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Impact of Morphine Treatment on Infarct Size and Reperfusion Injury in Acute Reperfused ST-Elevation Myocardial Infarction

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List of Abbreviations:

AAR	Area At Risk
ACE	Angiotensin-converting Enzyme
ACS	Acute Coronary Syndrome
ADHF	Acute Decompensated Heart Failure
AF	Atrial Fibrillation
AMI	Acute Myocardial Infarction
ARB	Angiotensin II Receptor Blockers
ARIC	Atherosclerosis Risk in Communities Study
BBB	Blood-brain Barrier
BNP	B-type Natriuretic Peptide
CABG	Coronary Artery Bypass Graft Surgery
CAD	Coronary Artery Disease
CCU	Coronary Care Unit
CHD	Coronary Heart Disease
CMR	Cardiac Magnetic Resonance Imaging
COX	Prostaglandin-endoperoxide Synthase
CS	Cardiogenic Shock
CVD	Cardiovascular Disease
DES	Drug-eluting Stents
DAPT	Dual Antiplatelet Therapy
EMS	Emergency Medical System
ET-1	Endothelin 1
FDG	18F-fluorodeoxyglucose

FMC	First Medical Contact
FWR	Free Wall Rupture
GFR	Glomerular Filtration Rate
GP	Glycoprotein
HF	Heart Failure
HIT	Heparin-induced Thrombocytopenia
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme A
HR	Hazard Ratios
IABP	Intra-aortic Balloon Pumping
ICCU	Intensive Coronary Care Unit
IMR	Ischemic Mitral Regurgitation
IQR	Interquartile Range
LAd	Left Atrial Dimension
LDL-c	Low-density Lipoprotein Cholesterol
LGE	Late Gadolinium Enhancement
LMWH	Low-molecular-weight Heparin
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Events
MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging
MVO	Microvascular Obstruction
M3G	Morphine-3-glucuronide
M6G	Morphine-6-glucuronide

NEP	Endopeptidase 24.11
NSTEMI	Non-segment Elevation Myocardial Infarction
NHANES	National Health and Nutrition Examination Survey
NHLBI	National Heart, Lung, and Blood Institute
PCI	Percutaneous Coronary Intervention
PapMI	Papillary Muscle Infarction
PET	Positron-Emission Tomography
PONV	Postoperative Nausea and Vomiting
PWR	Papillary Muscle Rupture
RIC	Remote Ischemic Conditioning
RIPC	Remote Ischemic Preconditioning
SK	Streptokinase
SPECT	Single Proton-emissionComputed Tomography
STEMI	ST-elevated Elevation Myocardial Infarction
tPA	Tissue Plasminogen Activator
TIMI	Thrombolysis in Myocardial Infarction.
TT	Thrombolytic Therapy
TTE	Transthoractic Echocardiography
TEE	Transesophageal Echocardiography
VSR	Ventricular Septal Rupture
UDPGT	Uridine Diphosphate Glucuronyl Transferase
UFH	Unfractionated Heparin
UGT	Glucuronosyltransferase
UK	Urokinase

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1. INTRODUCTION

ST--segment elevation myocardial infarction (STEMI) is one of the most serious cardiovascular diseases and leading cause of death worldwide.[1] Advances in the treatment of patients with STEMI have resulted in a decline in mortality over the past 4 decades, with 1-year cardiac mortality in all-comers patients with STEMI treated with primary percutaneous coronary intervention (PCI) reaching a plateau in European National Registers between 4% and 12%.[2, 3] However, although national system delays for patients undergoing primary PCI have been significantly improved over recent years, in-hospital mortality has remained substantially unchanged. Moreover, morbidity caused by the development of post–myocardial infarction left ventricular (LV) remodeling and heart failure (HF) remains significant and is on the rise.

