An in-depth analysis of the risk factors, treatments and outcomes of in-hospital acute myocardial infarctions: Results from the RHESA Study

Thesis

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Abstract

Introduction: Few studies reported differences in the patients' characteristics and outcomes between out-of-hospital and in-hospital acute myocardial infarctions (AMI). There is a lack of focused analyses on in-hospital Non-ST-segment myocardial infarction (NSTEMI), although it contributes to the majority of the in-hospital AMI cases. In addition, little is known about the treatment strategy and determinants of invasive intervention in patients with in-hospital AMI. The aims of this thesis were to identify the proportion of in-hospital AMI cases in The Regional Myocardial Infarction Registry of Saxony-Anhalt (RHESA), and examine if the previously identified differences between in-and out-of-hospital STEMI are observed when including NSTEMI as well. In addition, we aimed to provide new insights about risk factors and outcomes of in-hospital NSTEMI as well as predictors of invasive intervention in patients with in-hospital AMI.

Methods: Our analyses were based on data from the RHESA registry (2013–2019). First, included AMI cases were divided into two groups: in-hospital vs. out-of-hospital. Patients' characteristics, treatments and outcomes were compared based on AMI type. Second, a focused analysis on NSTEMI was performed to examine if the published findings for STEMI apply for NSTEMI as well. Finally, an analysis including in-hospital AMI only was conducted to examine the differences between patients treated with an invasive intervention and those treated conservatively to identify predictors of the treatment strategy. The main outcome in all of the analyses was 30-day mortality.

Results: 11% of the included AMI cases were in-hospital. Patients with in-hospital AMI were older and more comorbid than patients with out-of-hospital AMI. In-hospital AMI was an independent predictor of 30-day mortality (OR = 1.92, 95% CI: [1.52-2.46]). In the analysis including NSTEMI only, we found that 14% of the 2123 cases were in-hospital. Patients with in-hospital NSTEMI were more likely to be older than 75 years and more comorbid than those with out-of-hospital NSTEMI. In-hospital NSTEMI was also an independent predictor of 30-day morality (OR = 1.62, 95% CI: [1.15- 2.49]). Finally, in the analysis including only patients with in-hospital AMI (N= 259), two thirds of the patients were treated with an invasive intervention. Determinants of conservative treatment were older age, higher heart rate upon presentation, history of heart failure and STEMI. Invasive intervention was associated with lower 30-day mortality (OR= 0.25, 95%CI: [0.10-0.67]).

Conclusions: This thesis provides insight on the full spectrum of in-hospital AMI. The established differences between in-hospital and out-of-hospital STEMI are observed for NSTEMI also, but in-hospital NSTEMI is more prevalent. Some determinants of the treatment strategy for in-hospital AMI are consistent with those of out-of-hospital AMI, but invasive intervention lowered the odds of 30-day mortality.

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Referat

Einleitung: Bisherige Studien konzentrierten sich vornehmlich auf Myokardinfarkte mit ST-Strecken-Hebung (STEMI). Es mangelt daher an gezielten Analysen zum innerklinischen Nicht-ST-Hebungs-Myokardinfarkt (NSTEMI), obwohl dieser die Mehrheit der innerklinischen akuten Infarkte (AMI) ausmacht. Darüber hinaus ist nur wenig über die Behandlungsstrategie und die Determinanten der invasiven Intervention bei Patienten mit innerklinischem AMI bekannt. Ziel dieser Arbeit ist es, den Anteil der innerklinischen Fälle im Regionalen Myokardinfarkt-Register Sachsen-Anhalt (RHESA) zu ermitteln und zu untersuchen, ob die bisherigen beobachteten Unterschiede zwischen innerklinischem und außerklinischem STEMI auch bei NSTEMI zu beobachten sind. Darüber hinaus sollen neue Erkenntnisse über die Risikofaktoren und Outcomes des innerklinischen NSTEMI sowie über die Prädiktoren für eine invasive Intervention bei Patienten mit innerklinischen AMI gewonnen werden.

Methoden: Die eingeschlossenen AMI-Fälle wurden in zwei Gruppen unterteilt: innerklinisch vs. außerklinisch. Die Patienteneigenschaften, Behandlungen und Outcomes wurden je nach AMI-Typ verglichen. Eine auf NSTEMI fokussierte Analyse wurde durchgeführt, um zu untersuchen, ob die bereits bekannten Ergebnisse für STEMI auch für NSTEMI gelten. Schließlich wurde eine Analyse durchgeführt, die sich nur auf innerklinischen AMI bezog, um die Unterschiede zwischen Patienten, die mit einem invasiven Eingriff behandelt wurden, und solchen, die konservativ behandelt wurden, zu untersuchen und Prädiktoren für die Behandlungsstrategie zu ermitteln.

Ergebnisse: 11 % der eingeschlossenen AMI-Fälle waren innerklinisch. Patienten mit innerklinischen AMI waren älter und wiesen mehr Komorbiditäten auf. Der innerklinische AMI war ein unabhängiger Prädiktor für die 30-Tage-Mortalität (OR = 1,92; 95% KI: [1,52-2,46]). Bei der Analyse, die nur den NSTEMI einschloss, wurde festgestellt, dass 14 % der 2123 Fälle im Krankenhaus auftraten. Patienten mit innerklinischem NSTEMI waren mit größerer Wahrscheinlichkeit älter als 75 Jahre und wiesen mehr Komorbiditäten auf als Patienten mit außerklinischem NSTEMI. Innerklinischer NSTEM war auch ein unabhängiger Prädiktor für die 30-Tage-Mortalität (OR= 1,62; 95% KI: [1,15- 2,49]). Schließlich ergab die Analyse, die nur Patienten mit AMI im Krankenhaus einschloss, dass zwei Drittel der Patienten mit einem invasiven Eingriff behandelt wurden. Determinanten einer konservativen Behandlung waren ein höheres Alter, eine höhere Herzfrequenz bei der Vorstellung, eine Herzinsuffizienz in der Vorgeschichte, und ein STEMI. Die Chance für 30-Tage-Mortalität war niedriger bei Patienten mit einem invasiven Eingriff (OR= 0,25; 95%KI: [0,10-0,67]).

Schlussfolgerungen: Diese Arbeit gibt einen Einblick in das gesamte Spektrum des innerklinischen AMI. Die festgestellten Unterschiede zwischen innerklinischem und außerklinischem STEMI gelten auch für den NSTEMI, wobei innerklinischer NSTEMI jedoch häufiger vorkommt als der STEMI. Einige Determinanten der Behandlungsstrategie bei AMI im Krankenhaus stimmen mit denen bei AMI außerhalb des Krankenhauses überein, aber invasive Eingriffe waren mit einer niedrigeren 30-Tage-Mortalität assoziiert.
Assaf, Mohamad: Eine vertiefte Analyse der Risikofaktoren, Behandlungen und Outcomes von akuten Myokardinfarkten im Krankenhaus: Ergebnisse der RHESA-Studie, Halle (Saale), Univ. Med. Fac., Diss., 20 Seiten, 2024

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List of abbreviations

AMI: acute myocardial infarction

WHO: World Health Organization

EKG: electrocardiogram

ESC: European Society of Cardiology

ACC: American College of Cardiology

AHA: American Heart Association

WHF: World Heart Federation

IHD: ischemic heart disease

AMITIE: The Acute Myocardial Infarction Trends in Europe Study

PCI: percutaneous coronary intervention

RHESA: the regional heart attack registry in Saxony-Anhalt (Das Regionale Herzinfarktregister Sachsen-Anhalt)

BMI: body mass index

STEMI: ST-segment-elevation myocardial infarction

NSTEMI: Non- ST-segment-elevation myocardial infarction

CKD: chronic kidney disease

CABG: coronary artery bypass surgery

GRACE: Global Registry of Acute Coronary Events

TIMI: Thrombolysis in Myocardial Infarction

CAD: coronary artery disease

ACS: acute coronary syndrome

ACEI: Angiotensin-converting enzyme inhibitors

ARB: Angiotensin receptor blockers

NSTE-ACS: Non-ST-elevation acute coronary syndrome

RCT: randomized-controlled trials

GAM: Generalized Additive Models

DAG: directed acylic graphs

1 Introduction and Objectives

1.1 New definition of acute myocardial infarctions (AMI)

In the mid-20th century, the World Health Organization (WHO) put forth a universal definition for acute myocardial infractions (AMI) based on electrocardiogram (EKG) findings (1). The definition passed through several modification and adjustment rounds resulting in the recent Fourth Universal Definition of Myocardial Infarction Consensus Document, established by the Global MI TASK Force. The task force is comprised of the European Society of Cardiology (ESC), the American College of Cardiology (ACC), the American Heart Association (AHA) and World Heart Federation (WHF). In summary, any evidence of myocardial ischemia in addition to abnormal changes in cardiac biomarkers corresponding to acute myocardial injury (i.e. elevated or decreased cardiac Troponin level at least one value above the 99th percentile of the upper reference limit) is clinically defined as AMI (1, 2).

1.2 Epidemiology of AMI

A study analyzing trends of ischemic heart diseases (IHD) in 20 Western European countries showed that incidence and mortality in central European countries are higher compared to Mediterranean and Nordic countries (3). As for AMI specifically, the global prevalence in adults younger than 60 years reached nearly 4%, and in adults older than 60 years 10% (4). The Acute Myocardial Infarction Trends in Europe Study (AMITIE) aimed to analyze the trends of AMI prevalence and mortality in six European countries (including Germany) over 25 years (5). The study reported a general reduction in the rate of AMI attacks and mortality as well as in case-fatality, after stratifying for population, age and sex. An exception to this trend was seen in older women, where the case-fatality increased (5). Interestingly, mortality in the German population was among the highest.

From 2008-2011, the lifetime prevalence of AMI in Germany for individuals aged between 40 and 79 years was 5% among women vs. 7% among men (6). There has been a decreasing trend in the age- and sex-adjusted incidence of AMI in-hospital mortality, from 65 cases/1000 Person-Year in 2005 to 55 cases/1000 person-year in 2015 (7). Another study reported that between 2011-2020, there was a 27% reduction in the age-standardized mortality of AMI in men, and 33% in women (8).

1.3 High AMI mortality in Saxony-Anhalt and the need for a regional AMI registry

According to the German Heart report (8), the age and sex-standardized hospitalization for AMI in 2020 was 213/100000 persons. Saxony-Anhalt showed one of the highest rates of AMI hospitalization in 2020 (reaching 225/100000 persons) in comparison with the other 15 federal states. This was also true for AMI mortality, which reached 66.3/100000 persons in 2020. Various factors can explain the high morbidity and mortality of AMI in this federal state. The prevalence of AMI risk factors in Saxony-Anhalt is higher than in other German states. These include hypertension, diabetes, central obesity as well as smoking, lower educational level, and unemployment (9). Additionally, healthcare services for AMI patients in this state may be suboptimal as the numbers of cardiologists, certified as percutaneous coronary intervention (PCI) centers and chest pain units are lower than the national average. In fact, the density of cardiology care services in Saxony-Anhalt in 2020 was among the lowest in Germany (26000 inhabitants per cardiologist vs. 15000 inhabitants per cardiologist in Bremen, for example) (8). Finally, factors related to delivery of the healthcare services may in this federal state be inadequate as indicated by delays in clinical presentation and time to treatment (10).

Within this context, The Regional Heart Attack Registry in Saxony-Anhalt (Regionales Herzinfarktregister Sachsen-Anhalt, RHESA) (10, 11) was founded in 2012. The aim was to identify risk factors associated with the high AMI mortality in the region, and to explore potential targets for intervention in order to improve the healthcare outcomes. The population-based registry includes all fatal and no-fatal AMI-cases in adults aged 25 years or older and residing in Halle (urban region) or Altmark (rural region).

Sixteen different hospitals, three health departments, and centers for rescue services participate in the registry. Investigations and analyses are carried out by the Institute of Medical Epidemiology, Biometrics and Informatics at the Martin Luther University Halle-Wittenberg, Germany. The registry identified AMI based on The Third Universal Definition of AMI (12). Study nurses and trained physicians were responsible for collecting, via a questionnaire, the patients' characteristics, including demographic factors, body mass index (BMI) and pre-existing comorbidities, smoking status and other factors (described in more detail elsewhere) (10). The questionnaire included additionally information related to AMI onset such as location of onset (in-hospital or out-of-hospital), EKG classification, acute medical and procedural treatments, in-hospital complications, mortality and discharge medications for survivors.

1.4 Clinical presentation, risk factors and mortality of AMI

The most common symptom if AMI is chest pain or tightness, usually lasting longer than 15 minutes. The chest pain might radiate to the neck, jaw, arms, retrosternal area or epigastrium. Some of the commonly associated symptoms include dyspnea, nausea and vomiting, or sweating. A considerable proportion of patients, nearly 20%, may have a silent or atypical presentation (17). This is true for diabetic persons and those in the older ager groups, especially women. Atypical AMI presentation may also be experienced by patients with multiple comorbidities such as hypertension, diabetes, chronic kidney disease (CKD), and heart failure (17-20).

Various risk factors for AMI have been identified, including demographic, clinical, psychosocial, and lifestyle factors. Older age is associated with a higher risk of AMI incidence and mortality (13). When it comes to sex, incidence of AMI is reported to be higher among men (14, 15). However, women have a higher risk of AMI-attributed mortality and complications (16, 17), and this may be especially true for those in the younger age groups (18, 19). It also is well established that women experience AMI at a later age compared to men (20). Other major factors contributing to AMI and higher AMI mortality include modifiable risk factors such as hypertension, diabetes, hyperlipidemia, obesity, smoking, sedentary lifestyle and substance abuse (21-27). Furthermore, symptoms of depression and anxiety as well as panic disorders are positively associated with AMI mortality (28-30). Lower education levels and lower income are also associated with higher odds of short and long-term AMI mortality (31-33). This may be true even in countries with universal health coverage (32, 33).

1.5 Acute management of AMI

The European Society of Cardiology (ESC) (34, 35) recommends initial treatment of patients with a working diagnosis of AMI with Acetylsalicylic acid +/- P2Y12-inhibitor as well as anticoagulants. There are separate recommendations for the reperfusion therapy of AMI based on the EKG classification. In the case of ST-segment elevation AMI (STEMI), the default management is with PCI, preferably performed within 120 minutes from the time of diagnosis. If PCI is not possible in this time window, fibrinolysis can be a suitable alternative. Emergency coronary artery bypass graft surgery (CABG) is reserved for cases with inadequate anatomy for PCI or mechanical complications.

For patients with Non-ST-segment elevation AMI (NSTEMI), risk assessment and stratification should inform the urgency and timing of invasive intervention (34, 36). These patients can be classified into three risk groups: low, high and very high-risk. Immediate (within 2 hours) invasive intervention with PCI should be performed in cases of very high-risk NSTEMI. This group of patients is characterized by hemodynamic instability, potentially fatal arrhythmias, mechanical complications and recurrent angina pectoris despite treatment, or recurrent ischemic changes on ECG. PCI is also recommended for patients with high-risk NSTEMI and an early invasive intervention within 24 hours should be considered. High-risk criteria include: changes in high-sensitivity cardiac troponin corresponding to NSTEMI, transient or dynamic changes of the ST-segment on EKG or a Global Registry of Acute Coronary Events (GRACE) score higher than 140. For low-risk cases, ESC concluded that the evidence regarding the optimal timing for invasive intervention and the superiority of routine vs selective invasive intervention remains unclear. Therefore, an individualized assessment would be required. In patients who fail to meet any of the criteria for high or very high-risk stratification, clinical assessment as well as the degree of suspicion of unstable angina guide the need for invasive treatment. In case unstable angina is high on the differential diagnosis, a selective intervention is recommended (34).

According to the 2020 ESC guidelines (36), not opting for PCI in NSTEMI patients with severe CAD is a major risk factor for in-hospital and long-term cardiovascular mortality. A conservative treatment should be restricted to cases with high risk/benefit ratio due to anatomical or medical causes. In such cases, secondary prevention is of utmost importance to mitigate the very high-risk of recurrence of ischemic events.

1.6 Outcomes of AMI

An analysis of data from the Federal Bureau of Statistics in Germany showed a decrease in the age and sex adjusted incidence of AMI in-hospital mortality from 65 cases/1000 person-year in 2005 to 55 cases/1000 person-year in 2015 (7). Moreover, in the year 2020, the age and sex-standardized hospitalization rate of AMI was 213/100 000 persons, and the standardized mortality was 48/100 000 persons (8).

