4% of the study group had previously been treated by PCI, and 3.6% with CABG surgery. Among the study population 7.1% were suffering from renal failure, and 8.4% had history of stroke.

3.4.3 Admission mode of STEMI discharged patients with pre-hospital physician contact

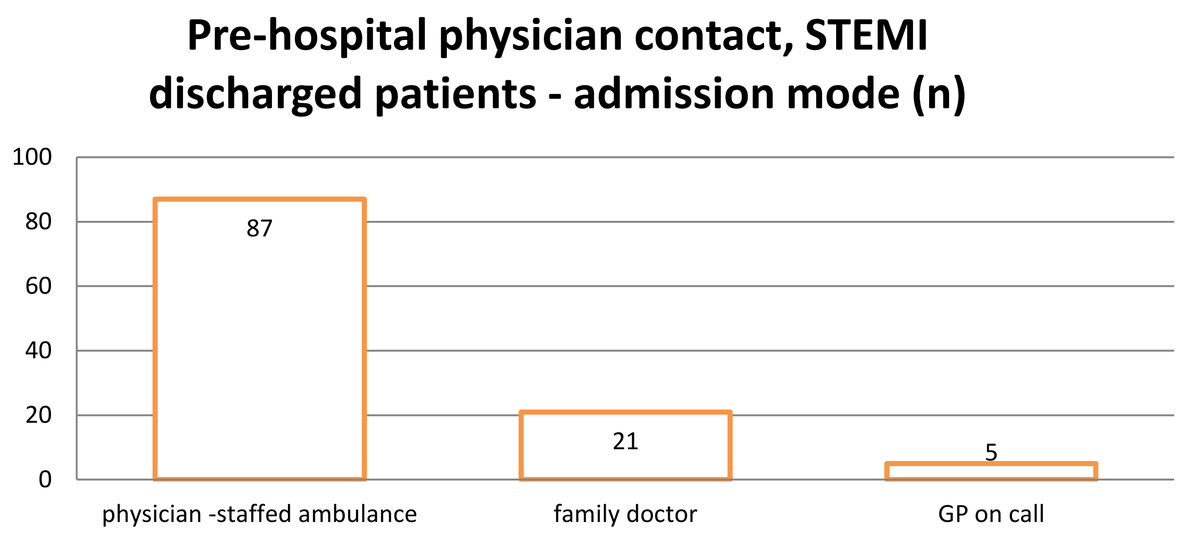


Chart 7. Admission mode of STEMI discharged patients with pre-hospital physician contact.

Most patients with pre-hospital emergency physician contact were admitted to the hospital by the physician-staffed ambulance (n=87, 77%). Twenty-one patients (19%) were initially treated by their family doctor, and five patients (4%) were initially seen by the GP on call.

3.4.4 First diagnosis of STEMI discharged patients with pre-hospital physician contact

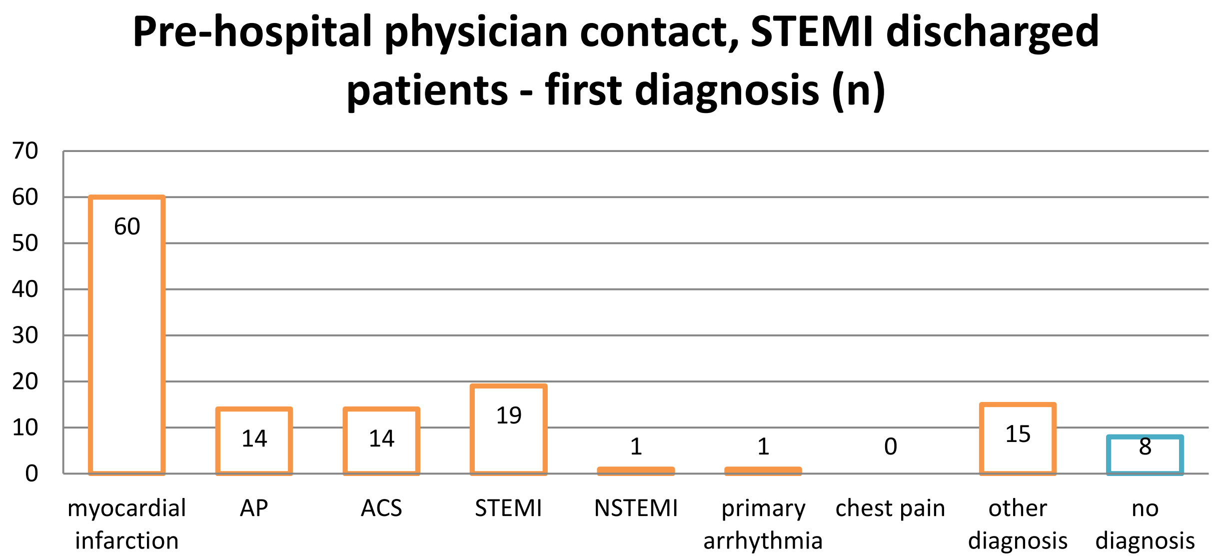


Chart 8. First diagnosis of STEMI discharged patients with pre-hospital physician contact.

The distribution of first diagnoses in STEMI discharged patients with pre-hospital emergency physician contact was similar to that of all STEMI-discharged patients. Overall, an MI diagnosis was suggested in 60 patients. In only 19 cases was the STEMI diagnosis stated during the pre-hospital phase of care. In a lower number of patients, no diagnosis was specified in the EMS protocol by the physician (n=8).

3.4.5 First ECG findings of STEMI discharged patients with pre-hospital physician contact

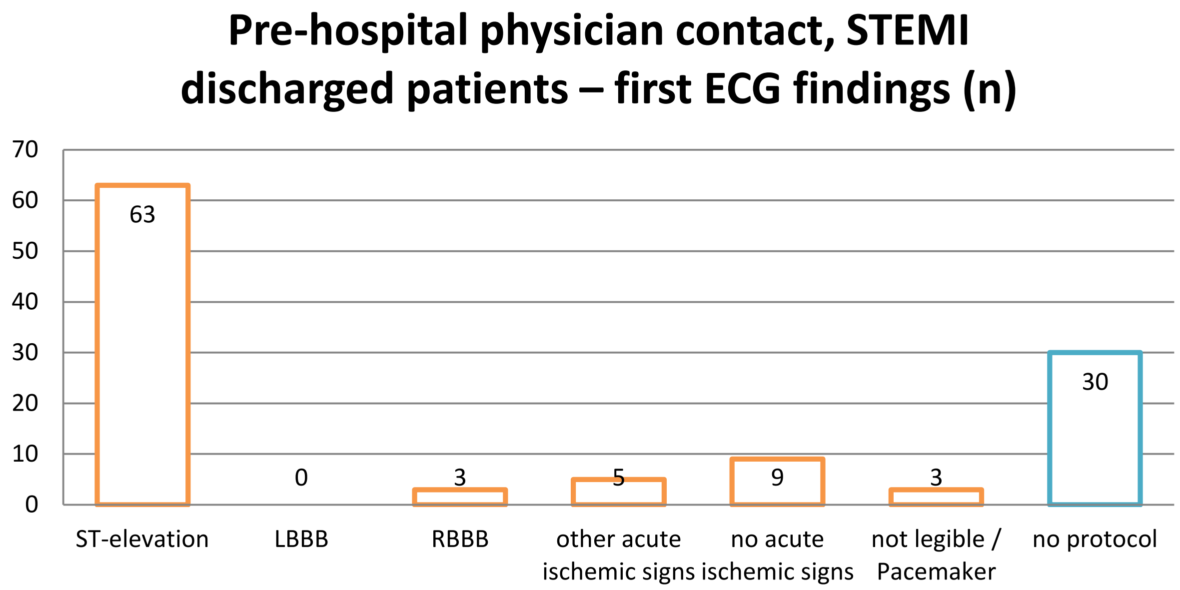


Chart 9. First ECG findings of STEMI discharged patients with pre-hospital physician contact.

In only 63 patients (56%) with a subsequently established STEMI diagnosis was the ST-elevation recognized and documented by the primary caring physician before the patient was admitted to the hospital. In 20 STEMI discharged patients (18%) with primary physician contact various ECG signs, but not an ST elevation, were documented (RBBB, other acute ischemic signs, not legible/pacemaker), whereas in 30 cases (27%) no description of the emergency ECG description was found.

3.5 Analysis of care delays in STEMI discharged patients with pre-hospital physician contact by initial diagnosis, initial ECG findings, and by time of admission (working hour admission versus off-hour admission)

Care delays of STEMI patients with primary pre-hospital physician contact were analyzed according to the primary ECG description and the primary diagnosis in these patients, as outlined below. In addition, analyses were carried out according to the time of admission.

Groups and subgroups of STEMI patients with primary physician contact according to the first established diagnosis and initial ECG findings:

I. pre-hospital-STEMI:

patients diagnosed pre-hospital as STEMI

II. pre-hospital-ST- elevation:

patients with ST-segment elevation documented at first ECG description
but without a pre-hospital STEMI diagnosis

III. pre-hospital-MI / -NSTEMI:

patients pre-hospital diagnosed as MI or NSTEMI
but without a pre-hospital STEMI diagnosis
and with no ST-segment elevation documented in first ECG description

IV - other:

patients without a pre-hospital diagnosis of MI, STEMI, or NSTEMI
and without a description of the ST segment elevation in the first ECG interpretation

a: subgroup of STEMI patients with primary physician contact admitted during working-hours

b: subgroup of STEMI patients with primary physician contact admitted during off-hours

In the following section on care delays by primary diagnosis and initial ECG findings, the population of included subjects can be lower than the total number of patients in the previously presented groups and subgroups. This is due to the fact that complete information regarding all three studied time intervals was not available for every patient. If, for example, the time of symptom onset time was missing for in a patient, they could not be included in the evaluation of the patient delay, but the same patient could still be part of the analyses of pre-hospital system delay or DTB.

3.5.1 Patient delay comparison in STEMI patients with pre-hospital physician contact by initial pre-hospital diagnosis and ECG interpretation

We did not include patients treated previously by GPs on call or family doctors into the patient delay analysis, thus we do not have any documented alarm times or FMC times. The Table and Chart show data related only to a patients with physician staffed ambulance as admission mode.