In the setting of STEMI ischemia of the damaged myocytes causes severe chest pain. Relief of pain is of paramount importance, not only for comfort reasons but also because persistant chest pain is associated with sympathetic activation, which causes vasoconstriction and increases the ventricular loading conditions in myocardial infarction.[2, 4] The recommended treatment for pain in myocardial infarction is titrating intravenous opioids (class IIa indication with level of evidence C),[2, 5] and morphine sulfate is the preferred choice, especially for those infarction patients whose course is complicated by acute pulmonary edema.[6]

However, morphine has side effects like inhibition of gastric emptying, reduction of intestinal peristalsis, nausea or vomiting.[7] These effects are related to slow absorption, delayed onset of action of antiplatelet therapy and may even reduce the effect of oral antiplatelet agents and subsequent failure of early antiplatelet treatment.[8] In addition, morphine administration was associated with higher mortality in patients with non-segment elevation myocardial infarction (NSTEMI),[9] and with suboptimal reperfusion in patients with STEMI after primary PCI.[10] In contrast, there is also evidence that opioid agonists may play a positive role in cardioprotective effects on the myocardium, in particular in the status of ischemia and necrosis eg. resulting in infarct size reduction.[11-13]

In consideration of the limitations of previous studies (single-center design, small sample size, and indirect infarct size assessment) and the reported contradictory results regarding

the effect of morphine on myocardial damage in patients with acute myocardial infarction (AMI),[14-17] it is necessary to further evaluate the impact of morphine on infarct size and reperfusion injury in STEMI. The use of cardiac magnetic resonance imaging (CMR) allows the exact assessment of infarct size and has been established as the reference standard technique for the assessment of myocardial damage.

The aim of our work was therefore to comprehensively assess the effect of morphine administration on infarct size and reperfusion injury assessed by CMR in patients with acute STEMI undergoing primary PCI in an adequately sized multicentre study.

2. BACKGROUND

2.1 ST-segment Elevation Myocardial Infarction

2.1.1 Definition and Classification of Myocardial Infarction

Myocardial infarction is a global health problem and a unified definition and standardized process are of great significance for the treatment and prognosis of myocardial infarction. The term AMI should be used when there is evidence of myocardial injury (defined as an elevation of cardiac troponin values with at least one value above the 99th percentile upper reference limit) with necrosis in a clinical setting consistent with myocardial ischaemia. For the sake of immediate treatment strategies such as reperfusion therapy, it is usual practice to designate patients with persistent chest discomfort or other symptoms suggestive of ischaemia and ST-segment elevation in at least two contiguous leads as STEMI. In contrast, patients without ST-segment elevation at presentation are usually designated NSTEMI. The categories of patients with STEMI, NSTEMI, or unstable angina are customarily included in the concept of acute coronary syndrome (ACS). In addition to these categories, AMI may be classified into various types based on etiology, pathological, clinical, and prognostic differences, along with different treatment strategies.[2, 18]

Based on the fourth universal definition of myocardial infarction, the concept of myocardial infarction is that there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile upper reference limit.[18]

Table 1: Types of myocardial infarction. Adapted from[18] PCI = percutaneous coronary intervention

Type of myocardial infarction	Definition
Type 1	Myocardial infarction related to acute athero-thrombosis in the coronary artery
Type 2	Myocardial infarction related to a myocardial oxygen supply imbalance
Type 3	Myocardial infarction resulting in death when biomarker values are unavailable
Type 4	
Type 4a	PCI related myocardial infarction
Type 4b	Stent thrombosis related myocardial infarction
Type 4c	Restenosis related myocardial infarction
Type 5	Coronary artery bypass graft (CABG) related myocardial infarction

Despite the fact that the majority of STEMI patients are classified as a type1 myocardial infarction (with evidence of a coronary thrombus), some STEMIs fall into other myocardial infarction types (see Table 1).