Due to advances in treatment of AMI a, there is a decreasing trend of the subsequent complications, but they still contribute to high morbidity and mortality (37). Potential complications include short and long-term events. It was reported that nearly 6% of patients experience Ventricular fibrillation in the early phase of AMI (37). Atrial fibrillation may also commonly occur within the first 24 hours of AMI onset. Within the firs 24-hours, re-infarction is possible and should be suspected when there is a repeat-ST-segment elevation. Additionally, pericarditis may develop in 10 % of AMI patients 24-96 hours after the event (38). Furthermore, some mechanical complications may occur throughout the hospital stay. Studies reported that in AMI patients who are treated with PCI, the proportion of mechanical complications was nearly 1% (39, 40). These include papillary muscle rupture and mitral valve regurgitation, free wall rupture, left ventricular aneurysm and ventricular septal defect. Late pericarditis may also occur within several weeks after AMI. Other potential complications of AMI may include mural thrombus and systemic embolism resulting in limb ischemia or stroke (38).

The most frequent AMI-related complication contributing to in-hospital AMI mortality is heart failure. A nationwide Norwegian study showed that 18% of patients developed new-onset heart failure after the first AMI occurrence (41, 42). In addition, cardiogenic shock is another potentially fatal AMI complication. A study in the United Stated showed that around 4% of AMI patients progressed into cardiogenic shock between 2001 and 2011 with little change over time (43). Due to improvement in early recognition and adequate treatment, the case-fatality rate of cardiogenic shocks decreased from 47% to 29%.

Within the context of AMI outcomes, two prognostic risk scores that were established and validated for all subtypes of ACS, namely GRACE and TIMI (Thrombolysis in Myocardial Infarction) (44). GRACE score (45) can be used to predict all-cause mortality beyond 6-months post AMI. It is comprised of eight parameters: age, history of heart failure, heart rate and systolic blood pressure upon presentation, ST segment depression, level of serum creatinine, abnormal changes in cardiac enzymes, degree of severity of post-AMI heart failure (if present). TIMI risk score (46) encompasses seven parameters including age, CAD risk factors or known history of CAD, severe angina, ST segment deviation on ECG, cardiac enzymes and use of Acetylsalicylic acid within one week prior to AMI. This score can be used to assess and predict risk of ischemic events and cardiovascular mortality in AMI patients, at 14 weeks.

1.7 Post-AMI management

Post-AMI care involves pharmacological treatments and lifestyle modifications to prevent recurrence of AMI and other ischemic events (34). In addition, cardiac rehabilitation and participation in integrated multidisciplinary care coordinated by cardiologists should be offered to all patients with acute coronary syndrome (ACS).

Pharmacological treatment includes antiplatelet therapy with Acetylsalicylic acid with P2Y12 inhibitor irrespective of acute treatment strategy. Long-term management with Beta blockers should be initiated within the first 24 hours, if there are no contraindications. Early and aggressive management with statins and other lipid-lowering medications is recommended in patients with ACS. Moreover, a meta-analysis showed the benefits of starting Angiotensin-converting enzyme inhibitors and/or Angiotensin receptor blockers (ACEI/ARB) within the first week after the AMI, and demonstrated a reduction in the 30-day mortality (47).

Furthermore, another meta-analysis showed the beneficial effect of smoking cessation on lowering the risk of mortality in AMI patients (48). It is considered as the most cost-effective preventive measure. Healthier diet, lower alcohol use, and physical activity were associated with better outcomes and lower mortality (34).

1.8 AMI classifications

AMI can be grouped into different classifications that are of clinical and epidemiological relevance. We list below three major classifications that are relevant for this thesis. In our publications, we explored they might be interconnected.

- Based on EKG classification:
  Classically, AMI can be classified into ST-segment elevation AMI STEMI or NSTEMI. Rupture or erosion of the atherosclerotic plaque and subsequent thrombus formation can lead to decreased blood flow to the cardiomyocytes and their necrosis. A complete occlusion of the coronary artery with a resulting necrosis involving all three layers of the myocardium causes elevations in the ST-segment, which can be detected on the EKG. Hence, this type of AMI is known as STEMI (49). If the coronary artery occlusion is partial and the necrosis does not extend to all three layers of the myocardium, ST segment would not be elevated on the EKG. Instead, there might be other ischemia-related changes on the EKG such as depression of the ST-segment or inversion of the T-wave, maybe even no changes at all. The presence of these EKG changes or simply ischemic chest pain, accompanied by troponin elevation, is diagnosed as NSTEMI (49). Studies reported an increase in the proportion of NSTEMI relative to STEMI. This was accompanied by a decrease in the incidence of STEMI and a stagnation or increase in the incidence of NSTEMI (50-52). In Germany, a nationwide study using data from the years 2005/2007/2009 showed that, although the AMI remained constant over the years, the proportion of STEMI decreased over time, while the proportion of NSTEMI increased (50).

- Based on the underlying pathophysiological mechanism:

There are five types of AMI based on the underlying pathophysiological mechanisms (1, 49, 53). The majority of cases are classified into Type 1, followed by Type 2 (prevalence ranging between 2 and 30%), while the rest are relatively scarce. When the ischemia is a consequence of rupture/erosion of an atherosclerotic plaque followed by thrombosis, the AMI is labeled as Type 1. Ischemia arising due to a mismatch in Oxygen demand and supply that does not involve coronary atherothrombosis is known as Type 2 AMI. This can be seen in cases of tachyarrhythmia, anemia, sepsis and hypotension, and coronary artery spasms. Type 3 AMI is diagnosed in cases of sudden cardiac death preceded by symptoms and signs suggestive of ischemia. Types 4a and 4b as well as Type 5 are iatrogenic infractions related coronary procedures, such as PCI and CABG (1, 49, 53).

- Based on location at the time of occurrence:

  Studies, especially randomized clinical trials, that examined the clinical presentation, risk factors, diagnostics, treatments and outcomes of AMI focused mainly on those occurring outside the hospital setting (out-of-hospital AMI) (54-56). Their findings informed guidelines and management protocols for AMI. Recently, there has been growing interest among researchers to examine AMI occurring in patients hospitalized for other medical conditions, otherwise known as in-hospital AMI. This is due to existing differences in the risk factors, treatment patterns and clinical outcomes between in-hospital and out-of-hospital AMI. In-hospital AMIs will be further developed in later sections of this thesis.

1.9 In-hospital AMI is a high-risk subgroup of AMI

Extensive research is being conducted to gain insights on risk factors, management and outcomes of AMI, and to identify strategies to reduce morbidity and mortality. However, most of the studies included only out-of-hospital AMI, or did not distinguish between out-of-hospital AMI and its in-hospital counterpart (54-56). This is important since in-hospital AMI, i.e. those occurring among patients hospitalized for other conditions, constitute a sub-group with different clinical profile and outcomes. The most common cause of in-hospital AMI is ACS (57), but the leading non-cardiac cause of in-hospital AMI is operations (58). A clinical trial reported an incidence of perioperative in-hospital AMI of 5% (59). Other causes of in-hospital AMI include infections and sepsis (60, 61), anemia, diabetes (62, 63) or iatrogenic diagnostic and therapeutic procedures (58, 64, 65).

Zahn et al. prospectively examined in-hospital STEMI between 1994-1997 (57). They reported that 7% of all STEMI cases managed in hospitals were classified as in-hospital. Compared to out-of-hospital STEMI, patients with in-hospital STEMI were older, have higher proportions of hypertension, diabetes, chronic kidney disease, and history of stroke. They were also less likely to receive Beta blockers, Heparin and Acetylsalicylic acid. Patients with in-hospital STEMI showed higher odds of in-hospital mortality compared to those with out-of-hospital STEMI (OR 1.54, 95% CI [1.28-1.86]). Various other studies confirmed the aforementioned findings and concluded that in-hospital STEMI patients tend to be older and more comorbid, receive less frequently invasive intervention and fare worse compared to out-of-hospital STEMI (66-69). In-hospital complications such as major bleeds and cardiogenic shocks , as well as short and long-term mortality, were found to be higher in in-hospital STEMI compared to out-of- hospital STEMI (66, 67, 70, 71).

The above-mentioned studies did not include NSTEMI in their examination of in-hospital AMI. A recent American study using US Veterans Health Administration facilities assessed in-hospital AMI by including both STEMI and NSTEMI (54). The incidence of in-hospital STEMI and NSTEMI among all hospital admissions was 4.3 cases/1000 admission. Surprisingly, NSTEMI contributed to 85% of the in-hospital AMI cases, similar to the finding by Maynard et al (90%) (72). There is currently no investigation focusing exclusively on the differences between in-hospital and out-of-hospital NSTEMI, although it constitutes the majority of all in-hospital AMI cases. Moreover, there are still no standardized protocols for acute management of in-hospital AMI, and the long-term pharmacological management remains sub-optimal (57, 58).

1.10 Research questions

As previously demonstrated, Saxony-Anhalt has one of the highest AMI mortality in Germany. Various studies aimed to investigate the associated risk factors, but there is a paucity of evidence on the prevalence of in-hospital AMI and its contribution to mortality in this federal state. In addition, the literature is lacking in terms of the number of studies examining in-hospital AMI in both of its classifications STEMI and NTEMI, as the majority focused on in-hospital STEMI only. This is relevant since over 85% of in-hospital AMI are attributed to NSTEMI. Moreover, the few existing studies including both in-hospital STEMI and NSTEMI are limited either by the lack of an out-of-hospital group for comparison (54), or by exclusion of a considerable proportion of in-hospital AMI cases (58, 72). In the RHESA registry, both of these limitations were mitigated, providing the possibility for a more comprehensive examination of the full spectrum of in-hospital AMI. In addition, few studies investigated the choice of treatment strategy and patterns of utilization of invasive intervention in in-hospital AMI. Why certain patients suffering from in-hospital AMI receive conservative treatment instead of invasive intervention remains unclear, and the relevant determinants require further exploration. Finally, a focused comparison of the risk factors, treatments and outcomes of in-hospital NSTEMI relative to out-of-NSTEMI remains insufficiently explored, and merits a more thorough research.

Given the gaps in knowledge depicted above, this thesis aimed to provide an in-depth analysis of in-hospital AMI by achieving goals relevant to the topic on the level of Saxony-Anhalt (herein referred to as specific objectives) as well as on the level of the existing literature (herein referred to as overall aims). The specific objective of this thesis was to shed light on the topic of in-hospital AMI in this federal state and on the factors influencing the treatment strategy, in order to improve health outcomes. The overall aims were: 1) to add to the findings of previous studies on the differences between in-hospital and out-of-hospital AMI while overcoming some of their limitations; 2) to provide novel insights regarding the choice of treatment strategy in in-hospital AMI, and 3) to explore whether the previously established findings for in-hospital STEMI can be observed for in-hospital NSTEMI.

The above objectives and aims were achieved through the findings of the following three publications:

(P1): The specific objective was to report the proportion of in-hospital AMI among all AMI cases in the regional registry, and assess its risk factors and its association with the outcome 30-day mortality. The overall aim was to provide a comprehensive comparison between in-hospital and out-of-hospital AMI, while avoiding the limitations of previous studies.

(P2): The specific objective of (P2) was to estimate the proportion of invasive intervention in patients with in-hospital AMI in Saxony-Anhalt, and to identify the determinants of opting for an invasive intervention in this group. The overall aim was to provide initial information about the differences in treatments strategies among patients with in-hospital AMI and the determinants of the treatment strategy choice, as there are currently no studies on this topic.

(P3): The specific objective of (P3) was to shed light on the prevalence of in-hospital NSTEMI among all NSTEMI cases in the RHESA registry, and compare risk factors, treatments and outcomes between in-hospital and out-of-hospital NSTEMI. The overall aim of (P3) was to narrow the knowledge gap between in-hospital NSTEMI and in-hospital STEMI.

2 Discussion

Corresponding to specific objectives and overall aims of the thesis, we investigated the prevalence and predictors of in-hospital AMI in the RHESA registry. We found that among all treated AMI cases in the RHESA study (2013 – 2019), 487 cases (11.4%) were in-hospital. A comparison with the out-of-hospital AMI group revealed that patients with in-hospital AMI were older and had higher proportions of preexisting medical conditions. In addition, the in-hospital group was less frequently treated with PCI, and had higher crude morbidity and 30-day mortality. After adjusting for preexisting medical conditions and other confounders, the chance of 30-day mortality of in-hospital AMI was almost twice that of out-hospital mortality. We were able to confirm the results of previous findings, but also provide comprehensive information on the full spectrum of in-hospital AMI (P1).

Since there were no available analyses on the differences between in-hospital NSTEMI and out-of-hospital NSTEMI, we conducted our own investigation using NSTEMI cases included in RHESA. We found that 14% of NSTEMI cases in the study regions occurred in hospitals. This is higher than what has been reported for STEMI by previous studies, whereby 5-7% of STEMI cases were found to be in-hospital (57, 66). Differences in risk factors, management, and outcomes between in-hospital and out of hospital STEMI were also observed for NSTEMI. The in-hospital NSTEMI group was older than the out-of-hospital NSTEMI group, and had higher proportions of diabetes, heart failure, CKD and atrial fibrillation. Regarding the acute management, patients with in-hospital NSTEMI received less frequently Acetylsalicylic acid and anticoagulants compared to patients with out-of-hospital NSTEMI, and they were less commonly treated with an invasive intervention. Odds of 30-day mortality were higher in the in-hospital NSTEMI group, which persisted even after adjusting for chronic medical conditions and other confounders. Therefore, we concluded that the difference established between in-hospital STEMI and out-of-hospital STEMI exist in NSTEMI, but NSTEMI may play a bigger role in the burden of in-hospital AMI (P3).

Furthermore, we were interested in examining the treatment strategy in patients with in-hospital AMI, and identifying the determinants of opting for invasive intervention vs. conservative treatment. We found that two thirds of the included patients with in-hospital AMI (259/386) underwent an invasive intervention, while the rest received a conservative treatment, although invasive intervention was associated with lower 30-day mortality. We could not compare the findings of (P2) with the literature since there are no previous studies, to our knowledge, examining this topic in patients with in-hospital AMI (73). Therefore, we compared our results to what is known for out-of-hospital AMI. Hereby, we found that age, history of heart failure, and heart rate on admission were relevant determinants of the treatment strategy in in-hospital AMI, similar to findings of studies on out-of-hospital AMI (74-76). Additionally, STEMI classification was associated with higher odds of receiving an invasive intervention compared to NSTEMI (74, 77). However, the remaining clinical and lifestyle determinants of invasive intervention in out-of-hospital AMI showed no association with the treatment strategy in our sample of in-hospital AMI cases. Even more, contrary to what is reported by Câlmâc et al. for out-of-hospital AMI (78), we found that hypertension is associated with higher odds of using invasive intervention in in-hospital AMI. We also demonstrated that it is possible that the choice of the treatment strategy in in-hospital AMI is associated with the number of medical comorbidities rather than the presence of specific comorbidities. Unfortunately, residual confounding could not be excluded. We could not adjust for the severity of the accompanying medical condition nor the time duration between onset of symptoms and treatment, both of which could influence the results.

2.1 Consistency in all reported proportions of in-hospital AMI

While the available studies examining in-hospital AMI are considered large, they are limited in number. They also differ in terms of the inclusion and exclusion criteria, limiting the ability to compare findings. Despite that, there is little variability in the reported proportions of in-hospital AMI to total AMI, with all being consistently lower than 10% (58, 72, 79). It is important to note that the proportions might be overestimated as none of the studies included patients with pre-hospital AMI mortality, which would contribute to a higher total number of out-of-hospital AMI. In other words, patients who died at home or in long-term care facilities as well as those who died while being transferred by emergency medical services before arriving to the hospital were not accounted for in the total number of AMI. This means that the number of out-of-hospital AMI (and thus total number of AMI) is higher than what is reported in the available studies. Thus, the proportion of in-hospital AMI might be lower than observed. It is challenging to gauge the influence of excluding patient with pre-hospital AMI mortality on the calculated proportion of in-hospital AMI. But, we believe that the influence is minimal given the decreasing trend in the incidence of pre-hospital AMI mortality in Germany (5, 80). In addition, exclusion of prehospital AMI deaths does not change the clinical implications of these studies in terms of the quality of health care services that ought to be provided by hospitals. A proportion ranging from 1-11% warrants the need to raise awareness of the medical staff about in-hospital AMI, especially in non-medical wards like the surgical wards where the occurrence of perioperative in-hospital AMI is common (81-83). It is worth noting that this range includes high-income countries only, as studies on in-hospital AMI in low-middle income countries are not available.

2.2 Heterogeneity of patients with in-hospital AMI

We were able to confirm the findings of previous studies (58, 72) regarding the association of age and medical comorbidities (e.g. heart failure, chronic kidney disease, and peripheral vascular disease) with the onset and worse outcomes of in-hospital AMI. However, we noticed a heterogeneity in the group of patients with in-hospital AMI in our sample. The prevalence of the cardiovascular risk factors among patients with in-hospital AMI differed considerably, with the exception of hypertension, whereby the vast majority (84%) were hypertensive. Diabetes, hyperlipidemia, CKD and obesity were prevalent in 30-40% of the patients with in-hospital AMI, but not the rest. Moreover, we could not examine the admission diagnosis, and hence we could not account for disease severity in patients with in-hospital AMI. It is highly likely that there is a heterogeneity in the reason for hospital admission and the severity of the concomitant disease giving rise to the in-hospital AMI. Therefore, prospective studies are still needed to elucidate the incidence of in-hospital AMI in Saxony-Anhalt and to identify specific risk factors of AMI among patients hospitalized for other reasons.