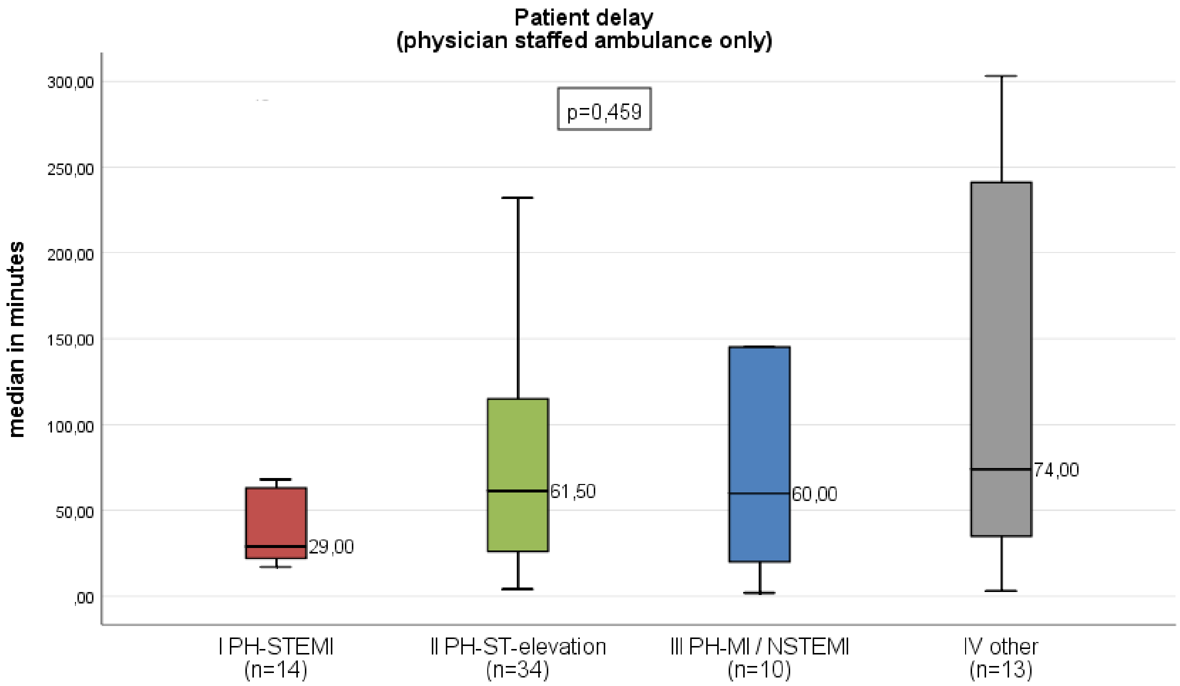


Chart 10. Median patient delay in groups with different ECG interpretation and initial diagnoses. The bands inside the boxes indicate median time in min. Boxes extend from the first to third quartile representing the interquartile range. The whiskers indicate the lowest datum still within 1.5 of the lower quartile, and the highest datum still within 1.5 IQR of the upper quartile. Outliers are not shown in the diagram. For diagrams including outliers see Supplementary Tables (Chart 17).

PH-MI	pre-hospital myocardial infarction diagnosis
PH-NSTEMI	pre-hospital non-ST elevation myocardial infarction diagnosis
PH-STEMI	pre-hospital ST elevation myocardial infarction diagnosis
PH-ST-elevation	ST elevation in pre-hospital ECG

Patient delay	median (min)	25th percentile	75th percentile	n	missing	total
I pre-hospital-STEMI	29	22	63	14	5	19
II pre-hospital-ST-elevation	62	26	115	34	10	44
III pre-hospital-MI / NSTEMI	60	20	145	10	11	21
IV other	74	35	241	13	16	29

Table 7. Median patient delay in groups with different ECG interpretation and initial diagnoses.

Pre-hospital STEMI patients had the shorter median patient delay time (29 min). In group IV patients were most reluctant to alert the EMS after symptom onset. For patients represented by group IV, it took in an average 45 min longer than for group I to make the decision to call 112. There were only slight differences between group II and III. The Kruskal-Wallis-Test was performed to test for differences between groups. There was no significant difference between the presented groups (p=0,459).

3.5.2 Pre-hospital system delay comparison in STEMI patients with pre-hospital physician contact by initial pre-hospital diagnosis and ECG interpretation

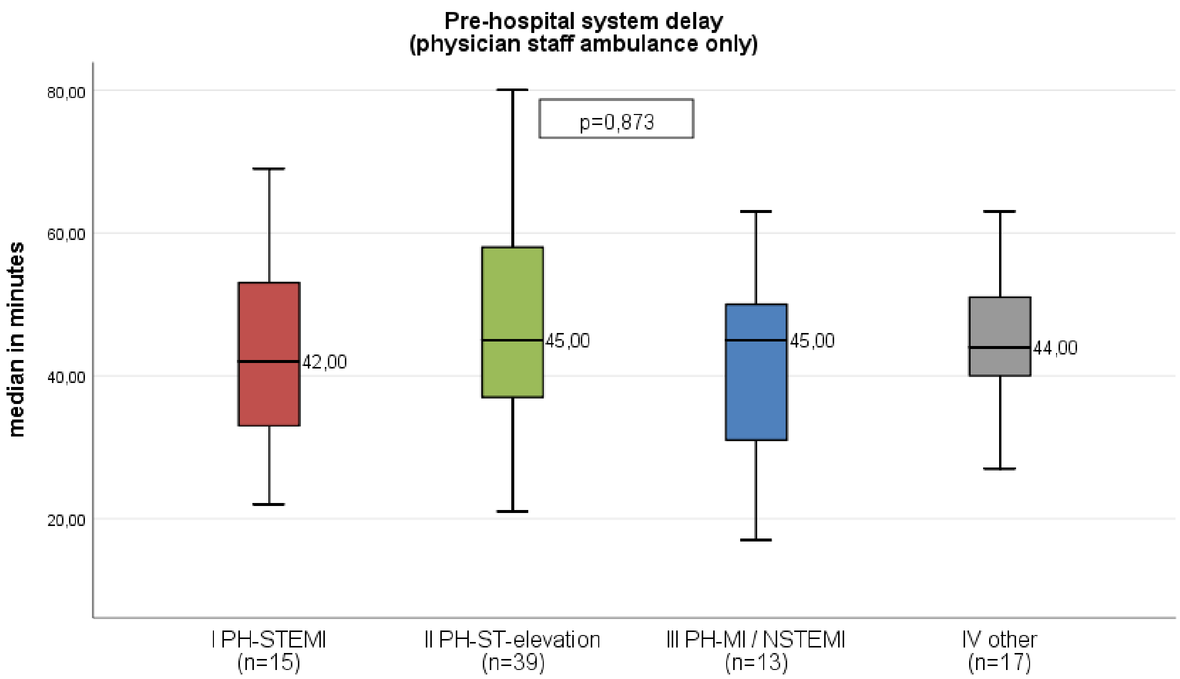


Chart 11. Median pre-hospital system delay in subgroups with different ECG interpretation and initial diagnoses. The bands inside the boxes indicate median time in min. Boxes extend from the first to third quartile representing the interquartile range. The whiskers indicate the lowest datum still within 1.5 IQR of the lower quartile, and the highest datum still within 1.5 IQR of the upper quartile. Outliers are not shown in the diagram. For diagrams including outliers see Supplementary Tables (Chart 18).

PH-MI	pre-hospital myocardial infarction diagnosis
PH-NSTEMI	pre-hospital non-ST elevation myocardial infarction diagnosis
PH-STEMI	pre-hospital ST elevation myocardial infarction diagnosis
PH-ST-elevation	ST elevation in pre-hospital ECG

Pre-hospital system delay	median (min)	25th percentile	75th percentile	n	missing	total
I pre-hospital-STEMI	42	32	55	15	4	19
II pre-hospital-ST-elevation	45	37	58	39	5	44
III pre-hospital-MI / NSTEMI	45	31	50	13	8	21
IV other	44	40	51	17	12	29

Table 8. Median pre-hospital system delay in subgroups with different ECG interpretation and initial diagnoses.

Chart 11 and Table 8 reflect the performance of the physician staffed EMS involved in MI pre-hospital care, measured as the time from FMC to hospital admission. As GPs on call and family doctors did not record alarm times or FMC times, the calculation of a pre-hospital system delay was impossible for the respective MI patients. On the other hand the ambulance physicians' protocols contained solid data about alarm time. The Kruskal-Wallis-Test was performed to test for pre-hospital system delay differences between groups. The analysis of pre-hospital system delays showed similar results across pre-hospital diagnosis and ECG interpretation groups without significant time differences.

3.5.3 DTB comparison in STEMI patients with pre-hospital physician contact by initial pre-hospital diagnosis and ECG interpretation

Among 113 STEMI-discharged patients with pre-hospital physician contact, 9 patients did not undergo reperfusion therapy. In 6 patients the admission time (DOOR) and/or the reperfusion time (BALLOON) were not available.

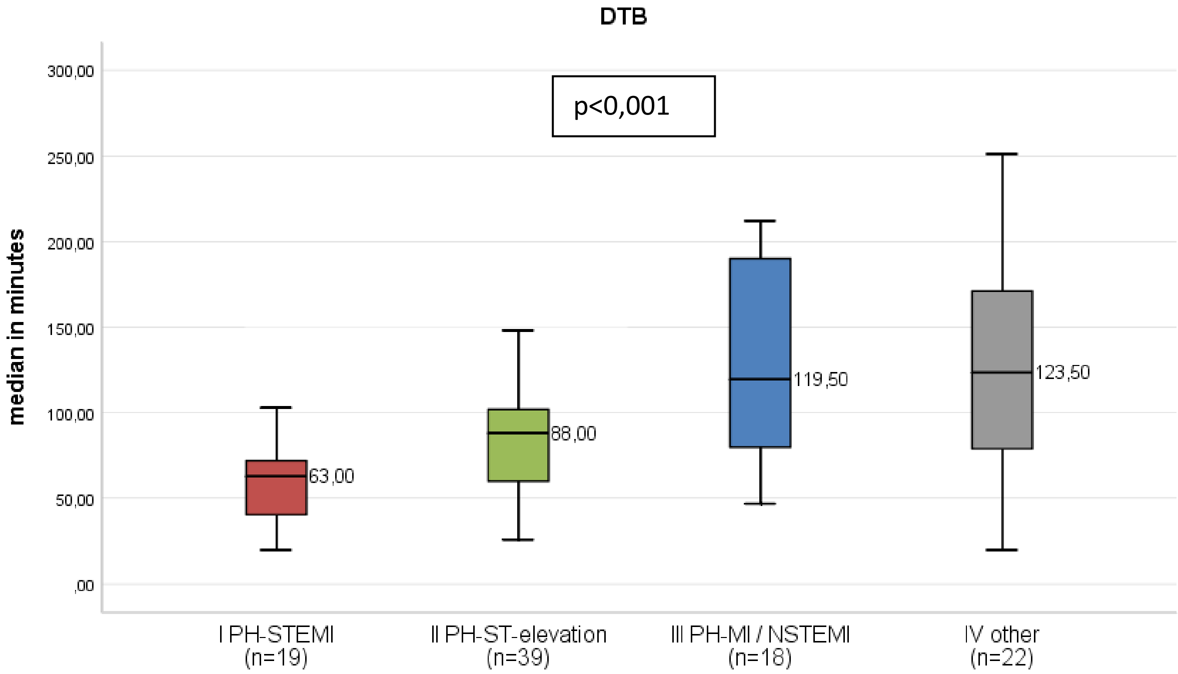


Chart 12. Median DTB in subgroups with different ECG interpretations and initial diagnoses. The bands inside the boxes indicate median time in min. Boxes extend from the first to third quartile representing the interquartile range. The whiskers indicate the lowest datum still within 1.5 IQR of the lower quartile, and the highest datum still within 1.5 IQR of the upper quartile. Outliers are not shown in the diagram. For diagrams including outliers see Supplementary Tables (Chart 19).