The general definition of class 1 myocardial infarction according to the new universal definition of myocardial infarction includes the essential criteria of the detection of a rise and/or fall of cTn values above the 99th percentile as marker of acute myocardial injury/ischemia and at least one of the following criteria needs to be fulfilled:

- Symptoms of acute myocardial ischaemia;
- New ischaemic Electrocardiography (ECG) changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology;
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy.

However, as stated above it is essential to integrate the ECG findings with the aim of classifying type 1 myocardial infarction into STEMI or NSTEMI in order to establish the appropriate treatment (immediate versus early invasive revascularization) according to current guidelines.[2, 19]

2.1.2 Pathophysiology of ST-segment Elevation Myocardial Infarction

Occlusion of an epicardial coronary artery leads to a large area of myocardial ischemia and necrosis and then causes acute depression on the systolic and diastolic function of left and/or right ventricular.[20, 21]

Prolonged myocardial infarction activates a typical "wavefront" of ischemia, that extends from the subendocardium in the center of the risk area to the subepicardium with ongoing duration of coronary occlusion.[22-25] The infarction leads to disorders of metabolism and ions in the abnormal myocardium and a rapid decline in contractile activity.[22]

The cardiomyocytes of human beings have negligible regenerative capacity. Unrelieved ischemia causing by the occluded artery gives rise to permanent damage on the myocardium, which replaced by fibrous scar tissue, characterized by dilation, hypertrophy of viable segments, progressive dysfunction and chronic HF.[22, 26]

Along with the great success of reperfusion therapies and modern medical treatment, there is a remarkable decline in mortality of STEMI, contributing more attention to the downstream consequence of survival: post-infarction HF.[26] Infarct size is the major determinant of long-term mortality and left ventricular ejection fraction (LVEF), which is the dominating factor of chronic HF worldwide.[27] Consequently, limiting the extent of necrosis during a STEMI is of great individual and socioeconomic value.

The myocardial salvage is not solely dependent on the duration of coronary artery occlusion, many other factors including collateral blood flow, extension of the AAR (the area submitted to ischaemia), haemodynamic status during ischaemia, the size of the occluded coronary artery and the amount of myocardium (bed) that it supplies (risk region).[28, 29]

The thrombotic occlusion of coronary artery resulting from the sudden rupture or erosion of an atherosclerotic plaque has two final results, most often followed by spontaneous or interventional reperfusion, but sometimes occurring without reperfusion.[20]

As estimated from CMR and biomarker analysis, 30 – 50% of the AAR is still viable after 4–6 h from the onset of symptoms, which is worth to salvage by reperfusion.[30] Even after more than 12 hours of symptom onset, there is some viable myocardium and interventional reperfusion demonstrated reduced infarct size in some sudies.[31] However, current guidelines do not routinely recommend primary PCI in subacute STEMI >12h (class IIa recommendation) and only late presenters with persistent symptoms should undergo routine PCI.[2]

Reperfusion therapy has clear benefits by limiting infarct size[32] and reducing the incidence of chronic HF, while there may be paradoxically ischaemia-reperfusion injury at the early stage.[26] Prevalent ischaemia with unregulated pathophysiological mechanisms leads to swelling of cardiomyocytes and endothelial cells, microvascular destruction, interstitial oedema and haemorrhages, and sterile inflammation.[28] Whereas reperfusion within time-limited windows may salvage a great part of myocardial tissues listed above, it might trigger recruitment and activation of inflammatory cells (neutrophils are the first ones within 30 minutes) in the systemic circulation and within the myocardial ischaemic area that might increase myocardial injury.[33] After 3–7 days post AMI, with the positive effect of neutrophil and inflammatory cells infiltration, the optimal healing of infarcted heart begins with scare formation and becomes gradual stabilized.[28]

There are several representations of ischemia-reperfusion injury including reperfusion arrhythmias, myocardial stunning, microvascular obstruction (MVO) and intramyocardial haemorrhage, and lethal myocardial reperfusion injury, which may occur alone or together, resulting in different clinical outcome and suboptimal microvascular perfusion.[32]