It is reasonable to assume that the heterogeneity in the clinical profile of patients with in-hospital AMI would affect the choice of treatment strategy as well as the risk of mortality. Surprisingly, we found that the group of patients treated with an invasive intervention was homogeneous with respect to the group treated conservatively, with the exception of preexisting heart failure (more common in the latter group). In the adjusted analysis, we found that hypertension and heart failure were relevant determinants of the treatment strategy in patients with in-hospital AMI. Other determinants of invasive strategy that were observed to be relevant in out-of-hospital AMI (such as sex, CKD and history of stroke) were not associated with the treatment strategy of in-hospital AMI in our sample. Unfortunately, there are no published findings on the differences in the treatment of in-hospital AMI, to which we could compare our results. This highlights the need for longitudinal studies to examine clinical and socioeconomic factors associated with the treatment strategy of in-hospital AMI.

2.3 In-hospital NSTEMI poses a bigger challenge than in-hospital STEMI

After we examined in-hospital AMI in the RHESA registry and related the results to what is known in the literature, we came to the realization that there is a lack of studies focusing exclusively on NSTEMI. This is relevant since NSTEMI is the more frequent EKG classification among in-hospital AMI. After we conducted our focused analysis on NSTEMI, we concluded that patients with in-hospital NSTEMI have different characteristics and worse prognosis than those with out-of-hospital NSTEMI, in accordance with previous findings on STEMI. However, in terms of diagnosis and treatment, in-hospital NSTEMI may pose a bigger challenge to medical staff than in-hospital STEMI. Unlike in-hospital STEMI – which may be more easily detected on the EKG – little to no EKG changes (by definition) can be observed with in-hospital NSTEMI. In-hospital NSTEMI may go undetected by the treating medical staff, especially when patients are not found on cardiology wards.

In addition, protocols for treatment of out-of-hospital STEMI are more standardized as compared to out-of-hospital NSTEMI. In fact, studies show the a wider variation of medical practices and lower adherence to guideline-recommended management of NSTEMI (34, 84, 85). One can assume that this higher complexity of treatment can also be observed when comparing in-hospital NSTEMI to in-hospital STEMI, especially when considering the underlying pathophysiological mechanisms of the in-hospital infarction (Types 1 vs. Type 2 AMI). Garberich et al. examined the outcomes of applying the standardized protocol for out-of-hospital STEMI in cases of in-hospital STEMI. It was found to be associated with improved detection of in-hospital STEMI, shorter time to therapy, and lower mortality (86). The effectiveness of applying the variable and more complex protocols for management of out-of-hospital NSTEMI to its in-hospital counterpart remains unclear, and warrants further exploration.

2.4 Interplay among the various classifications of AMI

In this thesis, we presented three different ways to classify AMI: based on underlying pathophysiological mechanisms, based on EKG classification, and based on location of onset (in or out-of-hospital). To what extent these classifications are separate from each other remains an intriguing topic that requires further research. Through our work and refering to what is published in the literature, we believe that there is an important interplay between the various classifications of AMI. Type 1 AMI involving atherothrombosis and Type 2 AMI resulting from non-atherothrombotic insufficient Oxygen supply can both be further subdivided into STEMI and NSTEMI based on EKG changes. However, STEMI is obsereved in less than 25% of the Type 2 AMI cases (87). Interestingly, recent studies show that Type 2 AMI might occur more frequently than Type 1 AMI, even though NSTEMI (the most common entity of ACS) tends to be caused more frequently by Type 1 AMI (reaching 65% -90% of Type 1 AMI) (88).

Underreporting of Type 2 NSTEMI may be associated with the diagnostic method, criteria of AMI classification, and the clinical setting.

When conisdering the third AMI classificaiton (based on location of onset), we see an association between NSTEMI and in-hospital AMI, whereby the most common EKG classification of in-hospital AMI is reported to be NSTEMI (54, 72). In addition, although no study to date investigated the association between the pathophysiological AMI Types and in-hospital AMI occurence, our results and the findings of previous investigations hint at a possible correlation between Type 2 AMI and in-hospital AMI. This is based on the observed similarity between the causes of Type 2 AMI and the risks factors associated with in-hospital AMI (including perioperative stress, sepsis and hypotension, chronic kidney disease, arrhythmias, anemia, heart failure, etc.) (1, 49, 53). Clearly, there is an interaction between the different AMI classifications, but future studies are needed to identify the pathophysiological mechanisms giving rise to in-hospital AMI.

2.5 Factors contributing to worse clinical outcomes in in-hospital AMI

When comparing in-hospital STEMI to out-of-hospital STEMI, in-hospital NSTEMI to out-of-hospital NSTEMI, or in-hospital AMI to out-of-hospital AMI, the risk of complications and mortality is always higher in the in-hospital group than in its out-of-hospital counterpart (54, 57, 58, 66-69, 72, 79, 86, 89). This association persists even after adjusting for pre-existing medical conditions. Nonetheless, it is challenging to determine to which extent the in-hospital AMI directly contributes to mortality in patients who were admitted to the hospital for another medical condition. In addition, in patients with in-hospital AMI who are unfit for coronary angiography (such as those with sepsis or post-operative patients), it would not be possible to assess the existence of a previously unidentified ACS, the most common cause of AMI occurrence.

Differences in outcomes between in-hospital and out-of-hospital AMI can be attributed to various reasons. One important factor associated with outcomes of AMI is time to diagnosis and management. In out-of-hospital AMI, longer time between symptom onset and presentation to the hospital (prehospital delay) increases the risk of mortality and in-hospital complications, especially in the case of STEMI (90, 91). A longer time between symptom-onset and ECG/treatment was reported in patients with in-hospital AMI compared to those with out-of-hospital AMI, which may be associated with increased risk of mortality (58, 67, 69, 72).

Patients with in-hospital AMI are more likely to experience atypical symptoms due to the high mutlicomorbidity, which leads to delays in timely diagnosis. In addition, the severity of the accompanying medical disease may complicate the hospital post-AMI occurrence and eventually to an increased risk of mortality of in-hospital AMI (54, 58, 66, 67, 71).

Another potential explanation for the worse outcomes in patients with in-hospital AMI may be due to lack of guideline-recommended management plans as well as lower rates of invasive intervention (58, 66, 67, 69, 72, 92). In our study, we found that patients with in-hospital NSTEMI for example received less frequently Acetylsalicylic acid and heparin, possibly due to contraindications. Mazzella et al. assessed factors preventing the use of cardiac catheterization and invasive intervention among patients with in-hospital NSTEMI. Older women with comorbidities were less likely to undergo cardiac catheterization (93), and the leading three reasons for not performing the catheterization were high risk for complications, severity of the medical condition, and against patient's wishes.

2.6 The need to optimize the acute and long-term management of in-hospital AMI

Similar to Erne et al. (58), we showed that patients with in-hospital AMI are less likely treated with ESC-recommended medications such antiplatelet and anticoagulants, compared to those with out-of-hospital AMI. ESC recommends immediate reperfusion therapy with PCI for patients with a working diagnosis of STEMI. As for patients with Non ST-elevation acute coronary syndrome (NSTE-ACS) , an invasive treatment is also recommended, but the urgency depends on the risk stratification (34). We confirmed the results of previous studies (58, 72) showing that patients with in-hospital AMI are less likely to be treated with PCI. We hypothesize this is due to higher risk of bleeding. As previously detailed, treatment of in-hospital AMI may be more complex and standardized treatment protocols are lacking. We also showed that the determinants of invasive intervention in in-hospital AMI might be different from those of out-of-hospital AMI.

In terms of long-term care, we found that patients with in-hospital AMI, regardless of whether they were treated conservatively or invasively, were less likely to be discharged on P2Y12 receptor inhibitor, statins and beta-blockers recommended by ESC. Similar findings were also reported by Erne at al. (58) . While antiplatelet might be less frequently prescribed due to contraindications, statins and beta-blockers ought to be prescribed, especially for the more comorbid subgroup of patients with in-hospital AMI.

Many studies showed that one to strategy to improve outcomes and quality of care for in-hospital cardiac arrest includes participation in registries. Detailed information regarding patients' characteristics, treatments and outcomes as well as hospital-related information can be collected by registries. This has allowed the possibility to make relevant comparisons, identify gaps, and find potential targets for improvement of healthcare outcomes. We believe this might translated to in-hospital AMI, as indicated by our analyses using registry data. We therefore encourage hospitals in Saxony-Anhalt to participate in the regional RHESA registry (94, 95).

2.7 Regional differences and in-hospital AMI

Various studies examined the differences in AMI mortality between rural and urban regions. Residents of rural regions were found to have lower proportions of utilization of invasive intervention and higher adjusted odds of AMI mortality, compared to residents of urban regions (96, 97). We found that residents of Halle (urban) had higher odds of developing in-hospital AMI than residents of Altmark (rural), OR= 1.44, 95% CI [1.14-1.83]. It remains unclear why the regionality showed an association with the occurrence of in-hospital AMI. We believe that it might be explained by the differences in the clinical characteristics between patients residing in the urban region vs. those residing in the rural region.

Moreover, in the focused analysis including only in-hospital AMI cases, we found that Altmark residents received less frequently an invasive intervention than residents of Halle, but the region of residence had no association with 30-day mortality. This could hint at existing differences in the patterns and strategy of treatment of AMI within the federal state of Saxony-Anhalt itself. Despite that, it seems that these differences have little influence on the short-term AMI mortality. Future studies comparing the current differences in characteristics, treatment, and outcomes of patients with AMI between urban and rural German areas are needed.

2.8 Availability of a cardiac catheter laboratory is not associated with the treatment strategy of in-hospital AMI

Previous studies on out-of-hospital AMI showed inconsistent findings regarding the association between availability of cardiac catheterization laboratories in the admitting hospital and mortality in patients with ACS (98-100). Therefore, we examined if the availability of a cardiac catheterization laboratory had an impact on the choice of treatment strategy and mortality outcome in in-hospital AMI. For this reason, we made a comparison between patients who developed in-hospital AMI in hospitals readily equipped with a cardiac catheterization laboratory, and those who were initially found hospitals with no catheter laboratory.

We found that 80/127 (63%) of patients who were treated conservatively were initially present in hospitals with no cardiac catheter laboratory upon onset of the in-hospital AMI. A small proportion of these 80 patients died in the first hospital. The remaining 86% of those patients (N = 69) were either discharged home or transferred to a second hospital that is equipped with catheterization laboratories, but eventually still received no intervention. We had expected that a diagnosis of in-hospital AMI in hospitals with no catheterization laboratory would be associated with higher mortality. Contrary to our expectation, we found higher odds of mortality in the group of patients who happened to be in hospitals equipped with catheterization laboratories when they received the diagnosis of in-hospital AMI. We believe that patients with severe diseases and comorbid profiles, and thus at higher risk of dying, are more likely to be admitted to bigger hospitals with more advanced management facilities (like catheterization laboratory), rather than to smaller hospitals. Another implication to lower association between the unavailability of a catheterization laboratory and lower mortality of in-hospital AMI is that the transfer to a more readily equipped hospital for treatment of in-hospital AMI (and hence potential delay in receiving proper treatment) may not necessarily lead to unfavorable outcomes.

2.9 The advantages of a registry-based study to provide initial information about in-hospital AMI

It is well known that the best type of evidence comes from randomized-controlled trials (RCT). But in many cases, a registry-based study can provide a sufficient level of evidence in order to show the need to re-conduct the same study in a RCT-study design, or to confirm the findings of an RCT in a „real word scenario“ (101). Certainly, registry-based studies have some limitations, including unavailability or misclassificaiton of information, lack of confounders, or poor data quality (102). But, their advantages make them attractive for conducting epidemiological studies. Registries can provide a represntative study sample since the aim is always to identify and include all cases (based on a predefined purpose and inclusion criteria). In addition, they permit to conduct follow-up studies since the status of patients is usually updated over time. Registry-based studies can provide basic epidemiological insights about chronic diseases (such as prevalence and mortality), but may also be relevant for establishing guidelines and influencing policy-making (103). Also, registries can serve as a basis for RCTs, which can help overcome some of the limitations of traditional RCTs (104). Based on the above, and given that the topic of in-hospital AMI is still not extensively examined and the cases are not very common, we conducted our analyses using data from the RHESA registry. This allowed us to gain preliminary insights and delve deeper into the topic of in-hospital AMI.

2.10 Strengths and limitations

The results of our study should be interpreted with caution, due to some inherent limitations. The biggest limitation is the cross-sectional study design. To better identify the incidence of in-hospital AMI in the population of Saxony-Anhalt and its associated risk factors, a prospective cohort study would be needed. This would also be useful for a better understanding of factors influencing the treatment strategy in in-hospital AMI, as well as the short and long-term differences in outcomes based on the choice of treatment strategy. In addition, the RHESA registry includes only two regions (Halle/urban and Altmark/rural) in Saxony-Anhalt, and over the years, the participation of hospitals had declined. This could limit the generalizability of our results. The RHESA sample might not be very representative of the residents of Saxony-Anhalt since 50% of the participants were from the rural region, when in fact 33% of the population lives in rural regions (105). Another limitation is that we used routine clinical data for our analyis, which is subject to problems of data quality and limited standardization. Important information and confounders such as the admission diagnosis and use of coronary angiography were not available. Both of these factors could have major implications on the treatment and outcomes of in-hopsital AMI.

The major strength of this thesis is that it provides novel and innovative information about a topic that is not well studied. To our knowledge, this is the first attempt to: a) assess in-hopsital AMI in Germany including both STEMI and NSTEMI, b) provide a focused examination of in-hopsital NSTEMI, and c) examine the differences in treatment strategy and associated outcomes in the subgroup of patients with in-hospital AMI. Moreover, we were able to adjust the results of our analyses to the type of residence (urban vs. rural) which is an important confounder in studies on AMI and its outcomes. An additional strength of our work is the relatively large sample size of patients with in-hopsital AMI compared to the previous investigations. In terms of statistical analysis, we utilized Generalized Additive Models (GAM) analysis, when possible, to examine the linearity of association between continuous independent variables (such as age and BMI) with the respective dependent variable. We also performed segmented logistic regression to calculate odds ratios for the relevant segments of continuous variables that showed non-linear association with the dependent variable. Finally, we used directed acylic graphs (DAG) analysis in (P2) and (P3) for selecting the minimum set of covariables to adjust for in the multivariable logistic regression analyses, in order to limit the degree of bias.

2.11 Conclusions

Similar to findings of the few previous studies, we showed that in-hospital AMI is not uncommon in the federal state of Saxony-Anhalt, whereby one in every nine myocardial infarctions was found to be in-hospital. We confirmed that patients with in-hospital AMI constitute an older and more comorbid subgroup of patients with AMI. They also have higher odds for complications and mortality. NSTEMI is more likely to occur among hospitalized patients than STEMI, and the recognition and management of in-hospital NSTEMI may be more complex compared to in-hospital STEMI. No investigation, to date, has been conducted to examine if the management protocols for out-of-hospital NSTEMI are effective in the case of in-hospital NSTEMI.

Moreover, our analysis involving patients with in-hospital AMI only showed that one third of patients with in-hospital AMI were treated conservatively. Interestingly, the unavailability of a cardiac catheter laboratory did not play a major role in the choice of the treatment strategy. Age, history of heart failure and STEMI diagnosis were consistent predictors of the treatment strategy in both in and out-of-hospital AMI. While ESC recommends use of invasive intervention in out-of-hospital AMI due to more favorable outcomes, the benefit of invasive intervention relative to conservative treatment in in-hospital AMI is still unclear. Additionally, the long-term pharmacological management and prevention among patients with in-hospital AMI is sub-optimal. This raises the question of whether the recommended post-AMI lifestyle modifications in the subgroup is also suboptimal. Follow-up studies involving patients with in-hospital AMI ought to be conducted to assess the long-term mortality and morbidity.

To the quality of healthcare for patients with in-hospital AMI, we recommend raising awareness of the medical staff about this medical entity, especially when caring for high-risk patients such as patients with many comorbidities who are undergoing surgeries. We believe that hospitals' participation in the regional registry, expanding the coverage across more regions in Saxony-Anhalt, and increasing efforts to include in-hospital AMI cases can help reveal opportunities for quality improvement. More longitudinal studies are needed to optimize the prognosis and management of in-hospital AMI, and to assess differences in prevalence and outcomes of in-hospital in other German federal states.

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4 Theses

(1) We found that 11.4% of included acute myocardial infarction (AMI) cases in the Regional Myocardial infarction registry in Saxony-Anhalt (RHESA) were in-hospital.