PH-MI	pre-hospital myocardial infarction diagnosis
PH-NSTEMI	pre-hospital non-ST elevation myocardial infarction diagnosis
PH-STEMI	pre-hospital ST elevation myocardial infarction diagnosis
PH-ST-elevation	ST elevation in pre-hospital ECG

DTB	median (min)	25th percentile	75th percentile	n	missing	total
I pre-hospital-STEMI	63	34	73	19	0	19
II pre-hospital-ST-elevation	88	59	102	39	5	44
III pre-hospital-MI / NSTEMI	119,5	80	190	18	3	21
IV other	123,5	79	171	22	7	29

Table 9. Median DTB in subgroups with different ECG interpretations and initial diagnosis.

A long median DTB time interval of 123.5 min resulted in STEMI discharged patients, in whom no ST elevation had been described and STEMI, MI or NSTEMI had not been diagnosed in the pre-hospital setting by the primary caring physician (group IV). In the STEMI discharged patients with a pre-hospital diagnosis of MI or NSTEMI, but without recognition of an ST elevation (group III), the median DTB was only slightly shorter numerically (119.5 min). Recognition of an ST elevation (but without an explicitly stated STEMI diagnosis, group II) resulted in a median DTB of 88 min. By contrast, STEMI discharged patients with a pre-hospital diagnosis of STEMI had the shortest median DTB interval (63 min). The Kruskal-Wallis-Test was performed to test for DTB delay differences between groups. The difference between groups was statistically significant (p<0,001).

3.5.4 DTB by ECG interpretation, initial diagnoses, and admission during working-hours versus off-hours in STEMI patients with pre-hospital physician contact

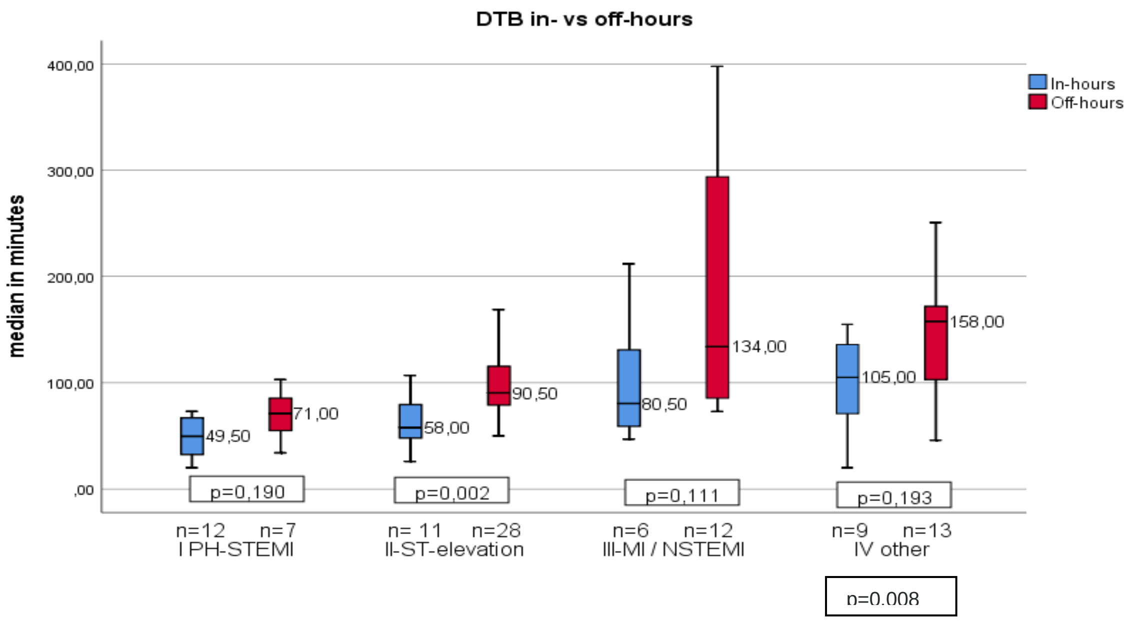


Chart 13. DTB in STEMI patients with primary physician contact by ECG interpretation, initial diagnoses, and admission during working-hours versus off-hours. The bands inside the boxes indicate median time in min Boxes extend from the first to third quartile representing the interquartile range. The whiskers indicate the lowest datum still within 1.5 IQR of the lower quartile, and the highest datum still within 1.5 IQR of the upper quartile. Outliers are not shown in the diagram. For diagrams including outliers see Supplementary Tables (Chart 20).

PH-MI	pre-hospital myocardial infarction diagnosis
PH-NSTEMI	pre-hospital non-ST elevation myocardial infarction diagnosis
PH-STEMI	pre-hospital ST elevation myocardial infarction diagnosis
PH-ST-elevation	ST elevation in pre-hospital ECG

DTB		median	25th percentile	75th percentile	n	missing	total
I pre-hospital-STEMI	working-hours n=12	49.5	32.5	67	12	0	12
	off-hours n=7	71	47	88	7	0	7
II pre-hospital-ST-elevation	working-hours n=11	58	46	84	11	4	15
	off-hours n=28	90.5	79	115.5	28	1	29
III pre-hospital-MI / NSTEMI	working-hours n=6	80.5	59	131	6	1	7
	off-hours n=12	134	85.5	294	12	2	14
IV other	working-hours n=9	105	71	136	9	4	13
	off-hours n=13	158	103	172	13	3	16

Table 10. Median DTB during working-hours vs off-hours in subgroups with different ECG interpretations and initial diagnoses. Admission during working hours was associated with numerically shorter median DTB in all subgroups. Patients with an explicit pre-hospital STEMI diagnosis received reperfusion therapy within a median DTB of 49.5 min if they were admitted during working-hours. STEMI patients with recognized ST elevation, but without an explicit pre-hospital STEMI diagnosis (group IIa) had a slightly numerically longer DTB by 8.5 min during working hours. STEMI discharged patients with a pre-hospital MI or NSTEMI diagnosis, but without an explicitly stated ST elevation (group IIIa, median DTB 80.5 min), and those STEMI discharged patients without a described ST elevation and without an MI diagnosis (group IVa, median DTB 105 min), had importantly longer DTB delays if they were admitted during working-

hours. In all groups, the time delays were numerically longer during off-hours. The Kruskal-Wallis-Test was performed to test for differences between groups I to IV separately for patients admitted during working-hours and off-hours (p=0,067 and p=0,008 respectively). The Mann-Whitney-U Test was performed to test for differences inside each group between patients admitted during working-hours and off-hours.

3.5.5 Proportion of patients with STEMI or NSTEMI and pre-hospital physician contact during working-hours versus off-hours

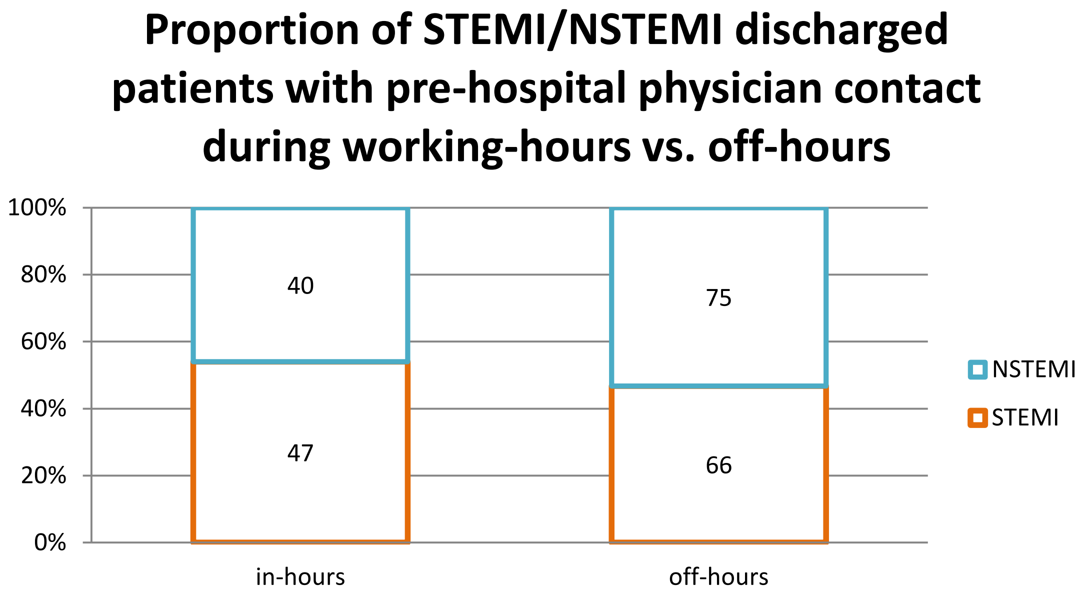
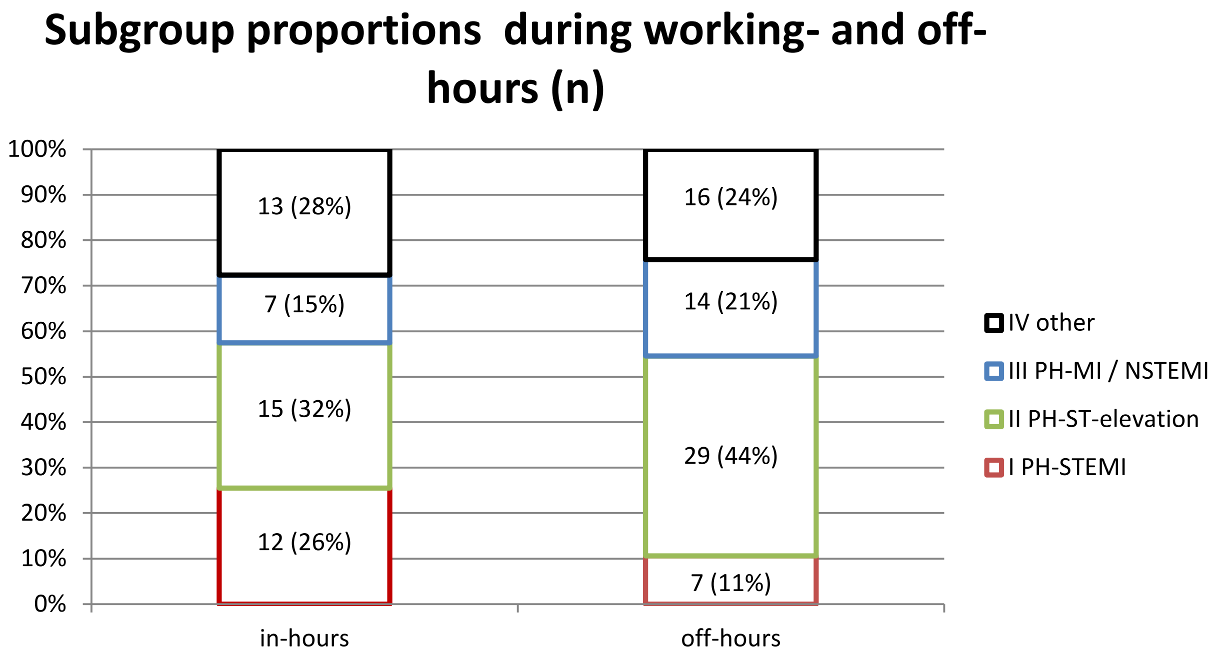


Chart 14. Proportion of STEMI/NSTEMI discharged patients with pre-hospital physician contact during working-hours versus off-hours

The proportion of STEMI versus NSTEMI discharged patients with pre-hospital physician contact admitted during working-hours was 54%, whereas during off-hours the majority (53%) of admitted patients were classified on discharge as NSTEMI.