2.1.3 Epidemiology of ST-segment Elevation Myocardial Infarction

2.1.3.1 Prevalence

The incidence of acute STEMI in developed countries has decreased over the last decades due to the progressive implementation of preventive therapies and better control of risk

factors.[2, 6] Despite the progressive and gradual decrease in its incidence, STEMI remains a significant health problem, representing a major contributor to mortality worldwide.[6]

Probably the most comprehensive European STEMI registry is found in Sweden, where the incidence rate of STEMI was 58 per 100 000 per year in 2015. In other European countries, the incidence rate ranged from 43 to 144 per 100 000 per year.[34]

Approximately every 40 seconds, an American will have an AMI.[35] On the basis of data from the National Health and Nutrition Examination Survey (NHANES) 2013 to 2016, the overall prevalence for myocardial infarction is 3.0% in US adults ≥20 years old, and the average age at first myocardial infarction is 65.6 years for males and 72.0 years for females from 2005 to 2014 in Atherosclerosis Risk in Communities Study (ARIC) of the National Heart, Lung, and Blood Institute (NHLBI).[35] According to the latest available data, cardiovascular disease (CVD) deaths occurred in at least 4 million European every year. As one of the main courses of CVD, coronary heart disease (CHD) causes more than 1.8 million deaths each year in Europe, accounting for 20% of all deaths. Across Europe, 1.4 million people under the age of 75 die from CVD every year and even 700,000 death under the age of 65.[36]

In patients with STEMI, the mean age decreased from 66.2±14.0 to 63.5±14.6 years old in France from 1995 to 2015.[37] Consequently, the proportion of younger patients with STEMI increased from 1995 to 2010 in France, particularly in women under 60 years (from 11.8% to 25.5%), in whom prevalences of current smoking (37.3% to 73.1%) and obesity (17.6% to 27.1%) increased.[38] In contrast there was a reverse tendency of younger STEMI patients in the USA, which displayed a decline from approximately two-thirds to two-fifths in all patients with an initial AMI.[39]

The incidence of AMI hospitalizations also declined significantly in the United States (4.5 per 1000 populations in 2001 to 3.2 per 1000 populations in 2011; 29% decrease; Ptrend<0.001). Particularly, the proportion of STEMI among AMI hospitalizations decreased (40.2% in 2001 to 26.9% in 2011; 33% decrease; Ptrend<0.001).[40]

2.1.3.2 Mortality Rates

In more than two decades, there has been a dramatic descent of early-stage and long-term mortality due to widespread use of immediate reperfusion therapies (especially primary PCI – see also 2.1.3.5) and use of optimized secondary prevention medications.[37, 38, 40-44] From 1990 to 2006, in-hospital AMI mortality in the United States declined from 10.4% to 6.3% (P<0.001; STEMI: 11.5% to 8.0%, P<0.001; NSTEMI: 7.1% to 5.2%, P<0.001). Up to 21% of the decline in the annual rate of mortality for patients with STEMI and 37% for patients with NSTEMI was judged to be attributable to improvements in acute treatments (including reperfusion therapy for STEMI).[44] The mortality among STEMI patients has also declined from approximately 20% in the late 1980s to below 7% in routine practice in European countries.[37, 45-47] The adjusted survival estimates for STEMI patients who received emergency reperfusion treatment were significantly higher than for those who did not.[41]

2.1.3.3 Sex Differences

For females, the incidence of CHD is generally 10 years behind that of males, and more than 10 years later for severe cardiovascular events (eg. myocardial infarction and sudden death).[35, 42] As compared with males, females with myocardial infarction have relatively much more and severe complications and poorer prognoses.[35, 48-50] In addition, younger women were less likely to present with STEMI in comparison to men in the overall AMI population (adjusted odds ratio [OR]: 0.74; 95% confidence interval [CI]: 0.73 to 0.75, p < 0.001). Nevertheless, in the event of suffering from STEMI, the in-hospital mortality was significantly higher in younger women compared with men (4.5% vs. 3.0%; adjusted OR: 1.11; 95% CI: 1.07 to 1.15) and lower rates of revascularization at acute stage.[3]