(2) Patients with in-hospital AMI in our sample were older, more comorbid, and less likely to receive an invasive intervention, compared to those with out-of-hospital AMI.

(3) In-hospital AMI was an independent predictor of 30-day mortality even after adjusting for comorbidities and other confounders (adjusted OR = 1.92, 95% CI: [1.52-2.46]).

(4) In the analysis including NSTEMI only, we found that 14% of cases were in-hospital, higher than what is reported for in-hospital STEMI.

(5) Patients with in-hospital NSTEMI were older and more comorbid than those with out-of-hospital NSTEMI. This is similar to what is known for STEMI.

(6) Patients with in-hospital NSTEMI received less frequently invasive intervention and higher adjusted odds of 30-day mortality (OR= 1.62, 95% CI: [1.15; 2.49]), compared to those with out-of-hospital NSTEMI.

(7) Two thirds of the patients with in-hospital AMI were treated with an invasive intervention, while the rest with a conservative treatment.

(8) Relevant determinants of conservative treatment were older age, higher heart upon presentation, history of heart failure and STEMI classification. These determinants are consistent with the determinants of invasive intervention in out-of-hospital AMI.

(9) Invasive intervention was associated with lower odds of 30-day mortality (OR= 0.25, 95% CI: [0.10-0.67]).

5 Publications

List of included publications

1. Comparison between In-Hospital and Out-of-Hospital Acute Myocardial Infarctions: Results from the Regional Myocardial Infarction Registry of Saxony-Anhalt (RHESA) Study (P1)

Assaf M, Costa D, Massag J, Weber C, Mikolajczyk R, Lückmann SL. Comparison between In-Hospital and Out-of-Hospital Acute Myocardial Infarctions: Results from the Regional Myocardial Infarction Registry of Saxony-Anhalt (RHESA) Study. Journal of Clinical Medicine. 2023 Sep 29;12(19):6305.

2. Comparison between Invasive Intervention and Conservative Treatment in Patients with In-Hospital Myocardial Infarctions: Results from the Regional Myocardial Infarction Registry of Saxony-Anhalt (RHESA) Study (P2)

Assaf M, Costa D, Efremov L, Holland K, Mikolajczyk R. Comparison between Invasive Intervention and Conservative Treatment in Patients with In-Hospital Myocardial Infarctions: Results from the Regional Myocardial Infarction Registry of Saxony-Anhalt (RHESA) Study. Journal of Clinical Medicine. 2024 Apr 10;13(8):2194.

3. In-Hospital versus out-of-hospital non-ST-segment-elevation myocardial infarction (NSTEMI)—findings of the RHESA Study (P3)

Assaf M, Lückmann S, Efremov L, Holland K, Costa D, Mikolajczyk R: In-Hospital versus out-of-hospital non-ST-segment-elevation myocardial infarction (NSTEMI)—findings of the RHESA Study. Dtsch Arztebl Int 2024; 121: in press. DOI: 10.3238/arztebl.m2024.0032

Personal contribution to publications relevant to the thesis

P1: Assaf M, Costa D, Massag J,. et al. 2023

Development of the research question, parts of data cleaning and data preparation, setting definitions, planning and execution of statistical analysis, reporting of results, interpretation of results, writing of the manuscript, revision of the manuscript.

P2: Assaf M, Costa D, Efremov L et al. 2024

Development of the research question, parts of data cleaning and data preparation, setting definitions, planning and execution of statistical analysis, reporting of results, interpretation of results, writing of the manuscript, revision of the manuscript.

P3: Assaf M, Lückmann S, Efremov L, et al. 2024

Development of the research question, parts of data cleaning and data preparation, setting definitions, planning and execution of statistical analysis, reporting of results, interpretation of results, writing of the manuscript, revision of the manuscript.

Publication 1 (P1)

Assaf M, Costa D, Massag J, Weber C, Mikolajczyk R, Lückmann SL. Comparison between In-Hospital and Out-of-Hospital Acute Myocardial Infarctions: Results from the Regional Myocardial Infarction Registry of Saxony-Anhalt (RHESA) Study. Journal of Clinical Medicine. 2023 Sep 29;12(19):6305.

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Article

Comparison between In-Hospital and Out-of-Hospital Acute Myocardial Infarctions: Results from the Regional Myocardial Infarction Registry of Saxony-Anhalt (RHESA) Study

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Abstract: Aims: Risk factors and outcomes of in-hospital ST elevation myocardial infraction (STEMI) are well explored. Recent findings show that non-ST elevation myocardial infarction (NSTEMI) accounts for the majority of in-hospital infarctions (IHMIs). Our aim was to identify differences between IHMI and out-of-hospital myocardial infraction (OHMI) in terms of risk factors, treatment and outcomes, including both STEMI and NSTEMI. Methods: We analyzed the Regional Myocardial Infarction Registry of Saxony-Anhalt dataset. Patient characteristics, treatments and outcomes were compared between IHMI and OHMI. The association between clinical outcomes and myocardial infarction type was assessed using generalized additive models. Results: Overall, 11.4% of the included myocardial infractions were IHMI, and the majority were NSTEMI. Patients with IHMI were older and had more comorbidities than those with OHMI. Compared to OHMI, in-hospital myocardial infarction was associated with higher odds of 30-day mortality (OR = 1.85, 95% CI 1.32–2.59) and complications (OR = 2.36, 95 % CI 1.84–3.01). Conclusions: We provided insights on the full spectrum of IHMI, in both of its classifications. The proportion of IHMI was one ninth of all AMI cases treated in the hospital. Previously reported differences in the baseline characteristics and treatments, as well as worse clinical outcomes, in in-hospital STEMI compared to out-of-hospital STEMI persist even when including NSTEMI cases.

Keywords: myocardial infarction; in-hospital; out-of-hospital; complications; 30-day mortality; Germany

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1. Introduction

Ischemic heart disease, specifically acute myocardial infraction (AMI), remains one of the leading causes of global mortality despite the decrease in prevalence and incidence [1]. Various medical and psychosocial risk factors for AMI have been identified, including coronary artery disease, heart failure, hyperlipidemia, obesity, smoking and substance abuse [2–5]. However, most of the previous studies included patients who developed AMI in the pre-hospital setting, otherwise known as out-of-hospital AMI (OHMI) [6–8]. Patients admitted to the hospital for cardiac or non-cardiac conditions may develop AMI during hospitalization, labeled as in-hospital AMI (IHMI), contributing considerably to the overall burden of the disease [6].

A number of studies have addressed this topic of IHMI but focused solely on STEMI. For example, a large US administrative analysis reported that in-hospital STEMI accounted for around 5% of total STEMIs, and it was associated with a 4-fold increase in in-hospital mortality [9]. Moreover, an Australian study confirmed that in-hospital STEMI was associated with higher 30-day mortality compared to out-of-hospital STEMI [10]. In Germany, a prospective study conducted in 1994–1997 in more than 50 hospitals revealed that 7% of all STEMI cases were in-hospital cases. The mortality of patients with an in-hospital

STEMI was higher compared to patients who developed an out-of-hospital STEMI, at 27% vs. 14%, respectively [11]. Furthermore, resource utilization and in-hospital charges were found to be higher among patients with in-hospital STEMI compared to those with the out-of-hospital counterpart [9].

Recent investigations, however, showed that the majority of IHMIs tend to be non-ST-segment elevation MI (NSTEMIs) [6,12]. Thus, it is important to include NSTEMI when assessing the burden of IHMI, especially since the proportion of NSTEMIs is increasing over time [13]. Our aim was to identify differences between in-hospital and out-of-hospital AMIs, including both AMI classifications (STEMI and NSTEMI). We estimated the proportion of IHMIs among AMIs that are treated in hospitals in the state of Saxony-Anhalt, including both STEMIs and NSTEMIs. Additionally, we compared the baseline characteristics, treatments and outcomes between patients with IHMI and OHMI. Finally, we examined the association between the type of AMI (IHMI vs. OHMI) and clinical outcomes.

2. Methods

2.1. Study Design, Dataset Description and Data Collection

This is a cross-sectional study using data from The Regional Myocardial Infarction Registry of Saxony-Anhalt (German: Regionales Herzinfarktregister Sachsen-Anhalt, or RHESA). RHESA is a population-based registry including consecutively enrolled patients with AMI (2013–2019) from two regions in the federal state of Saxony-Anhalt, Germany. The study design has been described in detail elsewhere [14,15]. Due to the high mortality of AMI in this federal state (43% above the national average in 2012) [16] RHESA was founded in 2012 with the goal of identifying contributing risk factors and potential targets for intervention to improve health outcomes. It covers the rural region, Altmark, and the urban region, Halle (Saale). Individuals aged 25 years or older are included in the registry.

Three health departments, 16 hospitals, 16 residence registration offices, as well as centers for rescue services, participated in the registry. During hospitalization, trained physicians or study nurses reviewed the medical charts and collected, via a questionnaire, information related to sociodemographic factors, medical comorbidities, medical and procedural treatments, in-hospital complications and discharge status. The questionnaire was developed based on the Berlin Myocardial Infarction Registry questionnaire by Schuler et al. [17]. To track the survival status of AMI patients at 30 days, the study personnel contacted the participating registration offices at different points in time. In case of death, the cooperating health departments shared the death certificates with the RHESA registry. Our analysis, however, included only patients with AMI who arrived alive at a hospital for treatment, from 2013 to 2019. The exclusion criterion was missing information on the main variable of interest, "type of AMI" (N = 193). In Table S1 of the Supplementary Material, we present the characteristics and outcomes of the study population.

The average age at AMI occurrence was 70 years, and it occurred more frequently among males (62%). There was a high prevalence of classical and modifiable AMI risk factors in the study population (85% with hypertension, 51% with hyperlipidemia, 35% with diabetes, and 44% current or former smokers). Saxony-Anhalt is known to have a higher prevalence of cardiovascular risk factors compared to other German federal states [18]. As expected, the majority of the AMI cases in our sample were classified as NSTEMI rather than as STEMI (62% vs. 38%). Around 70% of all included patients who were treated with percutaneous coronary intervention (PCI), the 30-day mortality rate amounted to 8.7%.

2.2. Ethical Consideration

RHESA was approved by the Ethics Committee of the Medical Faculty of the Martin Luther University Halle-Wittenberg (Nr.: 2020-188) and by the State Data Protection and Privacy Commissioner of Saxony-Anhalt.

2.3. Variables and Outcomes

In this study, we used the "Third universal definition of myocardial infarction" of the European Society of Cardiology, which defined AMI as any rise and/or fall of high-sensitivity cardiac troponin by at least one unit above the 99th percentile of the upper reference, accompanied by ischemic signs and symptoms [19]. These include ischemic symptoms, new-onset changes in the ST-segment T wave or new left bundle branch block on the electrocardiogram (EKG), presence of pathological Q waves, new loss of myocardium or abnormality of wall motion identified via imaging, or coronary thrombus as evident on angiography or autopsy. Variables related to AMI type (IHMI or OHMI), AMI classification (STEMI or NSTEMI), shock upon presentation, treatment (aspirin, heparin, P2Y12 inhibitor, GPIIb/IIIa inhibitor, thrombolysis, PCI or bypass surgery) and in-hospital complications (a binary variable defined as having or not having any intubation, another shock, resuscitation, re-infarct, stroke, severe bleeding or need for re-intervention) were collected via questionnaires filled out by medical doctors or study nurses in the hospitals. The questionnaires also included information on the patients' sociodemographic and risk factors, such as age at AMI occurrence (in years), sex, region of residence (Altmark/rural or Halle/urban), body mass index (BMI) that was categorized into four groups (<25, 25–29, 30–35, >35 kg/m^2), smoking status and pre-existing medical conditions (diabetes, hypertension, hyperlipidemia, stroke, atrial fibrillation, history of previous MI, chronic kidney disease, peripheral vascular disease and heart failure).

The outcomes were 30-day mortality and occurrence of in-hospital complications.

2.4. Statistical Analysis

Patients were dichotomized based on AMI type (IHMI and OHMI). Categorical variables were reported in the form of frequencies (percentages) and 95% CI of the percentage. Numerical variables were reported in the form of mean (standard deviation) and 95% CI of the mean. Multiple imputation was applied for variables with missing values in more than five percent of all cases, which included body mass index, history of previous AMI, hyperlipidemia, hypertension, heart failure, peripheral vascular disease, chronic kidney disease and smoking status. Using a fully conditional specification method, forty complete datasets were generated based on the rule that the number of imputations should be equal to the percentage of missing cases or greater [20]. Since age could have non-linear associations with the outcomes, a generalized additive model (GAM) using the binomial family was applied to identify variables associated with AMI type (IHMI vs. OHMI) and outcomes (30-day mortality and in-hospital complications). Age showed a non-linear association with AMI type, which is depicted graphically in Figure S1 of the Supplementary Materials.

We identified two inflection points (55 years and 80 years). Therefore, we performed segmented logistic regression to calculate adjusted odds ratios (ORs) for the segments <55 years, 55–80 years and >80 years in model A (dependent variable was AMI type).

For the dependent variables, 30-day mortality and in-hospital complications occurrence, GAM analysis revealed a linear association with age (results not shown). Hence, no segmentation was needed for age in the logistic regression models B and C for the outcomes 30-day mortality and in-hospital complications, respectively. ORs and 95% confidence intervals (CIs) were reported. We adjusted for the following confounders: AMI type (in models B and C for 30-day mortality and in-hospital complications), age, male sex, BMI (reference: <25 kg/m^2), region (reference: Altmark), AMI classification (reference: STEMI), smoking status, diabetes, hypertension, dyslipidemia, stroke, atrial fibrillation, history of previous AMI, chronic kidney disease, peripheral vascular disease and heart failure, based on previous studies. All statistical analyses were conducted using R-Studio version 4.2.1, Posit, PBC. Boston, MA, USA [21,22].

3. Results

The number of patients with AMI who were included in the study was 4272. Of those, 487 patients (11.4%) had IHMI, and the remaining had OHMI. Patients with IHMI were (on average) older than those with OHMI (72.28 ± 12.26 vs. 69.94 ± 13.36 years). There was no difference in the sex distribution between the two groups. Compared to patients with OHMI, patients with IHMI had a higher proportion of the following comorbidities: diabetes, hyperlipidemia, history of stroke, atrial fibrillation, heart failure, chronic kidney disease and peripheral vascular disease (Table 1). The proportion of patients with IHMI among all patients with AMI in the rural region (Altmark) was lower than in the urban region (Halle), at 9.2%, 95% CI: 8.0–10.5 vs. 13.6%, 95% CI: 12.2–15.0, respectively (row percentages, not shown in the table).

Table 1. Distribution of patients' sociodemographic parameters and risk factors based on AMI type.

	OHMI		**IHMI**	
	N (%) or Mean (SD)	**95% CI**	**N (%) or Mean (SD)**	**95% CI**
Total = 4272	3785 (88.6)		487 (11.4)	
Sociodemographic factors				
Age (years)	69.39 (13.36)	68.97–69.82	72.23 (12.29)	71.1–73.3
Male	2475 (65.4)	63.9–66.9	310 (63.7)	59.3–67.8
Altmark (rural)	1903 (50.3)	48.7–51.9	192 (39.4)	35.2–43.8
Halle (urban)	1882 (49.7)	48.1–51.3	295 (60.6)	56.2–64.8
Risk factors				
Body mass index (kg/m^2)				
<25	772 (20.4)	19.1–21.7	88 (18.1)	14.8–21.8
25–<30	1911 (50.5)	48.9–52.1	246 (50.5)	45.9–55.0
30–35	864 (22.8)	21.5–24.2	118 (24.2)	20.5–28.3
>35	238 (6.3)	5.5–7.12	35 (7.2)	5.1–9.9
Previous AMI	614 (16.2)	15.1–17.4	86 (17.7)	14.5–21.2
Diabetes	1289 (33.6)	32.6–35.6	202 (41.1)	37.2–45.9
Hypertension	3237 (85.5)	84.4–86.6	411 (84.4)	81.0–87.4
Hyperlipidemia	1976 (52.2)	50.6–53.8	209 (42.9)	38.6–47.3
Stroke	343 (9.4)	8.2–10.0	63 (13.6)	10.2–16.1
Atrial fibrillation	655 (17.9)	16.1–18.5	139 (29.8)	24.7–32.7
Heart failure	795 (21)	19.7–22.3	166 (34.1)	30.0–38.4
Chronic kidney disease	938 (24.8)	23.4–26.2	201 (41.3)	37.0–45.7
Peripheral vascular disease	374 (9.9)	9.0–10.9	101 (20.7)	17.3–24.5
Non-smokers	2117 (55.9)	54.3–57.5	271 (55.6)	51.2–60.0
Smokers	1175 (31)	29.6–32.5	142 (29.2)	25.3–33.3
Former smokers	493 (13)	12.0–14.1	74 (15.2)	12.2–18.6

Numerical variables are presented in the form of mean (standard deviation) and 95% CI of the mean. Categorical variables are shown in the form of frequency (%) and 95% CI of the percentage. SD: standard deviation. CI: confidence interval. OHMI: out-of-hospital myocardial infarction. IHMI: in-hospital myocardial infarction.