3.5.6 Subgroups of STEMI discharged patients with pre-hospital physician contact by initial pre-hospital diagnosis: distribution during working-hours versus off-hours

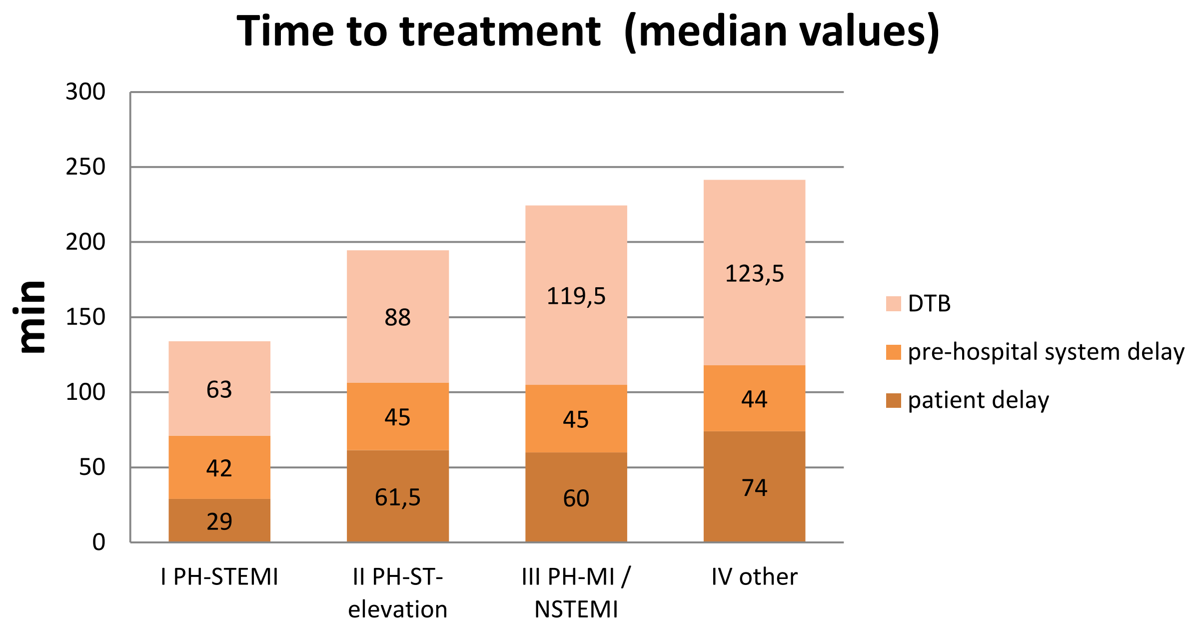


PH-MI	pre-hospital myocardial infarction diagnosis
PH-NSTEMI	pre-hospital non-ST elevation myocardial infarction diagnosis
PH-STEMI	pre-hospital ST elevation myocardial infarction diagnosis
PH-ST-elevation	ST elevation in pre-hospital ECG

Chart 15. Subgroup proportions during in- and off-hours

The number of explicitly diagnosed STEMIs during off-hours was significantly and importantly lower compared to working-hours (p=0,032). During off-hours, only 7 out of 36 patients (19%) with a described ST elevation were explicitly diagnosed as STEMI, whereas during working hours this proportion was 44% (12 out of 27 patients).

3.5.7 Care delays and overall time to treatment in STEMI discharged patients with pre-hospital physician contact analyzed by pre-hospital diagnosis



PH-MI	pre-hospital myocardial infarction diagnosis
PH-NSTEMI	pre-hospital non-ST elevation myocardial infarction diagnosis
PH-STEMI	pre-hospital ST elevation myocardial infarction diagnosis
PH-ST-elevation	ST elevation in pre-hospital ECG

Chart 16. Care delays and overall time to treatment

The complete timeline of MI care delays shows similar median EMS-alarm to Door time (pre-hospital system delay) in all pre-hospital diagnosis groups of STEMI discharged patients. In patients with an explicit primary STEMI diagnosis all three components of time to treatment, but mainly patient delay and DTB, were shorter. The 90 min guideline cut-off criterion for DTB in STEMI patients was only met by patients with an explicit pre-hospital STEMI diagnosis, or an at least recognized ST-segment elevation.

4. Discussion

4.1 Main study focus and main study findings

Our study collected data on all acute myocardial infarction patients from an urban academic teaching hospital over a four year period from 2008 to 2011. But as we sought to study the impact of pre-hospital diagnostic accuracy on subsequent care delays particularly in patients with the most urgent need of immediate coronary revascularization, we then focused our interest on STEMI patients and especially on the subgroup of STEMI patients who had initially been cared for by a physician, in most cases by an emergency physician-staffed ambulance. We investigated pre-hospital ECG interpretation and pre-hospital diagnoses and their association to subsequent care delays. In addition, we evaluated differences in the distribution of pre-hospital diagnoses and care delays according to admission during working hours versus off-hours. We observed a significantly reduced DTB interval in patients with an explicitly stated pre-hospital STEMI diagnosis compared to those without recognized ST elevation and without a pre-hospital diagnosis of MI, NSTEMI, or STEMI. A remarkable finding was the lower proportion of explicitly diagnosed STEMI cases during off-hours compared to working hours, despite a similar proportion of described ST elevations. Furthermore, in all pre-hospital diagnosis subgroups of STEMI discharged patients, DTB time intervals were at least as numerically long during off-hours as working hours. In the following, we will discuss these and more findings in detail; and we will consider possible reasons and possible strategic consequences of our findings with the goal of optimizing the prompt delivery of reperfusion for the STEMI suspected patient.

4.2 Regional, national, and international comparison of baseline characteristics and comorbidity from MI patient registries

Registry populations of MI patients differ considerably according to the inclusion and exclusion criteria of different series. Differences in inclusion criteria comprise the time period from symptom onset, patient age, possible exclusion of cardiogenic shock, unstable patients and early death, heterogeneous application of varying definitions of MI over the years, and inclusion of patients other than type I MI. These differences have to be kept in mind when the baseline characteristics and comorbidity of various MI registries are compared. The following considerations on baseline patient data refer to several registries with a similar population background (i.e. urban population of developed western world countries), namely the Berlin Myocardial Infarction Registry (BMIR), the Italian BLITZ registry, the American National Registry of Myocardial Infarction (NRMI), and the Euro Heart Survey.

The Italian BLITZ registry collected data of almost 2,000 MI patients from 296 coronary care units (87% of all active Italian units at the time of the study), who were enrolled according to previous MI definitions (2000 and earlier) and up to 48 h after symptom onset over a two week period in October 2001.[108] Hence this study reflects a broad and likely to be almost representative Italian MI population, but may differ from our current study due to different inclusion criteria, and due to the short and remote inclusion time period.[109] Due to fact that the patients included in our study were at the same time part of the BHIR database, the Berlin MI Registry was the natural reference for this investigation. The United States NRMI was the largest and longest running MI registry in the United States, collecting data from 1990 to 2006 of over 1.3 million patients with acute MI and a short symptomatic interval (<12 h after symptom onset) from 2,157 hospitals.[110] The Euro Heart Survey ACS-III enrolled 19205 MI cases from 138 hospitals and 21 countries over a 2 year inclusion period from 2006 to 2008.[111] The **proportion of STEMI** patients out of the overall MI population was 50.7% in our study. The STEMI proportion varies between the different registries, mainly according to the inclusion criteria, but in part also over time. The NRMI, with the very short symptomatic interval of enrolled patients of no longer than 12 h, comprised 54.6% of STEMI patients. It is worth noting, however; that over the years, the STEMI proportion within the NRMI series changed from over two-thirds to one-third.[112]

The BMIR also enrolled a much higher proportion of STEMI patients in its early inclusion period until 2002 (around 73%), while in 2003 to 2004 the proportion of STEMI decreased to 62%, and the proportion of NSTEMI showed a respective increase from around 23% to 38% of enrolled acute MI cases with a short symptomatic interval. The change in STEMI/NSTEMI proportions, on the one hand, reflected a change in definitions of MI and may, on the other hand, also be due to the enhanced recognition of NSTEMI through the broader application of cardiac troponin testing. The Italian BLITZ registry also enrolled patients according to early MI definitions and reported a similarly high STEMI proportion[113] , whereas the Euro Heart Survey reported a STEMI proportion of approximately 60% (presumed new left bundle branch block patients included)[114], or an even lower proportion of around 45% in earlier studies.[115] Taken together, the STEMI proportion in this study is within the expected range in a registry enrolling from 2008 to 2011.

The **mean age** of acute MI patients in this study was 66.6 y, which is in line with data from the BLITZ registry (67)[116]. The mean age of STEMI patients was somewhat lower (64 y), a finding comparing well to data from the Euro Heart Survey ACS III registry (running from 2006 to 2008 and including ACS patients within <12h from symptom onset) (64 y)[117] and the BMIR. A similar mean age was documented by the American NRMI registry, where the mean age varied from 64 y to 66 y) and in the BLITZ registry (66 y for STEMI patients). It is a well-known fact that STEMI patients are approximately 2 y younger than NSTEMI patients. In addition, a huge difference in age is usually present between men and women suffering from an acute MI, with female patients having their MI 7 to 9 y later compared to male patients. In our study, the difference in mean MI manifestation age between women and men was 8.4 y, again within the expected range for a current MI population. **Gender distribution** in our study revealed the proportion of women at 30%. This proportion was similar for all MIs and STEMI cases. Comparable gender distribution data for MI patients are available from the BLITZ registry (female proportion in STEMI 29%, for all MI 30%).[118] The Euro Heart Survey ACS III registry also reports similar data with 28-29% of STEMI patients being female.[119] The early BHIR analysis from 1999 to 2004 showed varying and overall somewhat higher proportions of female MI cases during these years (33.8% to 35.7% for STEMI, and 34.7% to 42.2% for NSTEMI).[120] The gender distribution of our study is compatible with the assumption that our population reflects a routine MI and STEMI cohort.

The **chief symptom** in our overall study population was chest pain in the vast majority of patients (81.9%). This is a common finding, although the extent of the preponderance of chest pain in MI varies. While the number of patients with chest pain in the BLITZ registry was higher at 92.6%[121] , other sources like a population based series from the Worcester Heart Attack study[122] and a series from Australia[123] reported a lower prevalence of chest pain. In the Worcester study, chest pain was shown to be age-dependent and sex-dependent, and the prevalence of chest pain varied between 46%

and 81%, whereas the Australian MI series reported an overall incidence of this chief complaint in 78% of patients. Taken together, our study population appears to be well in line with these previous series concerning symptomatic presentation.