2.1.3.4 Ischemic and Reperfusion Times

Prevention of delays is critical in STEMI as the most critical time of an AMI is the very early phase, during which the patient is often in severe pain and liable to cardiac arrest. In addition, early provision of therapy, particularly reperfusion therapy, is critical to its benefit. Thus, minimizing delays is associated with improved outcomes. In addition, delays to treatment are the most readily available, measurable index of quality of care in STEMI.

Optimal treatment of STEMI should be based on the implementation of networks between hospitals with various levels of technology, connected by an efficient ambulance service.

The goal of these networks is to provide optimal care while minimizing delays, in order to improve clinical outcomes.

In patients with STEMI, median time from symptom onset to hospital admission decreased from 240 (interquartile range, 140–540) minutes to 168 minutes (interquartile range, 100–398), whereas the use of mobile intensive care units increased.[37] Reports on the basis of analysis from AMI registries showed that 60% of 37 634 STEMI patients in the United States used emergency medical system (EMS) transport to get to the hospital. Older adults, women, adults with comorbidities (sicker patients) and long-distance transportation were more likely to use EMS than their counterparts. Symptom-onset-to-arrival time was shorter for those who used EMS (89 minutes) than self-transport (120 minutes).[42, 51]

Another important factor for reducing total reperfusion times are faster door-to-balloon times. Implementing strategies to target institutional specific delays are essential for improved patient care and are a key indicator of quality of care for the individual hospital. Several factors like 1) direct transfer to the cath lab with bypassing of the ICU and emergency department, 2) effective use of pre-hospital electrocardiograms, and (3) performance data monitoring/feedback is associated with rapid door-to balloon times.[52] Immediate activation of cardiac catheterization laboratory also has shorter mean door-to-balloon times and a higher percentage of achieving door-to-balloon target of 90 minutes.[53] Moreover, the interventional experience of the dedicated PCI centre is important to enable fast door-to-balloon times. Consequently, door-to-reperfusion times improved significantly (median door-to-balloon time, 63 versus 76 minutes, respectively, $P < 0.0001$; median door-to-needle, 23 versus 29 minutes, respectively, $P < 0.0001$).[42, 51] In conclusion, higher EMS together with improved door-to-balloon times resulted in shorter total ischaemic times and thereby better prognosis and lower in-hospital or 30-day mortality.[35, 54]

2.1.3.5 Use of Percutaneous Coronary Intervention

Primary PCI—defined as an emergent percutaneous catheter intervention in the setting of STEMI, without previous fibrinolytic treatment—is the preferred reperfusion strategy in patients with STEMI, provided it can be performed expeditiously (i.e. within guideline-mandated times), by an experienced team, and regardless of whether the patient presents to a PCI-capable hospital. Randomized clinical trials comparing timely primary

PCI with in-hospital fibrinolytic therapy in high-volume, experienced centres have repeatedly shown that primary PCI is superior to hospital fibrinolysis.[55-58] The advantages of primary PCI over thrombolysis are the higher vessel patency with contemporary techniques (>95% with stents) and the lower risk of intracranial hemorrhage. Consequently, the usage of PCI has significantly increased in the United States and European countries[37, 40, 59] with a dramatic increase for both the STEMI (75% increase; P<0.001) and NSTEMI patients (54% increase; P<0.001) during the first decade of the 20th century. By contrast, the CABG usage decreased for both.[40] There is a consistent pattern for France, intended PCI increased from 12% (1995) to 76% (2015) in STEMI patients in acute phase, with less use of fibrinolysis (37.5%–6%). In patients with NSTEMI, PCI ≤72 hours from admission increased from 9% (1995) to 60% (2015).[37]

2.1.3.6 Recommended Medications after Discharge

At hospital discharge, studies demonstrated a significant and relatively consistent increase in the proportion of patients receiving guidelines recommended medications from 2000 to 2010 [37, 59, 60] and remained stable in 2015.[37] Such medications are statins, dual antiplatelet therapy, beta-blockers, nitrates, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (see 2.1.7.3).