NSTEMI was more common in patients with IHMI compared to patients with OHMI (75.4%, 95% CI: 71.4–79.0 vs. 60.3%, 95% CI: 58.8–61.9). Of the total 2650 NSTEMI cases, 367 (13.8%) were in-hospital. Of all the included STEMI cases, 7.4% were in-hospital. In terms of treatment, patients with IHMI received treatment with anti-platelets (aspirin or P2Y12 inhibitor) or heparin less frequently. Nearly 2% of the patients in each group received thrombolysis treatment. A considerably smaller proportion of patients with IHMI were managed with PCI (56.7%, 95% CI: 52.2–61.0 vs. 71.1%, 95% CI: 68.7–71.6 in the OHMI group). The IHMI group had a higher proportion of in-hospital complications (14.6%, 95% CI: 13.5–15.8 vs. 29%, 95% CI: 25.1–33.1]. Considering the main outcome, patients with IHMI had a higher 30-day morality rate than patients with OHMI (12.5%, 95% CI: 9.8–15.7 vs. 8.2%, 95% CI: 7.4–9.2) (Table 2).

Table 2. Treatment and clinical outcomes of patients with AMI in Saxony-Anhalt based on AMI type.

	OHMI		IHMI	
	N (%) or Mean (SD)	95% CI	N (%) or Mean (SD)	95% CI
Total = 4272	3785 (88.6)		487 (11.4)	
Aspirin	3158 (83.4)	82.2–84.6	331 (68.0)	63.7–72.0
P2Y12 inhibitor	1548 (40.9)	39.3–42.5	167 (34.5)	30.4–38.8
GPIIb/IIIa inhibitor	26 (0.7)	0.5–1.0	3 (0.6)	0.2–1.06
Heparin	3004 (79.4)	78.1–80.6	321 (65.9)	61.6–70.0
Thrombolysis	73 (1.9)	1.5–2.4	9 (1.8)	0.9–3.3
PCI	2655 (70.1)	68.7–71.6	276 (56.7)	52.2–61.0
Bypass surgery	201 (5.3)	4.6–6.1	36 (7.4)	5.3–10.0
NSTEMI STEMI	2283 (60.3) 1502 (39.7)	58.8–61.9 38.1–41.2	367 (75.4) 120 (24.6)	71.4–79.0 21–28.6
Complications	554 (14.6)	13.5–15.8	141 (29.0)	25.1–33.1
30-day mortality	312 (8.2)	7.4–9.2	61 (12.5)	9.8–15.7

Numerical variables are presented in the form of mean (standard deviation) and 95% CI of the mean. Categorical variables are shown in the form of frequency (%) and 95% CI of the percentage. SD: standard deviation. CI: confidence interval. PCI: percutaneous coronary intervention. NSTEMI: non-ST segment elevation myocardial infarction. STEMI: ST-segment elevation myocardial infarction.

Patients with IHMI were 1.92 times more likely to have NSTEMI than STEMI (95% CI: 1.52–2.46) compared to patients with OHMI. In addition, patients with IHMI were more likely to have heart failure, chronic kidney disease and peripheral vascular disease compared to patients with OHMI. Residents of the urban region (Halle) were 1.44 times more likely to experience IHMI than OHMI compared to residents of the rural region (Altmark) (95% CI: 1.14–1.83) (Table 3), consistent with the crude difference in proportions.

Table 3. Factors associated with the odds of IHMI (reference: OHMI): model A.

Factors	Adjusted OR	95% CI
Age (in years) <55 55–80 >80	 0.99 1.035 0.90	 0.96–1.02 0.99–1.08 0.84–1.097
Male	0.93	0.74–1.16
Body mass index (reference group: <25 kg/m^2) 25–<30 kg/m^2 30–35 kg/m^2 >35 kg/m^2	 1.27 1.35 1.34	 0.95–1.69 0.97–1.87 0.85–2.12
Halle (Altmark as reference)	1.44	1.14–1.83
NSTEMI (reference: STEMI)	1.92	1.52–2.46
Non-smokers Smokers Previous smokers	1 1.22 1.12	 0.92–1.63 0.81–1.54
Diabetes	1.11	0.89–1.39
Hypertension	0.86	0.64–1.18
Dyslipidemia	0.74	0.59–0.94
Stroke	1.06	0.76–1.45

Table 3. *Cont.*

Factors	Adjusted OR	95% CI
Atrial fibrillation	1.24	0.96–1.60
History of previous AMI	1.11	0.89–1.39
Chronic kidney disease	1.86	1.6–2.4
Peripheral vascular disease	1.74	1.59–1.94
Heart failure	1.16	1.06–1.45

Variables included in the model: age, male sex, BMI (reference: <25 kg/m^2), region (reference: Altmark), AMI classification (reference: STEMI), smoking status, diabetes, hypertension, dyslipidemia, stroke, atrial fibrillation, history of previous AMI, chronic kidney disease, peripheral vascular disease and heart failure. OR: odds ratio. CI: confidence interval. IHMI: in-hospital myocardial infarction. OHMI: out-of-hospital myocardial infarction. STEMI: ST-segment elevation myocardial infarction. NSTEMI: non-ST-segment elevation myocardial infarction. AMI: myocardial infarction.

For each of the two dependent outcomes, 30-day mortality and in-hospital complications, we adjusted for medical comorbidities and other confounders in the multivariable analysis. We found that the adjusted odds of 30-day mortality was higher among patients with IHMI compared to patients with OHMI (OR = 1.81, 95% CI: 1.29–2.54) (Table 4). IHMI was also associated with a higher adjusted odds of in-hospital complications (OR = 2.35, 95% CI: 1.84–3.01) (Table 5).

Table 4. Factors associated with odds of 30-day mortality: model B.

Factors	Adjusted OR	95% CI
IHMI (reference: OHMI)	1.81	1.29–2.54
Age (in years)	1.06	1.05–1.08
Male	1.11	0.84–1.45
Body mass index (Reference group: <25 kg/m^2) 25–<30 kg/m^2 30–35 kg/m^2 >35 kg/m^2	 1.17 1.07 0.77	 0.84–1.63 0.72–1.59 0.39–1.51
Halle (Altmark as reference)	1.05	0.80–1.40
STEMI (reference: NSTEMI)	2.39	1.84–3.12
Non-smokers Smokers Previous smokers	 1.40 0.68	 0.99–1.97 0.43–1.10
Diabetes	1.35	1.04–1.75
Hypertension	1.01	0.67–1.52
Dyslipidemia	1.11	0.84–1.48
Stroke	1.63	1.16–2.39
Atrial fibrillation	1.17	0.87–1.58
History of previous AMI	0.79	0.55–1.13
Chronic kidney disease	1.40	1.04–1.88
Peripheral vascular disease	1.38	0.96–1.98
Heart failure	1.20	0.89–1.62

Variables included in the model: AMI type (reference: OHMI), age, male sex, BMI (reference: <25 kg/m^2), region (reference: Altmark), AMI classification (reference: STEMI), smoking status, diabetes, hypertension, dyslipidemia, stroke, atrial fibrillation, history of previous AMI, chronic kidney disease, peripheral vascular disease and heart failure. OR: odds ratio. CI: confidence interval. IHMI: in-hospital myocardial infarction. OHMI: out-of-hospital myocardial infarction. STEMI: ST-segment elevation myocardial infarction. NSTEMI: non-ST-segment elevation myocardial infarction. AMI: myocardial infarction.

Table 5. Factors associated with odds of in-hospital complications: model C.

Factors	Adjusted OR	95% CI
IHMI (reference: out of hospital AMI)	2.35	1.84–3.01
Age (in years)	1.02	1.01–1.03
Male	0.90	0.74–1.10
Body mass index (kg/m^2) (Reference: <25)		
25–<30	0.92	0.73–1.17
30–35	0.99	0.75–1.31
>35	1.07	0.71–1.61
Halle (Altmark as reference)	1.67	1.35–2.06
STEMI (reference: NSTEMI)	2.35	1.84–3.01
Non-smokers		
Smokers	1.02	1.01–1.03
Previous smokers	0.99	0.86–1.07
Diabetes	0.90	0.74–1.10
Hypertension	1.67	1.35–2.06
Dyslipidemia	2.35	1.84–3.01
Stroke	1.02	1.01–1.03
Atrial fibrillation	0.90	0.74–1.10
History of previous AMI	1.67	1.35–2.06
Chronic kidney disease	2.35	1.84–3.01
Peripheral vascular disease	1.02	1.01–1.03
Heart failure	0.90	0.74–1.10

Variables included in the model: AMI type (reference: OHMI), age, male sex, BMI (reference: <25 kg/m^2), region (reference: Altmark), AMI classification (reference: STEMI), smoking status, diabetes, hypertension, dyslipidemia, stroke, atrial fibrillation, history of previous AMI, chronic kidney disease, peripheral vascular disease and heart failure. OR: odds ratio. CI: confidence interval. IHMI: in-hospital myocardial infarction. OHMI: out-of-hospital myocardial infarction. STEMI: ST-segment elevation myocardial infarction. NSTEMI: non-ST-segment elevation myocardial infarction. AMI: myocardial infarction.

4. Discussion

The aim of this study was to identify differences between IHMI and OHMI in terms of risks factors and health outcomes, including both classifications (STEMI and NSTEMI), while avoiding the limitations of previous investigations. For this purpose, we estimated the proportion of IHMI among STEMI and NSTEMI cases managed in the hospitals in the regions of this study, and compared the characteristics, treatments and clinical outcomes between patients with IHMI and those with OHMI.

We found that 11.4% of the AMI cases in our sample were IHMI, with the majority being classified as NSTEMI. Patients with IHMI were older and had more comorbidities than those with OHMI. Additionally, they were less frequently managed with PCI. Patients with IHMI had higher 30-day mortality and higher proportion of complications, which did not change after adjusting for relevant confounders. Previous studies had been conducted to identify the potential cause of IHMI. The majority of IHMI cases among patients hospitalized for non-cardiac conditions were attributed to perioperative AMI [23], contributing to 50% of the cases. The PeriOperative ISchemic Evaluation trial (POISE) involving 23 countries reported a perioperative AMI incidence of 5% within 30 days of the random assignment date to the control or intervention group [24]. Furthermore, some cardiac [25,26], infectious [27,28] and metabolic diseases [29,30], as well iatrogenic causes [31–33], can lead to AMI as an in-hospital complication.

When considering the STEMI cases only, our estimate of in-hospital STEMI (7.4%) was found to be comparable to the results of previous investigations. Similar to our results, Zahn et al. demonstrated that 7% of STEMI cases treated in hospitals in Germany between 1994 and 1997 were IHMI [11], and Kaul et al. reported that 5% of the STEMI cases included in the California State Inpatient Database were in-hospital [9]. Both of these studies did not include NSTEMI. This is important since IHMI cases often tend to be NSTEMI, as evident in our study (75%) and supported by previous studies. Maynard et al. reported that 9.5% of the IHMI cases in their analysis were initially diagnosed as STEMI, and the remaining 90.5% were diagnosed as NSTEMI [12]. Additionally, Bradley et al. found that 85.4% of the identified IHMI cases in US Veterans Health Administration facilities were classified as NSTEMI [6]. Nonetheless, these proportions should be regarded with caution. Bradley et al. examined the incidence of IHMI in a case–control study, with the control group comprising any hospital admission with a diagnosis different from ischemic heart disease, rather than an OHMI group [6]. Maynard et al. examined the differences between IHMI and OHMI including both STEMI and NSTEMI, with a reported IHMI prevalence of 11.2%, which was similar to our result (11.4%) [12]. However, post-operative IHMI cases, which could contribute to 5% of total IHMI cases, were excluded [12,24,31]. A Swiss study also including both STEMI and NSTEMI used nationwide registry data and identified a substantially lower proportion of IHMI, amounting to 1% only, possibly due to lack of systematic inclusion of this AMI type in the study registry [31]. On the other hand, our analysis included, per design, only those patients who arrived at the hospital alive in the OHMI group. Patients who were found dead and later classified as AMI or who could not be successfully revived and died after their arrival to the emergency department were excluded from the analysis. With respect to the total number of AMI cases, IHMI fraction would be in fact lower.

Comparing the characteristics between patients with IHMI and OHMI, we found that patients with IHMI constituted an older and more comorbid subgroup of patients with AMI. Heart failure, chronic kidney disease and peripheral vascular disease were associated with a higher risk of IHMI, after adjusting for various confounders. This is consistent with the risk factors that were found to be associated with a higher risk of in-hospital STEMI in the multivariable analysis by Kaul et al. [9]. Patients with in-hospital STEMI were 1.7 times more likely to have preexisting heart failure (95% CI: 1.5–1.9), 1.2 times more likely to have kidney failure (95% CI: 1.04–1.3), and 1.5 times more likely to have peripheral vascular disease (95% CI: 1.3–1.6), relative to patients with out-of-hospital STEMI.

Previous studies that included both STEMI and NSTEMI did not perform a multivariable analysis to identify independent risk factors of IHMI. However, they confirmed that older age and comorbidities (such as diabetes, hyperlipidemia, history of stroke, atrial fibrillation, heart failure, chronic kidney disease and peripheral vascular disease) were more common in patients with IHMI, compared to those with OHMI [12,31]. Interestingly, Erne at al. reported that IHMI was more frequent among females, in contrast to our study where we found no difference between the two sexes [31]. We believe that this lowers the risk of bias in our study, given the established differences in the prevalence of AMI risk factors and outcomes between men and women [34,35].

In terms of clinical outcomes, studies including both STEMI and NSTEMI showed that in-hospital complications (in particular, bleeding, cardiogenic shock and cardiac arrest) were more frequent among patients with IHMI compared to those with OHMI [12]. Nevertheless, no adjustment for confounders was performed. We demonstrated that patients with IHMI had a higher adjusted odds of in-hospital complications compared to OHMI patients, even after adjusting for chronic medical comorbidities. The association between IHMI and a higher risk of in-hospital complications was reported in studies including STEMI only. Patients with in-hospital STEMI were at a higher risk of developing shock, major bleeding, stroke and major adverse cardiac events, relative to those with out-of-hospital STEMI [9,23,36]. Considering mortality associated with IHMI, we found that the 30-day mortality rate in patients with IHMI was higher compared to patients with OHMI, even after adjusting for age, comorbidities and EKG classification. This is consistent with the findings of previous studies on the association between IHMI and short-term AMI mortality, while including both STEMI and NSTEMI. For example, Erne et al. reported a higher adjusted odds of in-hospital mortality among patients with IHM compared to patients with OHMI (OR = 2.4, 95% CI: 1.6–3.4) [31]. Additionally, Maynard et al. found that compared to OHMI, IHMI was associated with a higher in-hospital mortality rate (27% vs. 9%), as well as a higher odds for 30-day mortality after adjusting for medical comorbidities and EKG diagnosis (OR = 2.0, 95% CI: 1.7–2.4) [12].

Four potential explanations have been suggested to justify the worse clinical outcomes among patients with IHMI compared to those with OHMI. First, older age and higher prevalence of pre-existing medical conditions among patients with IHMI are associated with atypical AMI presentations, leading to delays in diagnosis and subsequent treatment [23,36,37]. Second, the worse clinical condition and severity of the primary disease (underlying reason for hospitalization) in patients with IHMI can contribute to higher risks of morbidity and mortality in this group. In our study, we accounted for various confounding comorbidities, but it was possible residual confounding factors remained. Third, patients with IHMI received PCI less frequently than patients with OHMI, potentially contributing to their higher mortality [9]. Unfortunately, information related to coronary angiography and its findings was not available. This could have an impact on the choice of treatment strategy and clinical outcomes. Previous studies including STEMI cases only reported that patients with in-hospital STEMI undergo coronary angiography less commonly comparted to patients with out-of-hospital STEMI [23,37,38]. In addition, a considerably lower proportion of in-hospital STEMI cases (less than 56%) are managed with PCI in comparison to out-of-hospital cases. Despite adjusting for comorbidities and other confounders, patients with in-hospital STEMI were found to have a lower odds of undergoing coronary angiography and PCI [9]. However, when considering only patients who underwent coronary angiography, Jaski et al. found no difference in the proportion of performed intervention between in-hospital and out-of-hospital STEMI cases [38]. As for previous investigations that included both STEMI and NSTEMI, lower proportions of PCI were also reported in patients with IHMI compared to patients with OHMI [12,31]. The most common reason for not performing coronary angiography and subsequent PCI is high bleeding risk, followed by other factors like neurological and cognitive dysfunction, patients' preferences and severe comorbidities (such as pulmonary embolism or bowel ischemia) [23,38]. Another reason is that some IHMI cases result from pathophysiological mechanisms not involving atherosclerotic rupture and thrombus formation, known as type 2 AMI. This may be indicated by the presence of common risk factors between IHMI and type 2 AMI, such as perioperative stress, heart failure arrhythmia and sepsis. In such cases of IHMI, PCI is less often performed [6,39]. Interestingly, a study by Jaski et al. showed differences in factors influencing the ineligibility for PCI between patients with in-hospital and out-of-hospital STEMI [38]. While the risk of bleeding was the most common reason for PCI ineligibility in the in-hospital STEMI group, the most common reason in the out-of-hospital STEMI group was complex coronary artery disease. Regarding NSTEMI, there are currently no available studies comparing the patterns of PCI utilization and differences in ineligibility between in-hospital NSTEMI and its out-of-hospital counterpart.