The **time of presentation and admission** is known to impact on the care of MI patients and the outcome, in the sense that presentation during off-hours is linked to longer DTB times and higher mortality.[124] Out of our study population, 35% of all MI patients and 36% of STEMI patients were admitted during working hours. The proportion of STEMI patients admitted during working hours is slightly lower in our study compared to the proportion reported by an earlier analysis (2004 to 2007) from the BMIR, where the off-hour admission rate of STEMI cases in Berlin amounted to 38.9%.[125] In the American NRMI registry, the proportion of STEMI/LBBB patients presenting during regular working hours was 37%.[126] Out of the 7,655 STEMI patients included in the Euro Heart Survey ACS III registry, 42% were admitted during working hours.[127] In the ACTION-GWTG database study (2007-2010) involving 43,242 patients with STEMI, 37% of the patients presented during working hours.[128]

Cardiovascular risk factors and comorbidity

In order to make the comparative presentation of cardiovascular risk factors and comorbidities clearer and more transparent, we confronted the data of the present study with the data of the above mentioned large registries in two tables (see section 6 “Supplementary Tables”, Table 11) for overall MI cohorts and a second one for STEMI patients (Table 12). Compared to the BLITZ registry, the Euro Heart Survey and the overall BMIR series our study shows a numerically higher burden of comorbidity with a higher prevalence of diabetes, cigarette smoking, a higher rate of renal failure, heart failure and a higher prevalence of prior coronary revascularization (PCI and/or/CABG), although the pattern of comorbidity still appears to be compatible with previous studies. The observed differences, in particular the difference compared to the overall BMIR data, suggest that the studied hospital population appeared to be particularly comorbid; which may be due to the fact that Berlin is a heterogeneous city of socio-economic and ethnic diversity and a city with inhomogeneous age distribution between different districts. The present study just provides insight into a segment of mainly three Berlin districts that are covered by the single hospital for this study. The higher rate of prior coronary revascularization may reflect the more recent study period of the present investigation and the probably better access to this treatment option.

The pattern of comorbidity may also be influenced by administrative factors. In Germany the reimbursement system for hospitals changed from orientation to length of hospital stay to a diagnosis related group (DRG) system. The then new system enforced more accurate documentation of the principal diagnosis and cost-enhancing comorbidities.[129] Accordingly, the incidence of hypertension, hypercholesterolemia and smoking displayed a rapid increase between 1999 and 2006.[130]

The observed higher prevalence of smoking in our study is probably the result of regional differences within the city of Berlin. A second fact that has to be kept in mind is that we included former smokers in addition to current smokers into this parameter. This could also contribute to the difference compared to the BLITZ and Euro Heart Survey registries.

Altogether, despite the limited size of our study and the above mentioned particularities, the distribution of baseline characteristics, risk factors, and comorbidities in our study was in the expected range compared to other registries. This suggests that our findings are likely to be reliable and to some extent also generalizable.

4.3 Main categorical variables

4.3.1 Admission mode

The admission mode of MI patients strongly depends on EMS solutions in different countries. In the Berlin setting the patient, after making the decision to seek medical care due to symptoms like chest pain has several options. The patient can call the phone number 112, which is the universal number for medical emergencies and fire emergencies. A central control office then assorts various reaction modes according to the patient's reported chief complaints and to prespecified rules. The reaction modes include sending a physician-staffed ambulance (the typical mode if a patient reports angina pectoris, severe dyspnea, or impaired consciousness), a paramedic-staffed ambulance (in cases of intermediately severe illness), or counseling the patient without sending an ambulance (when the symptoms do not suggest an emergency). Another option is to seek help from the family doctor or the GP on call. This initial care physician can again call an ambulance or counsel the patient in another way. Apart from seeking pre-hospital physician contact, there is a still high number of patients who directly present at the emergency department and are admitted as walk-in patients. Special sub-cohorts include MI patients being transferred from a different hospital and those suffering from an intra-hospital MI. As the organization of pre-hospital EMS logistics varies widely among different regions and countries, the distribution of admission modes of MI patients enrolled in this study and the impact of admission modes on care delays, could only be compared to the overall BHIR data, but not to the other international registries. In our study, the proportion of admissions via physician-escorted ambulance was 44.7% for MI and 45.5% for STEMI patients. For this calculation we excluded intra-hospital infarctions, transfers from a different hospital, and patients previously treated by family doctor or GP on call. The overall BHIR dataset reports, for the early years (1999 to 2004), physician-escorted admission of MI patients in 46% to 51% of STEMI cases, and in 36% to 42% of NSTEMI cases. The slightly lower proportion of physician-escorted admission in our study may be due to the exclusion of unstable patients and the changes in the MI definition over time.

The proportion of different modes of admission was similar for the overall MI population and STEMI discharged patients. The small differences are surprising considering the severe nature of STEMI.[131]

4.3.2 Presence of a written primary ECG interpretation

The use of pre-hospital ECGs has been shown to reduce DTB.[132,133] Obtaining and interpreting an ECG, as an essential diagnostic step, should be performed promptly (within 10 min) after FMC.[134] Different solutions have been implemented worldwide, in order to obtain an immediate ECG interpretation at FMC. The ECG can be interpreted by an emergency physician on the ambulance, but this requires a physician-escorted ambulance. The interpretation might also be made by a specifically trained emergency paramedic, or automatically by computer analysis. In addition, the ECG can be transferred to an ED physician or an experienced cardiologist. Obviously, the different options can also be combined. Previously the application of pre-hospital ECGs was not satisfactory. Curtis *et al.* report that in the years 2000-2002 in the United States only 4.5% of patients received a pre-hospital ECG prior to fibrinolytic therapy, and only 8% of PCI treated patients received a pre-hospital-ECG[135]. After promotion of pre-hospital ECG use by the guidelines, the utilization of pre-hospital ECG increased substantially.[136,137]

In Berlin, only emergency physicians on the ambulance, GPs on call and family-doctors are allowed to provide a diagnostic ECG interpretation. This partially explains why almost all patients who are transported by a paramedic-staffed ambulance, but without an accompanying physician, enter the hospital without documented ECG findings. For the purpose of this work we did not evaluate if a pre-hospital ECG had been obtained, but we only investigated if a written ECG interpretation existed. The number of patients with primary physician contact at FMC by the family doctor or the GP on call, in whom a written ECG interpretation was found, was not satisfactory. The possible benevolent explanation could be that in the situation of a suspected STEMI, the written documentation of ECG findings may have been considered as time-consuming and may therefore have been omitted. Similarly, in the case of hospital-diagnosed MIs, an initial written ECG interpretation was rare. In the majority of ECGs performed on hospitalized patients with an in-hospital MI, a written retrospective ECG documentation was only available from discharge protocols. This contributed to a large number of patients with a "missing ECG description", although very likely not the ECG interpretation, but merely the written documentation of the findings was lacking in these patients. The reason why a written ECG protocol was available from the records at FMC in only a minority of intra-hospital MIs, or patients treated primarily in the ED, could be that in a suspected STEMI, the patient is immediately moved to the Intensive Care Unit or to the CCL. We observed a relatively high proportion of patients who received an explicit ECG protocol if the FMC was made by the physician-staffed ambulance (84%). But we have to remember that patients with typical complaints are more likely to be treated by a doctor, whereas patients presenting without typical symptoms are often initially treated by EPs or paramedics. The frequency and accuracy of ECG interpretations made by EPs or paramedics is probably higher than the number of their ECG protocols counted in our study. This may be due to fact that after obtaining an ECG suggesting a myocardial infarction, the physician-staffed ambulance is usually called and the ECG interpretation is documented in the emergency physician protocol. As our data show a clear association of primary explicit STEMI ECG diagnoses and the subsequent care intervals, it must be said that in the case of a suspected STEMI, obtaining a pre-hospital-ECG and interpreting it is not sufficient. The ECG interpretation must be followed by explicitly establishing the clear primary diagnosis of STEMI to accelerate the subsequent treatment cascade.

4.3.3 Primary diagnosis

Similarly to the documentation of ECG findings only physicians are obliged to record a primary pre-hospital diagnosis of EMS cases. This explains the considerable number of patients admitted to the hospital without an explicit suspected diagnosis. Also the perception of the documentation of a diagnosis as being time-consuming could be a reason for the low number of cases with a written diagnosis in MI and STEMI patients' protocols. In general, if the diagnosis was documented, in most cases the diagnosis was related to myocardial ischemia. The most frequently documented diagnosis was "myocardial infarction". Unfortunately, the further differentiation between STEMI and suspected ACS/NSTEMI was unsatisfactory, and was only documented in a minority of cases, regardless of the FMC setting.

4.4 Pre-hospital STEMI recognition, STEMI diagnosis definition, and subsequent care delays during working hours and off-hours

In only 56% of our study patients who were primarily cared for by a physician in the pre-hospital setting, and who later received a STEMI discharge diagnosis, was an ST segment elevation recorded in the EMS protocol, while in 18%, various ECG alterations but not an ST elevation were documented, and in 20% no written ECG interpretation was found. This low percentage of definite and reliable ECG interpretation is concerning and merits further consideration (see section 4.4.1). In addition, we observed that during off-hours the proportion of patients with a definitive STEMI diagnosis was significantly even lower compared to working hours, and the translation of a recorded ST elevation ECG into a clear STEMI diagnosis appeared to be considerably and significantly more reluctant during off-hours. As a consequence, during off-hours more STEMI discharged patients received a more general MI diagnosis instead of a clear STEMI diagnosis.

4.4.1 Possible reasons for inappropriate recognition, recording, and denomination of ST elevations and a STEMI diagnosis in STEMI discharged patients with primary physician contact

The following possible reasons for an inappropriately lacking pre-hospital STEMI diagnosis include general conditions that are independent from the admission time period, and other factors that may be elevated during off-hours EMS operations.

1. <u>The emergency physician may have assumed other reasons different to STEMI for ST elevations</u> in the pre-hospital ECG, like stress or takotsubo cardiomyopathy,

subacute or prior MI, ventricular aneurysm, ventricular hypertrophy, pulmonary embolism, pericarditis, or Brugada Syndrome, particularly in the absence of chest pain. [138]This could typically be a population where obtaining a second opinion (e.g. via telemedical ECG transfer to ED or hospital cardiologist) may increase diagnostic certainty. If a primary STEMI diagnosis is missed in these cases, additional diagnostic side steps and subsequent prolongation of care delays (above all DTB time) is likely to occur. 2. It could be that documentation of ECG and the STEMI diagnosis was left incomplete deliberately in order to avoid time-consuming paperwork. In these cases the STEMI diagnosis may have been recognized, but not recorded in the EMS protocol.

3. The ST-segment elevation did not meet strict criteria for a STEMI diagnosis in the first pre-hospital ECG or had a borderline ST elevation. It is readily possible that full diagnostic ST elevations only develop with time and a patient is discharged with a STEMI diagnosis, though the first ECG did not meet guideline STEMI criteria. And the recognition and appropriate interpretation can be challenging in some cases (e.g. in leads V2/V3 or in limb leads. It must be said, however, that a patient with symptoms suggesting myocardial ischemia, but without a fully diagnostic ECG, should be treated in the same way like STEMI patients are treated. The problem of an abnormal ECG without the exact STEMI criteria was evaluated in a previous study of limited size. This study showed that almost half of the patients with suspected MI who did not meet strict STEMI criteria had significant coronary disease documented by coronary angiography.[139]

4. The initial treating physician may have deliberately avoided the definite STEMI diagnosis. Stating a STEMI diagnosis elicits a chain reaction with CCL activation and ED bypass according to current guidelines. It is possible that physicians are reluctant to explicitly use the “STEMI” denomination despite typical ECG findings in combination with suggestive symptoms, because of diagnostic uncertainty and concern of being blamed for a possible inappropriate emergency CCL activation. They may then decide to admit the patient to the ED classified as “ST-segment elevation only”, and they may prefer discussing the patient with other physicians, or perform an additional ECG or an echocardiographic examination. Or they simply prefer shifting the responsibility of calling the CCL staff to others. In the described situation, again telemedical ECG transfer and teleconsultation with the ED physician or the hospital cardiologist would likely be helpful.