Patients who prescribed combination medication regularly were usually younger, with diabetes or hypertension, more likely to undergo coronary revascularization procedures, and have less serious comorbidities. They had a relatively longer hospital stay and received regular follow-up after discharge.[60]

2.1.4 Clinical Manifestation of ST-segment Elevation Myocardial Infarction

The distinguishing features of STEMI are the symptoms of myocardial ischemia (such as persistent chest pain, which may radiate to the neck, mandible, or left arm), at least two contiguous leads with dynamic ST-segment elevation of the ECG, and the history of coronary artery disease (CAD).[2] Furthermore, it is estimated that 20% of myocardial infarction are silent.[35]

- **Chest Pain:** Severe chest pain is the most frequent symptom in the onset of STEMI.

The notable evidence is severe precordial pain characterized by a feeling of tightness in precordial region, some of which can radiate to the mandible, neck, left arm, back, and upper abdomen, lasting for several hours or more before reperfusion, generally breaking out at daybreak, and can not be relieved by rest or/and Nitrates.

- **Arrhythmia:** Due to the uniqueness of coronary perfusion, different parts of coronary artery occlusion can cause relevant arrhythmias. The common ones are ventricular arrhythmia, atrioventricular block, and bundle branch block. Among them, ventricular fibrillation is the main cause of death in the early stage of STEMI, especially before admission.

- **HF:** Acute left HF is a common occurrence, most of which occur in the first few days of onset. The main manifestations are dyspnea, episodes of coughing and wheezing, orthopnea, paroxysmal nocturnal dyspnea, edema of lower extremity, etc. HF caused by AMI is called pump failure, which can be divided into four grades according to Killip classification. The Killip classification is a significant independent predictor for 1-year mortality, and higher Killip class is associated with increased mortality in patients with AMI.[61]

To provide an accurate estimation of the severity of the myocardial infarction, each patient with AMI should be ranked by Killip classification in the following way:

Table 2: Criteria of Killip classification. Adapted from[62] HF = heart failure

Killip classification	Classification criteria
Killip class I	No clinical signs of HF
Killip class II	Rales or crackles in the lungs, S3, and elevated venous pressure.
Killip class III	Frank acute pulmonary edema
Killip class IV	Cardiogenic shock or hypotension (measured as systolic blood pressure lower than 90 mmHg), and evidence of peripheral vasoconstriction(oliguria, cyanosis or sweating)

• **Hypotension and Shock:** Following extensive myocardial stunning and necrosis, cardiac output drops sharply in the early stage of STEMI and cause cardiogenic shock (CS). The main manifestations of the patients with CS are decreased blood pressure, increased heart rate, poor consciousness, oliguria or anuria, dysphoria, pale complexion, clammy skin, profuse sweating, and even syncope, etc.

• **Gastrointestinal Symptoms:** Severe chest pain may induce nausea and vomiting, and the decrease of cardiac output after coronary artery occlusion may lead to gastrointestinal ischemia, abdominal distension and decreased digestive capacity.

• **Atypical Symptoms:** In the acute stage of AMI there might be also, it presents some atypical symptoms, including fatigue, listlessness, low fever, palpitations, etc. Patients with diabetes or female patients have been identified as groups with frequent atypical presentations.