Finally, in some cases such as perioperative IHMI, patients are admitted to clinical wards other than internal medicine. Medical staff in other wards may be less trained in early recognition of AMI and initiation of the necessary work-up, especially since IHMI is relatively uncommon and its clinical presentation may be atypical, as previously mentioned.

This study has some limitations. Despite substantial effort, no complete coverage of AMIs in the considered regions was achieved. Furthermore, the two regions of Saxony-Anhalt might not provide representative estimates for the federal state. About 33% of the population lives in rural regions in Saxony-Anhalt [40], while in the registry, the rural and urban regions contribute equally. Additionally, there might be some variation among the rural regions in Saxony-Anhalt regarding mortality and likely morbidity of AMI. Another limitation is that our analysis is based on routine clinical data; thus, some inherent problems of data quality and availability, as well as limited standardization, could be present. This includes information related to the reason for hospitalization is not available. Finally, we could not adjust for the different kinds of coronary lesions identified during coronary angiography, which could influence the outcomes.

Nonetheless, to our knowledge, this is the first study conducted in Germany to assess IHMI, including NSTEMI and STEMI. The substantial sample size and the inclusion of urban and rural regions constitute additional strengths.

5. Conclusions

We estimated the proportion of IHMI to be at around one ninth of all AMI cases treated in hospitals based on the data of the regional AMI registry of Saxony-Anhalt, with a 75% chance of being classified as NSTEMI. Previously reported differences in baseline characteristics and treatments, as well as worse clinical outcomes, in in-hospital STEMI compared to out-of-hospital STEMI persist even when including NSTEMI cases. Patients with IHMI in our study tended to be older and had more comorbidities than patients with OHMI. Despite adjustment for these differences, IHMI was associated with a higher risk of in-hospital complications and mortality. This can be a consequence of differences in clinical condition beyond the available information (residual confounding) or difficulties in early diagnosis and proper management of IHMI. In conclusion, our study provides insights on the full spectrum of in-hospital AMI, in both of its classifications, and shows that NSTEMI is the bigger contributor to this medical entity and, thus, may play a bigger role in the clinical course of in-hospital AMI.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12196305/s1, Table S1: Characteristics and outcomes of the study population. Figure S1: Association between age and AMI type (IHMI vs. OHMI).

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AMI	acute myocardial infarction
BMI	body mass index
CI	confidence interval
IHMI	in-hospital myocardial infarction
NSTEMI	non-ST segment elevation myocardial infarction
SD	standard deviation

STEMI	ST-segment elevation myocardial infarction
OHMI	out-of-hospital myocardial infarction
OR	odds ratio

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Comparison between Invasive Intervention and Conservative Treatment in Patients with In-Hospital Myocardial Infarctions: Results from the Regional Myocardial Infarction Registry of Saxony-Anhalt (RHESA) Study

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Abstract: Background/Objectives: In-hospital myocardial infarctions (AMIs) are less often treated with invasive intervention, compared to out-of-hospital AMIs. We aimed to identify the determinants of invasive intervention in patients with in-hospital AMIs and assess its association with mortality, compared to conservative treatment. **Methods**: This was a cross-sectional study of in-hospital AMIs in The Regional Myocardial Infarction Registry of Saxony-Anhalt. Patients' characteristics and outcomes were compared based on the treatment strategy (invasive intervention vs. conservative treatment). Logistic regression was performed to assess the determinants of invasive intervention (vs. conservative treatment) and its association with 30-day mortality. **Results**: Nearly 67% of the patients (259/386) received invasive intervention, and the rest were treated conservatively. Those who were treated with an invasive intervention were younger and had a lower proportion of chronic heart failure than those treated conservatively. Age > 75 years compared to younger patients, pre-existing heart failure, and higher heart rate upon presentation were associated with lower odds of receiving invasive intervention. Hypertension (OR = 2.86, 95% CI [1.45–5.62]) and STEMI vs. NSTEMI (1.96, [1.10–3.68]) were associated with higher odds of invasive intervention. The adjusted odds of 30-day mortality were lower with invasive intervention compared to conservative treatment (0.25, [0.10–0.67]). **Conclusions**: One-third of the patients with in-hospital AMIs received conservative treatment. Younger age, absence of heart failure, lower heart rate, hypertension, and STEMI were determinants of invasive intervention usage. Invasive intervention had lower odds of 30-day mortality, but longitudinal studies are still needed to assess the efficacy of conservative vs. invasive strategies in in-hospital AMIs.

Keywords: in-hospital AMI; invasive intervention; conservative treatment; risk factors; 30-day mortality

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1. Introduction

Acute myocardial infractions (AMIs) occurring among patients hospitalized for other conditions, otherwise known as in-hospital AMIs, constitute between 1 and 11% of the total AMI cases managed in hospitals [1–3]. Compared to patients with out-of-hospital AMIs, those with in-hospital AMIs have a higher risk of in-hospital complications, as well as short- and long-term mortality [1–9]. Lower rates of invasive intervention (percutaneous coronary intervention and/or bypass surgery) in patients with in-hospital AMIs may be associated with the worse clinical outcomes observed in this group [1,4,8].

Insights on the determinants of invasive intervention compared to conservative treatment were provided by studies that solely included out-of-hospital AMIs or did not distinguish between out-of-hospital and in-hospital AMIs. These studies [10–15] identified patient-related determinants of invasive intervention utilization such as younger age, male sex, and lower heart rate on admission, in addition to the absence of specific pre-existing comorbidities such as stroke, chronic kidney disease, heart failure, and dementia. Moreover, a diagnosis of ST-segment elevation (STEMI) was found to be a determinant of invasive intervention usage compared to non-ST-segment myocardial infarction (NSTEMI) [10,12]. In contrast, less is known about the determinants of invasive intervention in patients with in-hospital AMIs specifically. Since in-hospital AMIs differ from their out-of-hospital counterpart in terms of associated risk factors, treatments, and consequently outcomes [1–9], it is important to identify the specific patterns of utilization and determinants of invasive intervention in patients with in-hospital AMIs.

Therefore, we aimed to examine the demographic, lifestyle, and clinical determinants of invasive intervention in patients with in-hospital AMIs, as well as its association with 30-day mortality. We compared the differences in the baseline characteristics of patients with in-hospital AMIs based on the treatment strategy (invasive vs. conservative) and identified factors associated with the use of invasive intervention. In addition, we assessed the 30-day mortality and post-AMI care of in-hospital AMI cases managed with an invasive vs. conservative strategy.

2. Methods

2.1. Study Design, Dataset Description, and Data Collection

In this cross-sectional study, we analyzed data from the population-based registry "The Regional Myocardial Infarction Registry of Saxony-Anhalt" (RHESA). The German federal state Saxony-Anhalt is known to have higher morbidity and mortality of AMIs compared to the other 15 federal states [16]. To identify contributing factors to the worse AMI outcomes and improve cardiovascular morbidity and mortality, the RHESA study was established in 2013. It includes fatal and non-fatal AMI cases occurring among patients older than 25 years, who reside in the urban region "Halle" or the rural region "Altmark" in Saxony-Anhalt [17,18].

Several rescue services centers, sixteen hospitals, and three public health departments participated in RHESA, enabling the identification of AMI cases. Trained physicians and nurses collected, via questionnaires, information related to the baseline characteristics of patients with AMIs, including pre-exiting chronic conditions and sociodemographic factors. In addition, they reviewed medical charts to obtain inpatient information related to the acute treatment of AMIs, complication occurrence, and discharge status of the included patients. Moreover, registration offices participating in RHESA informed the study personnel about the survival status of the included patients at different time points, to track mortality. Data collection was conducted through hospital collection forms (KEB). In the case of a non-fatal event or in-hospital death, a hospital physician or study assistant fills out the KEB based on medical chart review, in an anonymized/non-anonymized manner based on the availability of the consent form. In addition, an emergency protocol for consenting patients is submitted by the emergency doctors in ambulances, with information on symptom duration, arrival times, and emergency services provided during the transport. As for cases of pre-hospital deaths, the participating health departments share the death certificates with RHESA. In addition, those health departments send the last treating physicians or coroners a KEB questionnaire to fill out and submit back to RHESA. To determine the survival status for patients with AMIs who consented to participate in the registry, the registration offices are contacted across different time points. As for deceased patients, the corresponding health department would forward the death certificates to RHESA. Further follow-up studies using telephone interviews for patients participating in RHESA have been conducted since 2014, in order to obtain data about changes in cardiovascular risk factors and utilization of health services as well as cardiac rehabilitation.

In our current analysis, we included exclusively in-hospital AMI cases that were managed at the hospital, between 2013 and 2019. Patients with previous history of AMIs were excluded as only the first AMI occurrence was of interest. Additionally, we excluded patients with missing values for the availability of a cardiac catheterization laboratory where in-hospital myocardial infraction was initially diagnosed. In cases of transfer, patients with missing values for this variable in either the referring or the receiving hospitals were also excluded. This was conducted to ensure that the reason for opting for a conservative treatment was not the lack of a catheterization laboratory in the treating hospital. The characteristics and outcomes of the included patients are shown in Supplementary Table S1 of the Supplementary Materials.

2.2. Variables and Outcomes

AMIs were defined based on the Third Universal Definition of Myocardial Infarction [19], which describes AMIs as changes in the cardiac troponin by at least one unit above the 99th percentile of the upper reference associated with the presence of ischemic signs and/or symptoms. Information regarding the patients' characteristics was obtained via questionnaires filled out by medical doctors or study nurses. This included age at AMI occurrence (in years, we then categorized into above or below 75 years), sex, region of residence (urban area of Halle and rural area of Altmark), height in meters and weight in Kilograms to calculate body mass index (BMI) that we categorized into four groups (<25, 25–29, 30–35, >35 kg/m^2), smoking status (current, former, or never smoker), and comorbidities (presence of hyperlipidemia, hypertension, diabetes, chronic kidney disease, heart failure, atrial fibrillation, and/or history of stroke). In addition, the questionnaire included information on heart rate and systolic blood pressure upon presentation, electrocardiogram classification (STEMI vs. NSTEMI), treatments (Acetylsalicylic acid (ASS), P2Y12 inhibitor, heparin, thrombolytic drug, invasive intervention with either percutaneous coronary intervention (PCI), and/or bypass surgery), presence of shock upon presentation, onset of in-hospital complications, mortality, and time until death. The last section of the KEB questionnaire included a list of medications (ASS, P2Y12 receptor inhibitor, anticoagulant, ACE/ARB, beta-blocker, and statins), and the physicians or study nurses filling it out would choose the discharge medications for each participant based on the medical chart review. In-hospital complications were defined as having at least one or more of the following: intubation, another shock, re-infarct, stroke, severe bleed, or need for re-intervention. The availability of a cardiac catheterization laboratory in the hospital where the in-hospital AMI was first diagnosed was also collected. In the case of transfer to a second hospital, information on the availability of a catheterization laboratory in the second hospital was also obtained.

The main variable of interest was the treatment strategy: invasive intervention with PCI/bypass vs. no procedure (labeled as conservative treatment). The main outcome was 30-day mortality.

2.3. Statistical Analysis

Patients' characteristics, risk factors, outcomes, and treatments were compared based on the treatment strategy (invasive intervention or conservative treatment). Categorical variables were reported as frequencies (percentages). The numerical variables age and heart rate were reported as the mean (standard deviation). The following variables had missing values greater than five percent: BMI, smoking status, information on comorbidities including chronic kidney disease, hyperlipidemia, hypertension, and chronic heart failure. Therefore, multiple imputation via the fully conditional specification method was used. Forty complete datasets were generated based on the rule that the number of imputations should be no less than the percentage of missing cases [20]. One logistic regression model was performed to identify the determinants of invasive intervention in patients with in-hospital AMIs. Then, a directed acyclic graph (DAG) was constructed using DAGitty software (Version 3.1) [21] (Supplementary Figure S1 in Supplementary Materials) in order to identify the minimum set of covariates to adjust for in the second logistic regression model assessing the association between treatment strategy and the outcome, 30-day mortality.

2.4. Description of Directed Acyclic Graph (DAG)

Since we have not found (to date) studies on the factors associated with the treatment strategy in in-hospital AMIs, we used the results of the first logistic regression model (dependent variable: invasive intervention) to draw associations between the exposure "treatment strategy" and the rest of the variables in a DAG. Associations between the outcome "30-day morality" and the other variables were based on a literature review. The variables included older age, sex, hypertension, hyperlipidemia, BMI, diabetes, atrial fibrillation, heart failure, chronic kidney disease, smoking status, history of stroke, heart rate on admission, and electrocardiogram (EKG) classification. The minimum set of variables to adjust for in the logistic regression analysis for the association between the treatment strategy and the dependent variable (30-day mortality) included age > 75 years, hypertension, heart failure, heart rate, and EKG classification. It is worth mentioning that Generalized Additive Model (GAM) analysis was conducted to investigate the potential non-linear relationship between the continuous variable heart rate and each of the two dependent variables, treatment strategy and 30-day mortality. The results revealed a linear association between heart rate and each of the dependent variables (not shown), thus warranting the retention of heart rate as a linear term in the final logistic regression models. The DAG revealed the following set of minimum variables to adjust for in the association between treatment strategy and 30-day mortality: age > 75 years, hypertension, heart failure, heart rate, and AMI classification (Supplementary Figure S1 in Supplementary Materials). These were entered as independent variables in the second logistic regression analysis to minimize bias in the association between treatment strategy and 30 d mortality.

We reported the odds ratios (ORs) and 95% confidence intervals (CIs) yielded by the regression models. In the sensitivity analysis, we repeated the regression analyses excluding patients who had an immediate death (within 24 h, $N = 13$), which we had kept in the initial models to mitigate immortal-time bias, in order to gain more insight into the robustness of our results. Finally, discharge medications for patients who survived beyond 30 days were compared based on the treatment strategy. All statistical analyses were conducted with R-Studio R ® version 4.2.1 [22,23].

2.5. Ethical Consideration

RHESA was approved by the Ethics Committee of the Medical Faculty of the Martin Luther University Halle-Wittenberg (Nr.: 2020-188) and by the State Data Protection and Privacy Commissioner of Saxony-Anhalt. This study was conducted in accordance with the Declaration of Helsinki.

3. Results

The total number of patients with in-hospital AMIs in our sample was 386 (Figure 1).

Nearly 67% of the patients underwent an invasive intervention while the rest received conservative treatments. The invasive intervention group was slightly younger than the conservative treatment group (70 ± 12 years [68.4–71.4] vs. 75 ± 12 years [73.2–77.6]). The proportion of females was slightly higher in the conservative group than in the invasive intervention group (51.1% [42.1–50] vs. 36.6% [30.6–42.3]). There were no differences in the proportions of pre-existing comorbidities between the two groups, with the exception of heart failure. A history of heart failure was less common among patients who were treated with an invasive intervention (25.9% [20.8–30.4] vs. 40.2% [31.9–48.8]). The proportion of patients from the rural area (Altmark) was higher in the conservative treatment group than in the invasive intervention group (59.1% [50.4–67.3] vs. 23.9% [19.1–29.4]) (Table 1).

Two-thirds of the patients in the conservative treatment group ($N = 80$) were first diagnosed with in-hospital AMIs in hospitals with no available cardiac catheterization laboratory. Of those, eleven died in the same hospital and seven were discharged alive without needing an intervention. The remaining 62 patients were transferred to hospitals with an available catheterization laboratory and still received no intervention. Among patients treated invasively, 30% ($N = 78$) were first diagnosed with in-hospital AMIs in hospitals without an available cardiac catheterization laboratory. All of them were transferred to a second hospital with a catheterization laboratory where they received the intervention. There was no difference in systolic blood pressure and heart rate between the two groups. STEMI was diagnosed more frequently in the invasive intervention group than in the conservative treatment group (27.8% [22.6–33.5] vs. 15.0% [9.6–21.2]). There was no difference in the proportion of heparin and thrombolytic medication administration between the two groups. Additionally, there were no major differences in terms of shock upon presentation and in-hospital complications. The outcome 30-day mortality was lower in the invasive intervention group (8.5% [5.6–12.4] vs. 18.9% [13.8–26.4]) (Table 2).