5. Finally, a lack of skills in ECG interpretation and failure to draw valid conclusions from the ECG findings cannot be excluded with certainty, although reading an ECG is part of the emergency physicians' training. Again, telemedical ECG transfer and counseling could complement insufficient diagnostic skills.

During off-hours EMS operations, patients presenting with ST-segment elevation and/or MI were found in our study to be less likely to receive the appropriate STEMI diagnosis compared to working hours cases. Several possible reasons have to be considered.

The first reason could be that during working hours the emergency doctors or ambulance physicians have the opportunity more easily to discuss the patient's findings with an in-hospital resident cardiologist and to modify the diagnosis in their protocol. During off-hours, the chance to contact the cardiologist in the studied hospital was lower. It is impossible to derive from our data, however, if at all and in how many cases the diagnosis was actually revised.

Secondly, the STEMI diagnosis implies activation of the CCL staff, who are not present in the hospital during off-hours and have to arrive from home. FMC-involved physicians may avoid taking responsibility for inappropriate CCL activation especially during off-hours. During off-hours, inappropriate CCL activation may cause significant embarrassment for the responsible physician, and this can give rise to avoiding the "label" STEMI. Avoiding the STEMI denomination, in turn justifies admitting a patient to the hospital without prior pre-hospital CCL activation. A patient with "indefinite ECG findings" , or "ST-elevation only" , or the undifferentiated diagnosis of an MI, would routinely be admitted to the ED in order to undergo additional tests before CCL activation (e.g. echocardiography, serial ECG, troponin tests, or CT of the chest to rule out aortic dissection and/or pulmonary embolism).

Finally, a difference in baseline characteristics between patient sub-cohorts presenting during working hours versus off-hours was reported. In the National Heart, Lung, and Blood Institute Dynamic Registry analysis, patients treated off-hours were sicker than subjects treated during working hours.[140] Other authors report a lower median age of patients admitted during off-hours.[141,142] These differences may also influence the clinical picture and thus affect the recognition of STEMI in patients with suspicious ECG findings.

We do not think that there was an actual difference in the ability to establish a STEMI diagnosis between cases cared for during working-hours versus off-hours to account for the low STEMI proportion during off-hours. Interestingly, there is also a previous study demonstrating that the ability to make CCL activation decisions based on ECG findings does not appear to be impaired during overnight shifts, despite sleepiness and fatigue.[143]

One possible difference in the composition of personnel during working hours versus off-hours does not relate to the emergency physicians, but to the fact that family doctors in Berlin do not see patients during off-hours, and delegate their duties to GPs on call. These GPs on call do not know the patient like the family physician does, and their diagnoses and management strategies are probably different. Also the patients' way of accessing emergency care may differ between working hours and off-hours, in the sense that the care-seeking patient will more often directly present himself to the hospital, or call the emergency number 112, when his family doctor is not available. Our study population was too small to allow a reliable comparison of subgroups with regard to the admission mode. As the vast majority of our study patients were admitted via the EMS, we consider a decisive influence of the factors listed in this paragraph on the overall care delays to be very unlikely.

4.4.2 Inappropriate CCL activation

Although the primary goal of the logistics of a MI network is to provide immediate life-saving care to an MI patient, as a second objective it has to be ensured that inappropriate CCL activation should be avoided, because off-hours activation, or stopping the routine workflow of the CCL during working hours, produces considerable expenses and staff idle capacity.[144] Inappropriate CCL activation may especially occur in patients with indefinite and borderline findings.

There is very little scientific data on inappropriate CCL activation. There is not even an existant consensus regarding the definition of what an inappropriate CCL activation is. Some authors derive the criteria of inappropriate CCL activation directly from the STEMI guideline criteria, while making the decision retrospectively, and basing the appropriateness on coronary angiography findings and troponin levels (no culprit coronary artery lesion, no significant coronary artery disease, and no elevated or rising cardiac troponin level).[145] As a result of the heterogeneous definitions, widely varying rates of inappropriate CCL activation are reported in different studies. Moreover, comparative interpretation is difficult, because the logistics and responsibility for CCL activation differs between different EMS systems.

"When CCL activations were classified based on the final diagnosis of a confirmed STEMI, inappropriate CCL activations occurred in 46%, 33%, 27%, and 24% of the activations initiated by cardiology, EMS, ED, and pre-hospital physicians, respectively."[146] Criticism may be made, however, of applying final STEMI diagnoses as the criterion of appropriateness, because a certain rate of inappropriate activations are unavoidable, even if STEMI criteria are applied correctly (e.g. takotsubo cardiomyopathy, pericarditis). Contrasting the above mentioned results, other studies found evidence that inappropriate CCL activation is infrequent and occurs in 5.2% to 14% of cases. Understandably the rate of inappropriate CCL activation depends on the mode and quality of ECG interpretation. If CCL activation was based on computer interpreted ECGs, the rate of inappropriate activations attained the level of 20%.[147] Brian *et al.*, in their paper on automated ECG diagnosis, support the prospective definition of appropriate CCL activation and state: "Therefore, if the false positive CCL activation should reflect the ability to make appropriate decision in the early MI care, the gold standard definition of a false positive should rely on a cardiologist's retrospective determination using limited clinical information and initial ECG findings. The MI may be aborted spontaneously before the development of myocardial cell necrosis. Therefore, it is difficult to determine the appropriateness of emergency physician CCL activation with angiographic findings."[148]
Another possibility could be to simply count the cases where after CCL activation the cardiac catheterization was subsequently cancelled. Garvey *et al.* recently reviewed all CCL activations in the North Carolina Reperfusion of Acute Myocardial Infarction in Carolina Emergency Departments (RACE) initiative in this regard. In that study, inappropriate activations, defined according to the cardiac catheterization cancellation rate, were found in 15% of all CCL activations.[149] Taken together, it can be said that the appropriate activation of the CCL activation chain, as well as the avoidance of inappropriate CCL activations, requires the best possibly skilled and experienced guideline-based pre-hospital decision making.

4.4.3 Consequences of unrecognized STEMI discharged patients on DTB time during working-hours and off-hours.

The influence of an appropriate pre-hospital STEMI diagnosis on the prompt delivery of catheter-based reperfusion therapy was important and significant in this study. Missing the pre-hospital STEMI diagnosis in patients with recognized ST-elevation implied a delay in DTB time of 88 min, a time delay clearly jeopardizing the patients' subsequent quality of life and probability of survival. The respective delay in DTB was gradually prolonged with less specific ECG interpretation and diagnosis from an explicit STEMI diagnosis to non-specific or lacking description, with the description "ST elevations" (but not "STEMI") relating to around 25 min longer DTB, and the denomination "MI" or "NSTEMI" relating to a DTB prolongation of 56 min. Recently these findings were clearly confirmed by the BHIR-initiated First Medical Contact Study. This study enrolled more than 1,000 patients from the entire Berlin area and all pre-hospital ECGs underwent blinded re-evaluation by experienced cardiologists. The FMC study corroborated the findings of the present study, that a considerable percentage of pre-hospital STEMI ECGs were not clearly interpreted as STEMI (26% in the FMC study). Moreover, the FMC study undoubtedly confirmed the negative impact of an unclear pre-hospital ECG diagnosis on DTB time, with a marked and significant DTB prolongation by 85 min in comparison with correctly diagnosed STEMI patients.[150]

While discussing differences in DTB during working hours and off-hours, it has to be mentioned that the studied hospital is equipped with one single CCL. If this CCL is occupied by an ongoing procedure, the DTB time for an incoming STEMI patient can also be prolonged by a certain waiting period. This waiting period will usually occur during working hours, and again mainly if the patient has not been announced as a STEMI case by the pre-hospital staff. Announcing the STEMI patient before admission at least gives the CCL some time to finish the previous procedure and to hold the planned program.

The shortest DTB times were observed in the subgroups with a clear pre-hospital diagnosis of STEMI regardless of the admission time (working hours versus off-hours).This finding is congruent with recently published results from the First Medical Contact Study in the context of the Berlin Myocardial Infarction Registry.[151]

The DTB time difference during working- vs off-hours was significant only for group II (ST elevation) (p=0,002 Mann Whitney U test).

Possible explanations for the additional off-hour delay, also affecting pre-hospital recognized STEMI patients, include the time required for arrival of CCL staff and CCL preparation. It might also be that during off-hours, phone calls and direct contact between the emergency physician on the ambulance and the ED team and/or the cardiologist takes additional time, if a STEMI is suspected. As regards the DTB time, the intra-hospital delays during working hours were acceptable if a pre-hospital-STEMI diagnosis, a pre-hospital ECG interpretation of “ST elevation”, or diagnosis of MI had been made. The difference in DTB time was only 8 min between the “STEMI” diagnosed group (group Ia) and the group with “ST elevation” ECG interpretation (group IIa), suggesting that the latter did not undergo additional time consuming diagnostic measures. During working hours, both groups with denominated ST elevations (either as “STEMI” or as “ST elevation”) were treated within the time range that is recommended by the guidelines.

The situation was different during off-hours, where the difference was that the “STEMI” denominated subgroup had a shorter DTB time by 20 min compared to the subgroup described as “ST elevation”, but no STEMI diagnosis. Our study data do not provide information as to why this important off-hour difference in DTB time occurred. Previous studies suggested that additional delays during off-hours may be due lacking measures to shorten the DTB interval, like field CCL activation, ED bypass or the arrival of the CCL staff at the catheterization lab within 20 min of the alarm call.[152,153] The DTB time could be also prolonged by additional diagnostic steps or consultations.

It appears that during working hours the hospital can better compensate for the consequences of an indefinite pre-hospital diagnosis. Prompt reevaluation in the ED will have less impact on the DTB time, if the interventional cardiologist is present at the hospital. However, if the patient is admitted to the ED during off-hours without a pre-hospital STEMI diagnosis, the additional delay due to CCL staff activation and arrival will definitely prolong the time to reperfusion. It is well possible that an indefinite pre-hospital diagnosis in our study did not usually result in a pre-hospital CCL activation, although this cannot be proven by our data.

In conclusion, our study demonstrates that a surprisingly low proportion (26%) of STEMI-discharged patients who were admitted during working hours received a STEMI diagnosis by the physician in the pre-hospital setting. During off-hours the denomination of an explicit STEMI diagnosis occurred even less frequently (11%). This difference was statistically significant (p=0,032). The study shows that missing the initial STEMI diagnosis has important consequences, in the sense that the time to revascularization was markedly prolonged. This issue appears to distinctly concern patients who are admitted during off-hours. In the meantime our findings have been confirmed and corroborated by the BHIR FMC study.[154]

It is worthwhile to more specifically characterize specific reasons for longer DTB times in patients with a missed pre-hospital STEMI diagnosis, especially during off-hours. The question of why STEMI diagnoses are missed in the pre-hospital setting remains without a definite answer, but undoubtedly measures to increase diagnostic certainty in pre-hospital operations by telemedical means, like ECG transmission to the experienced cardiologist and tele-counselling to establish a common firm diagnosis, should be applied and evaluated. Obstacles preventing appropriate pre-hospital diagnoses and CCL activations appear to particularly concern off-hour operations. Common efforts of EMS services and hospital cardiologists should be undertaken to identify useful steps that improve early diagnosis and reduce care delays in acute MI.