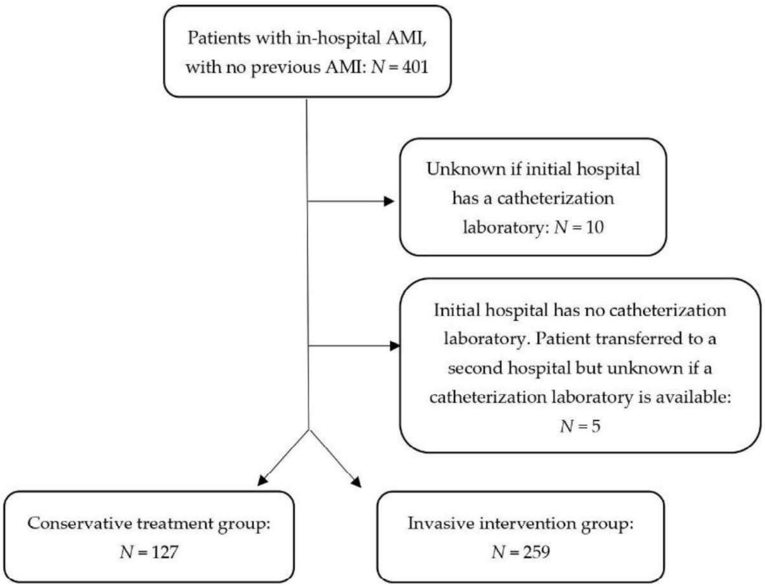

Figure 1. Total number of patients included in the analysis.

Table 1. Distribution of patients' characteristics and risk factors based on treatment strategy.

Total Number of In-Hospital AMIs *N* = 386	**Conservative Treatment: *N* = 127**		**Invasive Intervention: *N* = 259**	
	***N* (%) or Mean (SD)**	**95% CI**	***N* (%) or Mean (SD)**	**95% CI**
Characteristics				
Age (years)	75.4 (12.7)	73.2–77.6	69.9 (12.4)	68.4–71.4
Age > 75 years	84 (66.1)	57.6–73.9	111 (42.9)	36.9–48.9
Female	65 (51.1)	42.1–60	95 (36.6)	30.6–42.3
Region:				
Halle (urban)	52 (40.9)	32.7–54.3	197 (76.1)	70.6–80.9
Altmark (rural)	75 (59.1)	50.4–67.3	62 (23.9)	19.1–29.4
Body mass index group (kg/m^2)				
<25	21 (16.5)	10.9–23.7	46 (17.8)	13.5–22.8
25–<30	63 (49.6)	41.0–58.2	135 (52.1)	46.0–58.2
30–35	30 (23.6)	16.9–31.5	61 (23.6)	18.7–29.0
>35	12 (9.4)	5.3–15.4	17 (6.6)	4.0–10.1

Table 1. *Cont.*

Total Number of In-Hospital AMIs N = 386	Conservative Treatment: N = 127		Invasive Intervention: N = 259	
	N (%) or Mean (SD)	95% CI	N (%) or Mean (SD)	95% CI
Smoking Status				
Never smoker	85 (66.9)	58.4–74.7	133 (51.4)	45.3–57.4
Smoker	28 (22.0)	15.5–29.8	89 (34.4)	28.8–40.3
Former smoker	14 (11.0)	6.5–17.3	37 (14.3)	10.4–18.9
Pre-existing comorbidities				
Diabetes	53 (41.7)	33.4–50.4	106 (40.9)	35.1–47.0
Hypertension	100 (78.7)	71.0–85.2	222 (85.7)	81.1–89.6
Hyperlipidemia	46 (36.2)	28.2–44.8	94 (36.6)	30.6–42.3
Stroke	20 (15.7)	10.2–22.8	26 (10.1)	6.8–14.1
Atrial fibrillation	35 (27.6)	20.4–35.8	66 (25.5)	20.5–31.0
Heart failure	51 (40.2)	31.9–48.8	67 (25.9)	20.8–30.4
Chronic kidney disease	52 (40.9)	32.7–49.6	91 (35.1)	29.5–41.1

Numerical variables are presented in the form of the mean (standard deviation); 95% CI of the mean. Categorical variables are shown in the form of frequency (%); 95% CI of the percentage. SD: standard deviation. CI: confidence interval.

Table 2. Distribution of inpatient clinical metrics, medical treatments, and outcomes of patients with in-hospital myocardial infarctions based on treatment strategy.

Total Number of In-Hospital AMIs: N = 386	Conservative Treatment: N = 127		Invasive Intervention: N = 259	
	N (%) or Mean (SD)	95% CI	N (%)	95% CI
	Inpatient clinical metrics			
Patient initially found in a hospital with no cardiac catheter laboratory	80 (63)	54.4–71	78 (30.1)	24.8–35.9
If yes, number of patients transferred to a hospital with cardiac catheterization laboratory	11 died in original hospital (5 within 24 h) 7 were discharged home 62 were transferred to a hospital with a catheterization laboratory but still received no intervention		0 died in KH1 0 were discharged home 78 were transferred to a hospital with a catheterization laboratory where they received intervention	
Heart rate on presentation (beats/min)	88 (23)	84–93	82 (23)	79–86
Systolic blood pressure on presentation (mmHg)	140 (31)	135–146	139 (30)	136–143
STEMI	19 (15.0)	9.6–21.2	72 (27.8)	22.6–33.5
Occurrence of shock upon presentation	7 (5.5)	2.5–10.5	25 (9.7)	6.5–13.7
	Initial medical treatments			
ASS	94 (74.0)	65.9–81.0	164 (63.3)	57.3–69.0
P2Y12 inhibitor	51 (40.2)	31.9–48.8	101 (39.0)	33.2–45.0
Heparin	80 (62.4)	53.0–69.4	180 (69.8)	63.7–75.2
Thrombolytic agent	1 (0.8)	0.1–3.6	7 (2.7)	1.2–5.2
	Outcomes			
In-hospital complications	40 (31.5)	23.9–39.9	73 (28.2)	23.0–33.9
30-day mortality	24 (18.9)	13.8–26.4	22 (8.5)	5.6–12.4

Numerical variables are presented in the form of the mean (standard deviation); 95% CI of the mean. Categorical variables are shown in the form of frequency (%); 95% CI of the percentage. SD: standard deviation. CI: confidence interval. STEMI: ST-segment elevation myocardial infarction. ASS: Acetylsalicylic acid.

The multivariable logistic regression analysis for identifying the determinants of invasive intervention in patients with in-hospital AMIs revealed lower odds with increasing age among patients older than 75 years (adjusted OR = 0.85, 95% CI [0.76–0.94]), as well as with heart failure (adjusted OR = 0.52, 95% CI [0.30–0.90]) and increasing heart rate (adjusted OR = 0.98, 95% CI [0.97–0.99]). Hypertension, however, was associated with higher odds of receiving invasive intervention (OR = 2.86, 95% CI [1.45–5.62]). Compared to in-hospital NSTEMIs, patients with in-hospital STEMIs were 1.96 times more likely to receive invasive intervention (95% CI [1.10–3.68]). After adjusting for other factors, we found that there was no difference in the odds of utilization of invasive intervention between males and females (Table 3).

Table 3. Determinants of invasive intervention in patients with in-hospital myocardial infarctions, compared to conservative treatment.

Factors	Adjusted OR	95% CI
Age $\leq$ 75 years	0.99	0.95–1.03
Age > 75 years	0.85	0.76–0.94
Sex (reference: male)	1.16	0.63–2.12
BMI group (reference: <25 kg/m^2)		
25–<30	1.54	0.71–3.36
30–35	1.02	0.42–2.44
>35	0.43	0.14–1.33
Smoking status (never smoker)		
Current smoker	1.41	0.66–2.99
Previous smoker	0.97	0.42–2.29
Diabetes	1.34	0.71–2.53
Hypertension	2.86	1.45–5.62
Hyperlipidemia	0.59	0.32–1.12
History of stroke	0.71	0.30–1.69
Atrial fibrillation	1.19	0.63–2.36
Chronic kidney disease	1.95	0.97–3.91
Heart failure	0.52	0.30–0.90
Heart rate	0.98	0.97–0.99
Systolic blood pressure	0.99	0.98–1.01
STEMI (reference: NSTEMI)	1.96	1.10–3.68

Variables included in the model: age (years), sex (reference: male), BMI group (reference: <25 kg/m^2), smoking status (reference: never smoker), diabetes, hypertension, hyperlipidemia, history of stroke, atrial fibrillation, chronic kidney disease, heart failure, heart rate on admission, systolic blood pressure on admission, and STEMI classification (reference: NSTEMI). OR: odds ratio. CI: confidence interval. BMI: body mass index. STEMI: ST-segment elevation myocardial infarction. NSTEMI: non-ST-segment elevation myocardial infarction.

In terms of the main outcome, invasive intervention was associated with lower odds of 30-day mortality in comparison with conservative treatment (OR = 0.25, 95% CI [0.10–0.67]), after adjusting for relevant confounders. The diagnosis of in-hospital AMIs in hospitals with a catheterization laboratory was associated with higher odds of 30-day mortality compared to hospitals with unavailable catheterization laboratories and subsequent hospital transfer (8.75, 95% CI [2.68–25.39] (Table 4).

The region of residence showed no association with the outcome 30-day mortality.

Considering patients who survived beyond 30 days, the majority in both groups were discharged on ASS. The conservative treatment group had lower proportions of P2Y12 receptor inhibitor, beta-blocker, and statins medications upon discharge. Patients who were treated conservatively were more commonly discharged on an anticoagulant (37.9% [28.9–47.5] vs. 21.1% [16.3–26.6]) (Table 5).

Table 4. Factors associated with 30-day mortality in patients with in-hospital myocardial infarctions.

Factors	Adjusted OR	95% CI
Invasive intervention	0.25	0.10–0.67
Available catheterization laboratory in the hospital where in-hospital AMI was diagnosed (reference: no)	8.75	2.68–25.39
Urban region (reference: rural)	0.22	0.06–1.20
Age $\leq$ 75 years	0.28	0.14–3.01
Age > 75 years	4.60	0.32–6.7
Hypertension	0.53	0.23–1.37
Heart failure	1.91	0.84–4.40
Heart rate upon admission	1.01	0.99–1.02
STEMI (reference: NSTEMI)	2.85	1.19–6.84

Variables included in the model: age (years), hypertension, heart failure, heart rate on admission, and STEMI classification (reference: NSTEMI). OR: odds ratio. CI: confidence interval. STEMI: ST-segment elevation myocardial infarction. NSTEMI: non-ST-segment elevation myocardial infarction.

Table 5. Comparison of discharge medications of patients who survived beyond 30 days, based on treatment strategy.

Number of Patients Who Survived beyond 30 Days after In-Hospital AMI Onset: *N* = 340	Conservative Treatment: *N* = 103		Invasive Intervention: *N* = 237	
	N (%)	95% CI	*N* (%)	95% CI
ASS	87 (84.5)	76.6–90.5	216 (91.1)	87.0–94.3
P2Y12 receptor inhibitor	52 (50.5)	40.9–60.0	192 (81.0)	75.7–85.6
Anticoagulant	39 (37.9)	28.9–47.5	50 (21.1)	16.3–26.6
ACE/ARB	68 (66.0)	56.5–74.6	173 (73.0)	67.1–78.3
Beta-blocker	72 (69.9)	60.6–78.1	204 (86.1)	81.2–90.0
Statin	47 (45.6)	36.2–55.3	179 (75.5)	69.8–80.7

Variables are shown in the form of frequency (%); 95% CI of the percentage. ASS: Acetylsalicylic acid. ACE/ARB: Angiotensin converting enzyme inhibitors and/or Angiotensin II receptor blocker.

In the sensitivity analysis, we repeated the regression analyses excluding 13 patients with in-hospital AMIs who died within the first 24 h. The determinants of invasive intervention remained the same, except that chronic kidney disease showed an association with the use of invasive intervention (Supplementary Table S2). The factors associated with 30-day mortality remained the same as in the former model (Supplementary Table S3).

4. Discussion

In line with previous findings from studies including only out-of-hospital AMIs, we found that the majority of the patients with in-hospital AMIs in our sample were treated with invasive intervention. Similar to what is known for out-of-hospital AMIs, invasive management of in-hospital AMI cases in our study was less common in patients with a higher age, heart failure, and NSTEMI. Our analysis revealed that lower age, hypertension, heart failure absence, lower heart rate, and STEMI were relevant determinants for utilizing invasive intervention in patients with in-hospital AMIs. In terms of outcomes, the 30-day mortality in the invasively managed group was lower than that in the conservatively treated group, whereby invasive intervention was associated with a 55% reduction in the odds of 30-day mortality.

Clinical trials and registry studies showed that invasive intervention is the favorable option for patients with stable coronary artery disease (CAD) [10,14,24] due to lower short- and long-term mortality. We also found that patients with in-hospital AMIs who are treated conservatively had higher odds of 30-day mortality, compared to those treated conservatively. However, a recent systematic review showed that there was no difference in post-AMI all-cause mortality between patients treated invasively and those treated conservatively [25], but the rate of major cardiac adverse events (MACEs) was lower with invasive intervention. Due to the low sample size of patients with complications in our study population, we could not confirm the association between the treatment strategy and occurrence of MACEs in the case of in-hospital AMIs. The European Society of Cardiology (ESC) provides guidelines for the acute and long-term management of AMIs. These guidelines are mostly based on studies that included only out-of-hospital AMIs or did not distinguish between in- and out-of-hospital AMIs. In fact, there is currently a lack of standardized protocols for the evaluation and risk stratification of patients with in-hospital AMIs [26]. According to the ESC, the mainstay treatment of STEMI is PCI, performed within 12 h of symptom onset. Coronary artery bypass graft (CABG) surgery may be utilized alternatively in AMI cases complicated by cardiogenic shock or mechanical complications [24,27]. As for non-ST-elevation entities of the acute coronary syndrome, the ESC supports the individual risk stratification of patients and the decision to accordingly opt for invasive intervention vs. conservative treatment [24]. The clarity of these guidelines regarding the default use of invasive intervention in STEMI compared to the need for a case-by-case assessment in NSTEMI could explain why STEMI patients in our sample were more likely to receive invasive intervention, relative to NSTEMI patients. Nonetheless, opting for no PCI in NSTEMI is considered a major risk factor for recurrent ischemic events. Thus, conservative treatment should be restricted to individual cases where the risks outweigh the benefits due to anatomical or clinical reasons. Such cases ought to be managed optimally with antiplatelet medications and secondary prevention, while taking into consideration the prevalent comorbidities [24]. To address the efficacy of conservative treatment vs. invasive intervention in elderly patients with NSTEMI, the British Heart Foundation is currently conducting a prospective and multicentric randomized controlled trial, the SENIOR-RITA Trial [28]. We anticipate that in this group as well, invasive intervention would be more favorable.

In terms of post-AMI management, the ESC recommends triple pharmacological treatment with an oral anticoagulant and dual antiplatelet therapy for the majority of STEMI patients [24,27]. We found that in-hospital AMI patients who were treated conservatively were less frequently discharged on P2Y12 receptor inhibitor, potentially due to an increased risk of bleeding, and especially that these patients were more commonly discharged on anticoagulants. In addition, physicians are recommended to discharge all AMI patients on statins, regardless of the cholesterol levels upon presentation, as this reduces the risk of early and long-term adverse cardiovascular events. The ESC additionally recommends the use of beta-blockers post-AMI (in cases of no contraindications), as well as ACE/ARB in AMI patients with hypertension, heart failure, and/or diabetes [24,27]. Contrarily to this, participants in our study who received conservative treatment were less frequently discharged on beta-blockers and statins, warranting the need for evaluation and optimization of the post-AMI care in this group.

Another interesting finding in our analysis was that patients who were staying in hospitals without a catheterization laboratory when they were initially diagnosed with an in-hospital AMI had lower odds of mortality than patients who were initially diagnosed with an in-hospital AMI in hospitals with available catheterization laboratories. We believe that patients who were initially present in more readily equipped hospitals were more likely sicker and comorbid than those who were present in hospitals not equipped with catheterization laboratories, contributing to higher mortality. One prospective study [29] involving patients with out-of-hospital AMIs showed that the availability of a PCI facility was the strongest predictor of the utilization of PCI as a treatment strategy. Patients who were directly admitted to hospitals readily equipped with PCI laboratories were five times (95% CI [3.6–7.9]) more likely to receive PCI, and this was independent of the time of symptom onset or hospital arrival. Another factor that could play a role in the choice of treatment strategy is the rationality. Evidence on the differences in the outcomes of AMIs between urban and rural regions remains conflicted. On one hand, patients from rural areas might have worse outcomes and higher mortality, potentially due to lower rates of invasive intervention in rural areas [30,31]. On the other hand, some studies found no association between rationality and the outcomes of AMIs [32,33]. Our results were in line with the latter. While the proportion of patients from the rural area was higher in the conservative treatment group, the multivariable analysis showed no association between the region of residence and 30-day mortality.