4.5 Limitations

The study was performed on a modest number of patients at a single hospital in the city of Berlin and may therefore not be representative for other study environments.

We identified STEMI patients using their discharge diagnosis and did not blindly re-evaluate the initial ECGs. Hence, in some patients the STEMI pattern may only have evolved after the pre-hospital phase, and in these patients the emergency physician on the ambulance was actually unable to establish the STEMI diagnosis. But this limitation does not appear to have importantly influenced our results, as the BHIR-led FMC study with a more meticulous methodology and blinded ECG reevaluation clearly confirmed our findings.[155]

An additional limitation relates to the fact that we could not ensure that the clocks used to determine the EMS alarm, the admission to hospital, and determination of DTB time were synchronized.

Finally, as off-hours, we defined on weekdays the period from 04.00 pm to 7.30 am, and in addition Saturdays and Sundays. But the off-hours attribution did not include holidays, although during holidays no cardiologist was routinely present at the hospital.

5. Appendix

Figure 7. BMIR survey sheet.

Erhebungsbogen
Berliner Herzinfarktregister e.V.

Klinik-Code ________ **lfd. Pat.-Nr.** ________

am Fachgebiet Management im Gesundheitswesen
Technische Universität Berlin
Müller-Breslau-Str. 15 VWS4 HI 10623 Berlin
Tel. 030 / 314 76672 Fax: 030 / 314 76663
herzinfarktregister@tu-berlin.de www.herzinfarktregister.de

Einschlusskriterien
gesicherte Diagnose Myokardinfarkt
(STEMI/LSB und NSTEMI)
nach neuer Definition **Typ I** (s.a. Hinweise)
Prähospitalzeit **≤ 24 h**

WICHTIG
NUR DIESE SEITE AN TU-BERLIN SCHICKEN
- Seite 2 -

1. Patientendaten

Name [redacted] **letzten 2 Buchst.** ____/____

Geburtsdatum [redacted] ____ ☐ **Mann** ☐ **Frau**
Tag / Monat / Jahr

Krankenkasse [redacted]

Telefonnr. Patient [redacted]

Name des Hausarztes [redacted]

Wohnbezirk ____________________
alter Berliner Bezirk/Bundesland

Größe ________ **cm** Gewicht ________ **kg**

2. Erstversorgung

Infarktbeginn ___/___/___ ___/___ ☐ n.b.
Tag/ Monat/ Jahr Std./ Min.

Klinikankunft ___/___/___ ___/___ ☐ n.b.
Tag/ Monat/ Jahr Std./ Min.

intrahospital ☐ ja ☐ nein ☐ n.b.

Erstversorgung ☐ NEF ☐ RTW ☐ Hausarzt ☐ KV-Dienst ☐ selbst ☐ n.b.

falls NEF, Einsatz-Nr. ____________ *(5 Ziffern)*

NEF-Diagnose ☐ STEMI ☐ keine Heb./uneindeutig

prähospitale Reanim. ☐ ja ☐ nein

Zuweisung ☐ ja ☐ nein ☐ n.b.

falls ja, welche Klinik ____________________

3. Präexistierende Risikofaktoren und Nebendiagnosen

Raucher	☐ nein	☐ ehemals	☐ ja	☐ n.b.
Diabetes	☐ nein	☐ neu	☐ ja	☐ n.b.
Hypertonie	☐ nein		☐ ja	☐ n.b.
Hypercholesterinämie	☐ nein		☐ ja	☐ n.b.
Z.n. Infarkt	☐ nein		☐ ja	☐ n.b.
Z.n. PCI	☐ nein		☐ ja	☐ n.b.
Z.n. Bypass-OP	☐ nein		☐ ja	☐ n.b.
Z.n. Apoplex	☐ nein	☐ TIA	☐ ja	☐ n.b.
Vorhofflim./-flat.	☐ nein		☐ ja	☐ n.b.
Herzinsuffizienz	☐ nein		☐ ja	☐ n.b.
Niereninsuffizienz	☐ nein		☐ ja	☐ n.b.

4. Akutdiagnostik bei Aufnahme

bei Aufnahme HF ____/Min. RR ____/____mmHg
☐ KILLIP I ☐ KILLIP II
☐ KILLIP III ☐ KILLIP IV

Erst-EKG *(Aufnahmediagn.)* ☐ STEMI ☐ NSTEMI ☐ RSB ☐ LSB

Rhythmus ☐ SR ☐ Vorhofflimmern/-flatt. ☐ Schrittmacher

LV-Funktion ☐ >50 % ☐ 41-50% ☐ 31-40% ☐ ≤30% ☐ n.b.

4a. Erstbetreuende Station ☐ IMC/CPU ☐ ITS
☐ Normalstation ☐ Stat. mit Monitorüberw.

5. Akuttherapie

☐ unfrakt. Heparin ☐ niederm. Heparin. ☐ Fondaparinux
☐ Clopidogrel ☐ Prasugrel ☐ Ticagrelor
☐ GPIIb/IIIa ☐ Bivalirudin

Reperfusion ☐ keine ☐ PCI ☐ nur Koronarangio.
☐ Lyse (<12h) ☐ Bypass-OP

Falls PCI
Stent ☐ BMS ☐ DES ☐ kein Stent
Zugang ☐ transradial ☐ transfemoral

Datum PCI ___/___/___ Gefäßpunktion ___/___
Tag/ Monat/ Jahr Std./ Min

Erster Ballon ___/___ TIMI (vor) ____ (nach) ____
(o. first device) Std./ Min.

Thrombus (angiographisch) ☐ ja ☐ nein
Thrombektomie-Device ☐ ja ☐ nein

Falls Bypass-OP ☐ elektiv
☐ Notfall-OP: ___/___/___ *verlegt in* ____________
Tag / Monat / Jahr *(welches Herzzentrum)*

ASSIST-System ☐ nein ☐ ja
wenn ja, ☐ IABP ☐ Impella ☐ ECMO

Warum weder Lyse noch PCI noch CABG ____________

6. unerwünschte Ereignisse

intraprozedural PCI ☐ Schock (neu) ☐ Intubation
☐ keine ☐ Reanimation ☐ Sonstige

stationär ☐ Reinfarkt ☐ Schlaganfall
☐ keine ☐ Reinterven. ☐ Sonstige

Blutung *(GUSTO Krit.)*
☐ keine ☐ leicht ☐ moderat ☐ schwer

7. Entlassungsmedikation

☐ ASS ☐ Beta-Bl. ☐ ACE/ARB-Hemmer
☐ Clopidogrel ☐ Prasugrel ☐ Ticagrelor
☐ Heparin ☐ VKA ☐ Dabigatran ☐ Rivaroxaban ☐ Apixab.
☐ Diuretikum ☐ Aldosteronantagonist
☐ Statin ☐ anderer Cholesterinsenker
☐ Insulin ☐ orales Antidiabetikum

8. Entlassung, Verlegung oder Tod

Entlassungsdiagnose: ☐ STEMI ☐ NSTEMI

☐ **Pat. entlassen** Datum: ___/___/___
Tag / Monat / Jahr

☐ **Pat. verlegt** Datum: ___/___/___
Tag / Monat / Jahr

☐ **Pat. verstorben** Datum: ___/___/___ ___/___
Tag / Monat / Jahr Std./ Min.

Bogen ausgefüllt: ____/____/____
Tag Monat Jahr

____
Name und Unterschrift erhebender Arzt / erhebende Ärztin

6. Supplementary Tables

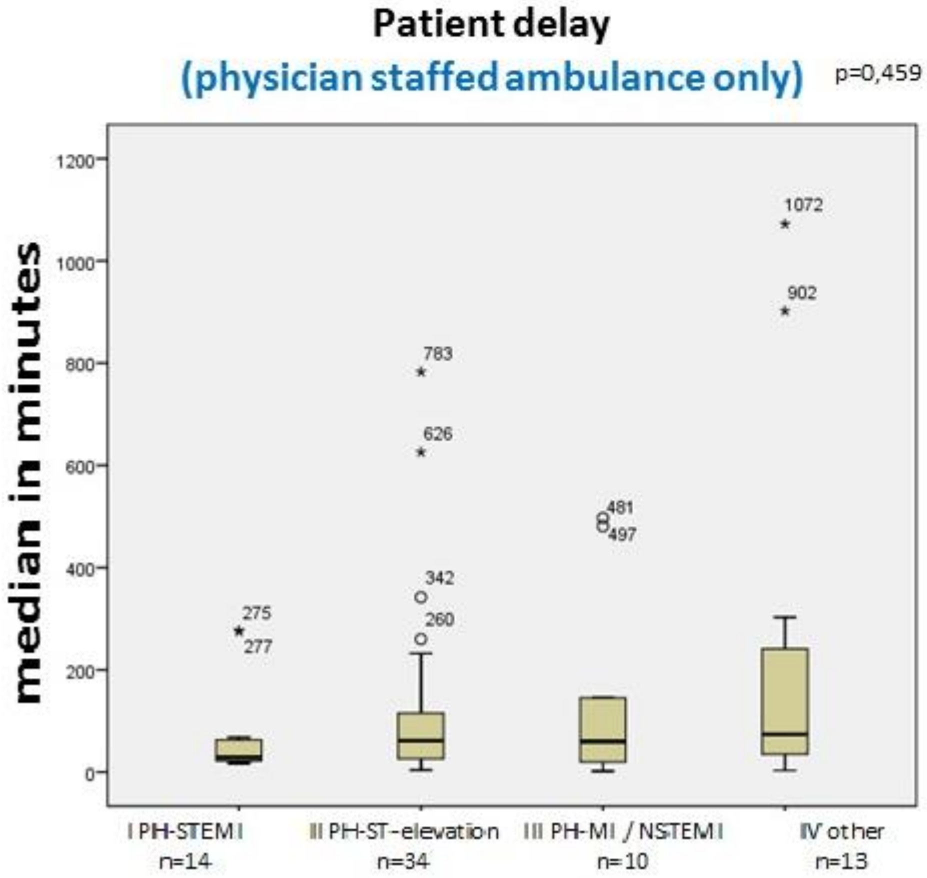
Table 11. Comparison of risk factors and comorbidities in overall MI populations from the present study and various large registry studies.

	Our study	BLITZ[156]	BMIR[157]
	2008-11	2001	2014
	SO<24h	SO<48h	SO<24h
			2
Hypertension	71.6	56	78
Smoking	61	58	40
Hypercholesterolemia	42.5		50
Diabetes mellitus	30.3	22	
MI history	19.1	20	
History of stroke	7.6	7.8	
Renal failure	17.0		
Heart failure	13.4	6.6	
Previous PTCA	19	4.3	
Previous CABG	5.3	4.3	

Table 12. Comparison of risk factors and comorbidities in STEMI populations from the present study and various large registry studies.

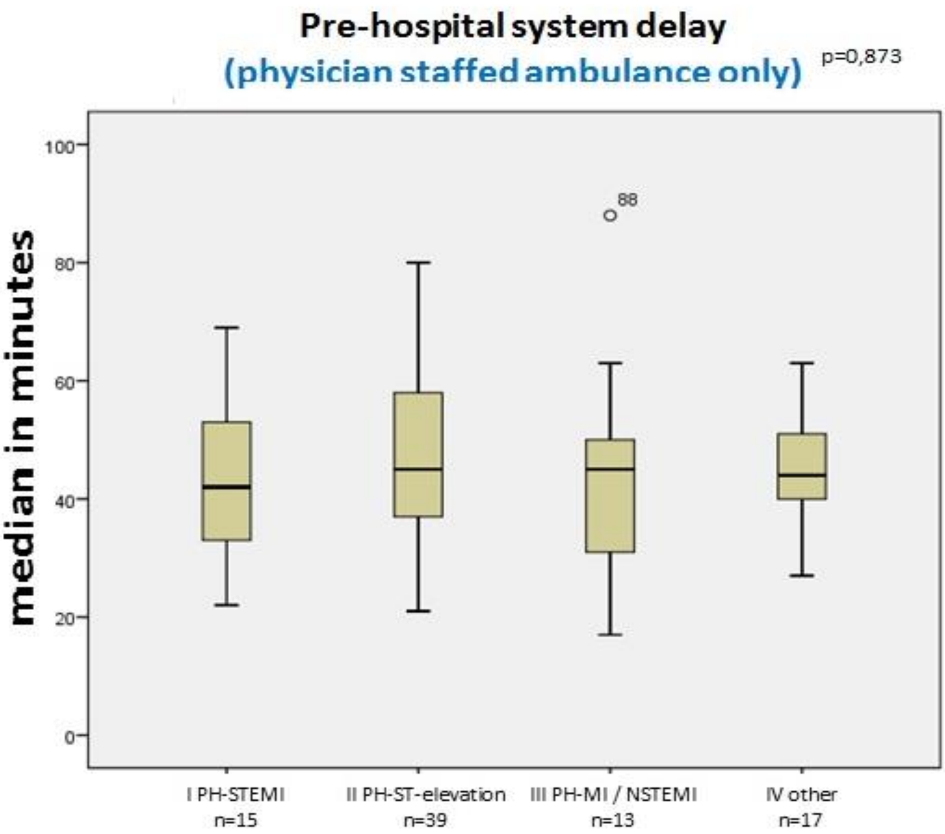
	Our study 2008-11 SO<24h	Euro Heart Survey III 2006-08 SO<12h[158]	BMIR 1999-2004 SO<48h[159]	BLITZ 2001 SO<48h [160]
Hypertension	62.9	56-58.9	55.9-70.5	51
Smoking	69.4		39.4-46.4	60
Hypercholesterolemia	37.5	38.1-41	35.6-61.5	
Diabetes mellitus	24.4	20.2-25.5	22.6-27.6	20
MI history	14.4		14.2-19.2	15
History of stroke	8.8	4.5-6.1		6.8
Renal failure	11.2	3.7-4.6	3.2-13.6	
Heart failure	9.3		4.0-13.5	3.5
Previous PTCA	15.0	7-9.4		3.2
Previous CABG	2.6	1.4-2.4		2.2

Chart 17. Median patient delay in groups with different ECG findings and first diagnosis. Outliers included in the chart.



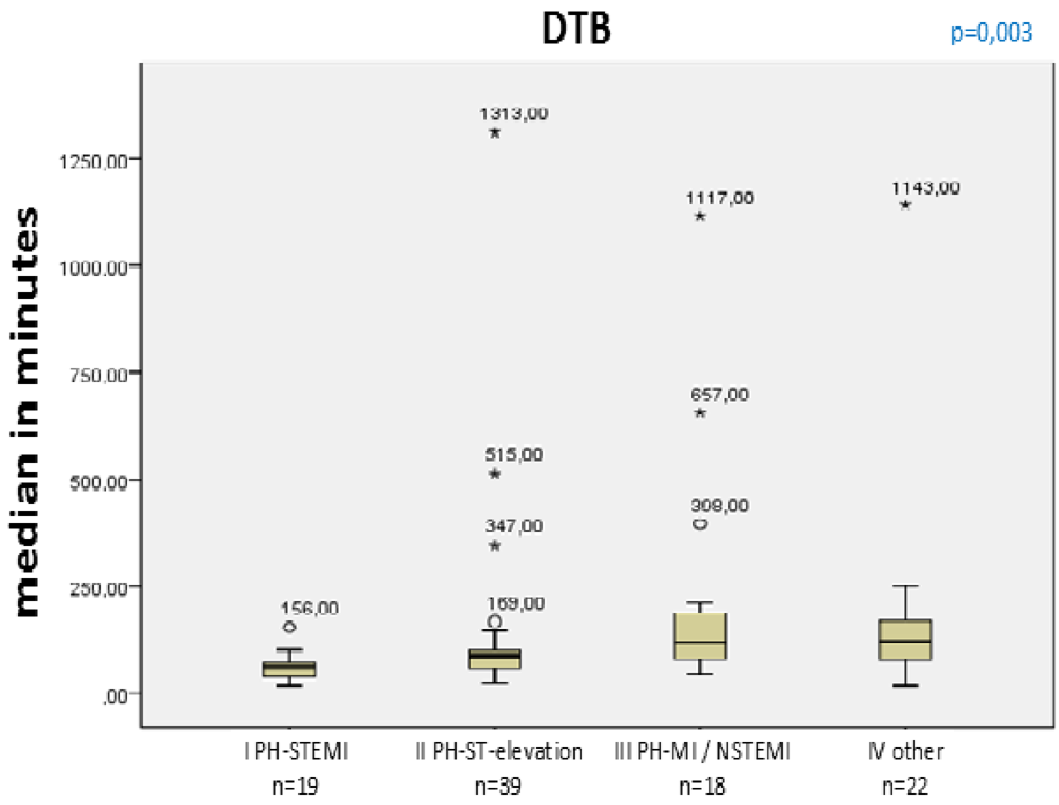
PH-MI	pre-hospital myocardial infarction diagnosis
PH-NSTEMI	pre-hospital non-ST elevation myocardial infarction diagnosis
PH-STEMI	pre-hospital ST elevation myocardial infarction diagnosis
PH-ST-elevation	ST elevation in pre-hospital ECG

Chart 18. Median pre-hospital system delay in subgroups with different ECG findings and first diagnosis. Outliers included in the chart.



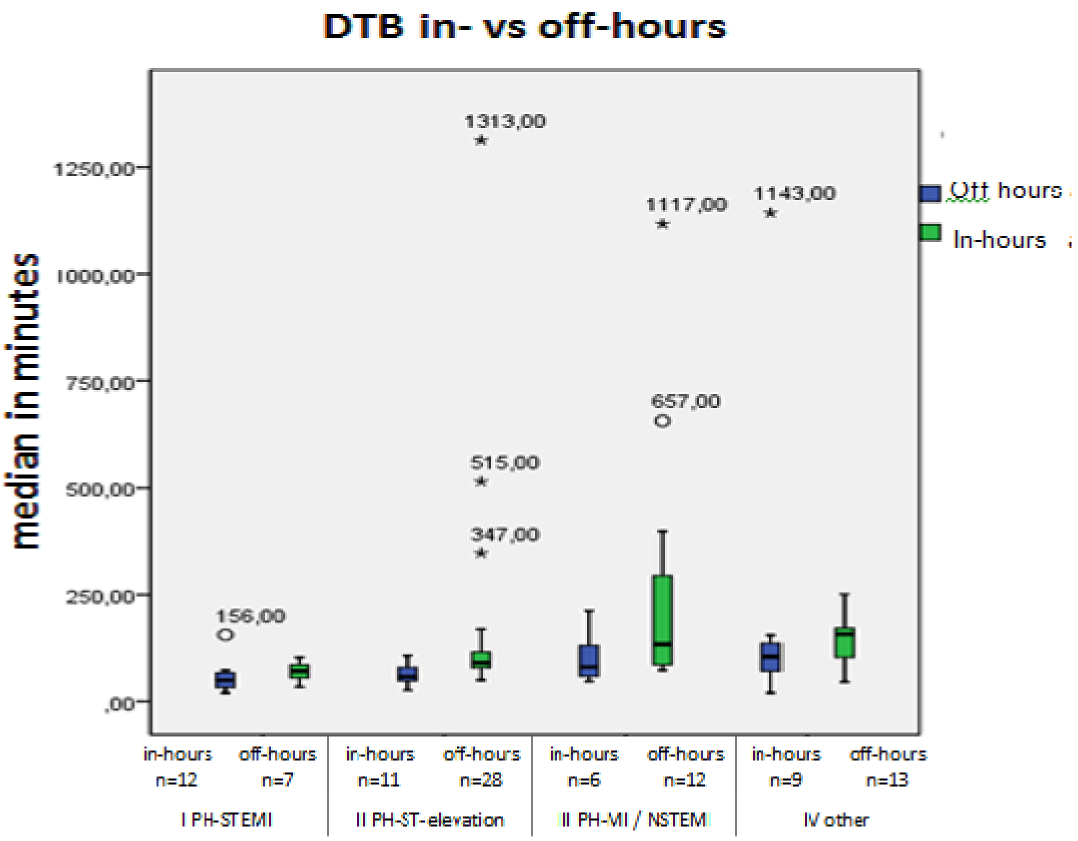
PH-MI	pre-hospital myocardial infarction diagnosis
PH-NSTEMI	pre-hospital non-ST elevation myocardial infarction diagnosis
PH-STEMI	pre-hospital ST elevation myocardial infarction diagnosis
PH-ST-elevation	ST elevation in pre-hospital ECG

Chart 19. Median DTB in subgroups with different ECG findings and first diagnosis. Outliers included in the chart.



PH-MI	pre-hospital myocardial infarction diagnosis
PH-NSTEMI	pre-hospital non-ST elevation myocardial infarction diagnosis
PH-STEMI	pre-hospital ST elevation myocardial infarction diagnosis
PH-ST-elevation	ST elevation in pre-hospital ECG

Chart 20. DTB in STEMI patients with primary physician contact by ECG interpretation, initial diagnoses, and admission during working-hours versus off-hours. Outliers included in the chart.



PH-MI	pre-hospital myocardial infarction diagnosis
PH-NSTEMI	pre-hospital non-ST elevation myocardial infarction diagnosis
PH-STEMI	pre-hospital ST elevation myocardial infarction diagnosis
PH-ST-elevation	ST elevation in pre-hospital ECG

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Eidesstattliche Versicherung

„Ich, Pawel Mentuch, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „ASSOCIATION OF PRE-HOSPITAL CARE AND INVASIVE MANAGEMENT IN PATIENTS WITH MYOCARDIAL INFARCTION. A SINGLE CENTRE STUDY BASED ON THE BERLIN MYOCARDIAL INFARCTION REGISTRY" selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst."

Datum ....   Unterschrift ....

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Areit nicht veröffentlicht.

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