To understand why some patients with in-hospital AMIs receive conservative treatment despite the guidelines favoring invasive intervention, it is important to consider the various factors that play a role in the choice of the treatment strategy. Previous studies reported that older age and higher heart rate are negative determinants of invasive treatment in patients with AMIs [10,13,14]. We found that among patients with in-hospital AMIs, age (especially among those aged 75 years or older) and heart rate are implicated in the choice of treatment strategy. A high heart rate could be an indicator of hemodynamic instability, which could prompt physicians to avoid the use of invasive intervention. Evidence on the association between sex and the choice of treatment strategy in patients with AMIs is inconclusive. Some studies reported that women diagnosed with acute myocardial infractions are less likely to receive an invasive intervention [10,29]. One study identified an interaction between age and sex, whereby females older than 75 years were found to be equally likely to receive an invasive intervention [34], while another multicenter study reported no influence of sex on the choice of treatment strategy [35]. In our study, we found differences in the crude percentages of females between the two treatment groups, but in the adjusted analysis, we found that sex had no impact on the utilization of invasive intervention in patients with in-hospital myocardial infarctions.

In addition, certain comorbidities (mentioned previously) are associated with the underutilization of invasive intervention [10–12,14,15]. Of these comorbidities, only hypertension and the absence of heart failure were relevant determinants of invasive intervention in our analysis of in-hospital AMIs. Interestingly, unlike one study that found that hypertension was associated with conservative treatment in out-of-hospital STEMIs [11], we found that it is associated with higher odds of using invasive intervention in patients with in-hospital AMIs. Another potential determinant for not treating patients with in-hospital AMIs invasively may be multi-comorbidity rather than the presence or absence of specific comorbidities. This may be supported by the fact that the two treatment groups in our sample were homogenous in terms of the prevalence of pre-existing conditions. Negers et al. suggested that multi-comorbidity might be the most prominent clinical determinant in the physicians' decision-making instead of the specific comorbidities, even though there is no clinical evidence to support the benefits of this practice [13]. Moreover, a longer time duration between symptom onset and treatment may be a contributing factor. The ESC recommends the use of conservative treatment as an alternative to invasive intervention in cases where the time from diagnosis of STEMI exceeds 2 h [27]. Given that in-hospital AMIs are more likely to have an atypical presentation and are associated with delayed diagnosis [7–9,26,36], conservative treatment would be a suitable alternative. It is also possible that the pathophysiological mechanisms contributing to in-hospital AMIs are related to a mismatch in oxygen demand/supply not arising from plaque rupture and thrombosis (Type 2 AMI), where invasive intervention would be of little benefit [37]. Finally, the acuity of the concomitant medical condition in patients with in-hospital AMIs might hinder the use of invasive intervention. Unfortunately, adjusting for the severity of the disease was not possible in our study, as this information was not available. It is interesting to point out that one would expect the unavailability of a catheterization laboratory to play a role in opting for a conservative treatment. However, this was not the case in our sample. We found that the majority of the patients in the conservative treatment group who were initially present in hospitals without catheterization laboratories were transferred to hospitals with a catheterization laboratory but still received no intervention.

The results of our study must be interpreted with caution, due to some limitations. The RHESA covers only two regions in the federal state of Saxony-Anhalt, and mortality and morbidity might vary across the different rural districts in Saxony-Anhalt. This limits the generalizability of our findings. Additionally, the 16 hospitals participating in the registry may differ in terms of the volume and availability of tertiary cardiac health services compared to those not participating. This could have an influence on the treatment decision. Finally, residual confounding could not be eliminated, since other relevant comorbidities, such as cancer and cognitive impairment, as well as the duration of symptoms and data on the use of coronary angiography and its findings, were not collected.

To the best of our knowledge, this is the first study assessing the determinants of invasive intervention in in-hospital AMIs. The substantial sample size represents the foremost strength of our research, given that in-hospital AMIs are not common. Furthermore, we conducted DAG analysis to identify the minimum set of variables sufficient to reduce bias in the multivariable analysis.

5. Conclusions

One in every three patients with an in-hospital AMI received a conservative treatment, but lower odds of 30-day mortality were observed with invasive intervention. Younger age, absence of heart failure, and STEMI were consistent determinants of invasive intervention use between out-of-hospital and in-hospital AMI cases. The remaining determinants of invasive intervention in out-of-hospital AMIs were not relevant in the case of in-hospital AMIs. Thus, the protocols informing the use of invasive intervention in out-of-hospital AMIs might not be translatable to in-hospital AMIs, prompting the potential need for adaptations of the guidelines. In addition, the long-term post-AMI pharmacological care in patients with in-hospital AMI cases is suboptimal, warranting further examination. Longitudinal studies are required to assess the efficacy of conservative treatment and its long-term effects in patients with in-hospital AMIs, compared to invasive intervention.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm13082194/s1, Table S1: Characteristics and outcomes of patients with in-hospital myocardial infarctions. Table S2: Results of the sensitivity analysis after removing those who died immediately (N = 13) showing determinants of invasive intervention in patients with in-hospital myocardial infarctions, compared to conservative treatment. Table S3: Results of the sensitivity analysis after removing those who died immediately (N = 13) showing factors associated with 30-day mortality in patients with in-hospital myocardial infarction. Figure S1: Directed acyclic graph (DAG) showing the hypothesized association between invasive intervention (exposure) and 30-day mortality (outcome). Description of variable selection in the directed acyclic analysis (DAG): Variables associated with the treatment strategy were identified based on the results of the first logistic regression analysis (dependent variable: invasive intervention and reference conservative treatment), due to the lack of previous studies on predictors of invasive intervention in in-hospital AMI, compared to conservative treatment. The identified factors included: older age (>75 years), heart rate, hypertension, heart failure, chronic kidney disease (CKD) and Electrocardiogram (EKG) classification. Variables associated with the outcome 30-day mortality based on literature review included: older age, sex, hypertension, hyperlipidemia, BMI, diabetes, Atrial fibrillation, heart failure, CKD, smoking status, history of stroke, heart rate on admission and EKG classification. The minimum set of variables to adjust for in the logistic regression analysis for the association between treatment strategy and the main outcome (30-day mortality) included: age > 75 years, hypertension, heart failure, heart rate and EKG classification. It is worth mentioning that Generalized Additive Model (GAM) analysis was conducted to investigate the potential non-linear relationship between the continuous variable heart rate and each of the two dependent variables; treatment strategy and 30-day mortality. The results revealed a linear association between heart rate and each of the dependent variables (not shown), thus warranting the retention of heart rate as a linear term in the final logistic regression models. CKD: chronic kidney disease; A fib: atrial fibrillation; EKG: electrocardiogram.

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Abbreviations

AMI	Acute myocardial infarction
BMI	Body mass index
CI	Confidence interval
RHESA	The Regional Myocardial Infarction Registry of Saxony-Anhalt
NSTEMI	Non-ST segment elevation myocardial infarction
SD	Standard deviation
STEMI	ST-segment elevation myocardial infarction
OHMI	Out-of-hospital myocardial infarction
OR	Odds ratio
ESC	European Society of Cardiology
CABG	Coronary artery bypass surgery
PCI	Percutaneous coronary intervention
ACE/ARB	Angiotensin converting enzyme inhibitors and/or Angiotensin II receptor blocker
DAG	Directed acyclic graph
CAD	Coronary artery disease

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Publication 3 (P3)

Assaf M, Lückmann S, Efremov L, Holland K, Costa D, Mikolajczyk R: In-Hospital versus out-of-hospital non-ST-segment-elevation myocardial infarction (NSTEMI)—findings of the RHESA Study. Dtsch Arztebl Int 2024; 121: in press. DOI: 10.3238/arztebl.m2024.0032

Research Letter

In-Hospital Versus Out-Of-Hospital Non-ST-Segment-Elevation Myocardial Infarction (NSTEMI)

Findings of the RHESA Study

Studies on acute myocardial infarction (AMI) have focused on ST-segment-elevation myocardial infarction (STEMI) and found that 5–7% of cases occur in the hospital setting (1, 2). Compared to patients with out-of-hospital STEMI, patients with in-hospital STEMI are older, more frequently have chronic comorbidities, and show a higher risk of complications and mortality in the hospital (1, 3). It remains unclear whether these differences also apply to non-ST-segment-elevation myocardial infarction (NSTEMI). We set out to answer this question.

Methods

We used data for the period 2013–2019 from The Regional Myocardial Infarction Registry of Saxony–Anhalt (RHESA). AMI was defined based on the Third Universal Definition of Myocardial Infarction from the European Society of Cardiology (ESC). We excluded patients who did not survive until hospital admission, as treatments and 30-day mortality could not be assessed in this case, as well as those with previous AMI, since we were interested only in risk factors associated with the first occurrence of NSTEMI. We compared patients' characteristics, treatment, and outcomes between in-hospital and out-of-hospital NSTEMI. A literature review was conducted to identify (using a directed acyclic graph, not shown) the minimum set of covariables that had to be adjusted for in the logistic regression analysis to assess the association between NSTEMI type and 30-day mortality.

Results

We identified 2123 cases of NSTEMI in our sample, of which 14% occurred in the hospital setting. Compared to patients with out-of-hospital NSTEMI, patients with in-hospital NSTEMI were more commonly older over 75 years of age and had higher proportions of heart failure, chronic kidney disease, diabetes, and atrial fibrillation.

Patients with in-hospital NSTEMI were less likely to receive acetylsalicylic acid and heparin than persons with out-of-hospital NSTEMI. The proportion of patients receiving invasive intervention was lower in the in-hospital NSTEMI group (61.5% [55.9; 66.9] versus 69.7% [67.6; 71.8]). Crude 30-day mortality was higher for in-hospital NSTEMI than for out-of-hospital NSTEMI (11% [7.9; 15.0] versus 6.5% [5.4; 7.1]) *(Table)*. After adjustment the difference was less pronounced (odds ratio = 1.62 [1.15; 2.49]) *(Figure)*.

Discussion

The proportion of AMI occurring in the hospital setting was higher for NSTEMI than for STEMI. The established differences between in-hospital and out-of-hospital STEMI were also observed for NSTEMI. Patients with in-hospital NSTEMI were older and had more comorbidities. Mortality was higher for in-hospital NSTEMI and medicinal treatments and invasive interventions were carried out less frequently, in line with the published findings on STEMI.

To better understand why certain comorbidities may be associated with in-hospital NSTEMI, it is necessary to consider the underlying pathophysiological mechanisms. Type 2 AMI arises from a mismatch in cardiac oxygen demand and oxygen supply that, in contrast to type 1 AMI, does not involve plaque rupture and thrombosis. This can happen especially in perioperative stress, sepsis, chronic kidney disease, cardiac arrhythmias, anemia, heart failure, coronary spasm, etc., particularly in the older population (4). Interestingly, we noticed an overlap between the risk factors for in-hospital NSTEMI that we

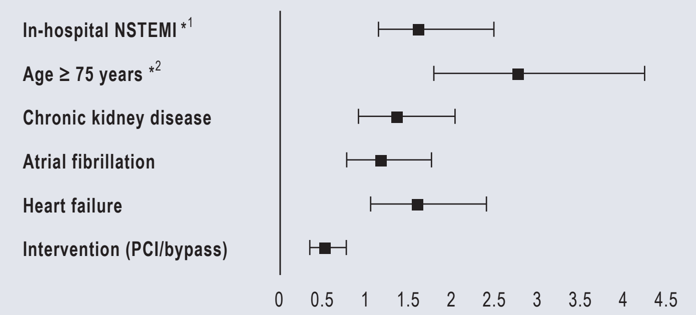
Table

Comparison of baseline characteristics, treatment, and outcomes between patients with in-hospital and out-of-hospital NSTEMI (n = 2123)

	Out of hospital n = 1824 (85.9%)		In hospital n = 299 (14.1%)	
	Mean (SD)	95% CI	Mean (SD)	95% CI
BMI (kg/m^2)	28.4 ± 4.6	[28.2; 28.6]	28.9 ± 4.8	[28.3; 29.5]
	N (%)	95% CI	N (%)	95% CI
Age ≥ 75 years	799 (43.8)	[41.5; 46.1]	164 (54.8)	[49.2; 60.4]
Female	665 (36.5)	[34.3; 38.1]	127 (42.5)	[38.7; 48.1]
Comorbidities				
Diabetes	642 (35.2)	[33.0; 37.4]	129 (43.1)	[37.6; 48.8]
Hypertension	1574 (86.3)	[84.7; 87.8]	257 (86.0)	[81.7; 89.5]
Hyperlipidemia	944 (51.8)	[49.5; 54.09	109 (36.5)	[31.2; 42.0]
Stroke	51 (2.8)	[2.1; 3.6]	15 (5.0)	[3.0; 7.9]
Atrial fibrillation	336 (18.4)	[16.7; 20.2]	87 (29.1)	[24.2; 34.4]
Heart failure	333 (18.3)	[16.5; 20.1]	92 (30.8)	[25.7; 36.2]
CKD	468 (25.7)	[23.7; 27.7]	119 (39.8)	[34.4; 45.4]
Smoke status	1075 (58.9)	[56.7; 61.2]	175 (58.5)	[52.9; 64.0]
– Non-smoker	512 (28.1)	[26.0; 30.2]	82 (27.4)	[22.6; 32.7]
– Smoker	237 (13.0)	[11.5; 14.6]	42 (14.0)	[10.5; 18.3]
– Former smoker				
Treatment and mortality				
ASA	1466 (80.4)	[78.5; 82.1]	202 (67.6)	[62.1; 72.7]
P2Y12 receptor inhibitor	626 (34.3)	[32.2; 36.5]	115 (38.5)	[33.1; 44.1]
GPIIAIIB antagonist*1	8 (0.4)	[0.2; 0.8]	2 (0.7)	[0.1; 2.1]
Heparin	1343 (73.6)	[71.6; 75.6]	192 (64.2)	[58.7; 69.5]
Thrombolytic agent	9 (0.5)	[0.2; 0.9]	3 (1.0)	[0.3; 2.7]
Invasive intervention*2	1272 (69.7)	[67.6; 71.8]	184 (61.5)	[55.9; 66.9]
Thirty-day mortality	118 (6.5)	[5.4; 7.1]	33 (11.0)	[7.9; 15.0]

*1 Glycoprotein IIb/IIIa receptor antagonist; *2 PCI/bypass
ASA, Acetylsalicylic acid; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; NSTEMI, non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention

Figure



Characteristics associated with 30-day mortality for in-hospital NSTEMI compared to out-of-hospital NSTEMI (multivariable logistic regression analysis for all patients with NSTEMI, adjusted for all presented variables; the squares represent adjusted odds ratios, the bars, the 95% confidence intervals).
*1 Reference group: out-of-hospital NSTEMI; *2 reference group: < 75 years
Nagelkerke R^2 for adjusted model = 0.18
NSTEMI, Non-ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention

identified (older age, atrial fibrillation, chronic kidney disease, and heart failure) and some of the triggers of type 2 AMI. This indicates that the pathophysiological mechanisms of in-hospital NSTEMI are more related to type 2 AMI.

The literature shows that in-hospital STEMI has higher in-hospital mortality and 1-year mortality than out-of-hospital STEMI (1, 3). Similarly, we found that the 30-day mortality of in-hospital NSTEMI was nearly two times that of out-of-hospital NSTEMI. The potential explanations include the following:

- The presence of concomitant medical conditions in inpatients with atypical symptoms of AMI may lead to delays in diagnosis and treatment (1, 3).
- Patients with in-hospital NSTEMI are probably not initially treated on cardiology wards, which could further delay treatment.
- There are no guideline recommendations for the management of in-hospital NSTEMI.

In our study, we found that patients with in-hospital NSTEMI were treated suboptimally when considering the ESC guidelines for acute coronary syndrome without persisting ST-segment elevation (5), possibly due to contraindications.

Our study has the following limitations: The analysis is confined to two regions of a single federal state of Germany, and only a fraction of AMI cases in these regions were covered by the registry. Additionally, patients with in-hospital NSTEMI may not be referred to cardiology and may thus be less likely to be included in our data, potentially leading to selection bias. Moreover, we had no information on the time of onset of the AMI during the hospital stay. Finally, a Nagelkerke R^2 of 18% indicates that the considered variables explain only a small part of the variation in 30-day mortality.

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Conflict of interest statement
Different phases of the project were financed from 2013 onwards by various health insurance funds, the Federal Ministry of Health, the German Heart Foundation (Deutsche Herzstiftung), the State Ministry of Labor and Social Affairs, and internal funds of Martin Luther University. The authors declare that no further conflict of interest exists.

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An Assaf, Mohamad

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I declare that this work is the first attempt of writing a dissertation. Also, I declare that this work is exclusively submitted as a dissertation for the Medical Faculty of Martin Luther University Halle-Wittenberg.

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