2.1.5 Complications of ST-segment Elevation Myocardial Infarction

2.1.5.1 Cardiogenic shock

CS as one of the most frequent and major complications after AMI is a physiologic state of inadequate tissue perfusion resulting from cardiac pump dysfunction. It is characterized by circularly unstable refractory hypotension as well as insufficient end-organ perfusion requiring pharmacological or mechanical intervention.[63]

The incidence of CS is approximately 5% to 8% in patients with STEMI and 2.5% of non-STEMI cases with approximately 60,000 to 70,000 cases per year in Europe[64, 65] and mortality remained nearly unchanged in the range of 40-50% during the last two decades.[66] AMI accounts for 80% of patients in CS.[63, 67]

CS directly related to the severity of the haemodynamic disorder and the most common procedure is multiple organ dysfunction syndromes due to ongoing organ hypoperfusion.[63, 67] Decreased coronary perfusion pressure and depression of myocardial contractility resulting in reduced cardiac index, low blood pressure, and further coronary ischaemia along with increased myocardial oxygen demand play a potentially deleterious downward

spiral that leads to an impaired cardiac output with subsequent severe tissue hypoperfusion and ultimately death.[63, 67]

Immediate PCI/CABG is the most important treatment strategy for patients with CS after myocardial infarction with recommendation Class Ib.[2] Extracorporeal membrane oxygenation setting may result in significant mortality benefit as well as an increase in favourable neurological outcome.[68]

2.1.5.2 Left ventricular Aneurysm

LV aneurysms are thinned, abnormally contracted and scarred myocardium after infarction, with characteristic reverse wall motion abnormality.[69] Less than 5% of STEMI patients with large areas of transmural myocardial infarction developed a ventricular aneurysm[2,70]. The apical-anterior is the most common site of LV aneurysms.[71]

Although ST-elevation is not a predictor of LV aneurysm[72] and ECG is not an effective method in the diagnosis of LV aneurysm in patients with STEMI,[70] LV aneurysm was more common in patients with persistent ST-segment elevation in precordial ECG leads than resolved patients.[73] Echocardiography and CMR are more valid examination methods for the detection of LV aneurysm.[69]

LV aneurysm constitutes a significant independent predictor of late sudden cardiac death after myocardial infarction.[71, 74] The incidence of LV thrombosis in patients with LV aneurysm is significantly higher than in patients without aneurysm.[70]

2.1.5.3 Left ventricular Thrombus

Based on the large national database, 0.2% of patients after STEMI developed acute in-hospital LV thrombus in the USA.[75] Predisposing factors associated with LV thrombus following STEMI included: anterior/anterolateral STEMI, acute or chronic HF with reduced ejection fraction, atrial fibrillation (AF), LV aneurysm, Left heart valvular disease, acute or chronic deep venous thrombosis/pulmonary embolism and alcohol use.[75] In contrast to other STEMI patients, patients with LV thrombus following STEMI were more likely to have high-risk of systemic embolism.[75, 76] CMR with delayed enhancement has considered a better identification for detecting LV thrombus when compared to transthoractic

echocardiography (TTE) and transesophageal echocardiography (TEE).[75, 77, 78] LV thrombus prevalence assessed by CMR was 3.5% and associated with decreased myocardial salvage, larger infarcts, and more pronounced reperfusion injury.[79]

2.1.5.4 Ventricular Rupture

With contemporary reperfusion therapy, ventricular rupture is a rare complication of AMI with a reported incidence of 0.5%.[80, 81] There are three categories of ventricular rupture 1) free wall rupture (FWR), 2) ventricular septal rupture (VSR), and 3) papillary muscle rupture (PWR).[82] Clinical manifestations in the early phase of LV rupture were cardiac arrest, shock, and congestive HF.[83] In marked contrast to late rupture, the early rupture demonstrated extremely adverse clinical outcomes.[83] Thrombolytic use, extensive anterior myocardial infarction, treatment > 2 h after symptoms onset, advanced age, and female gender were considered as independent predictors of ventricular rupture.[82, 84, 85] FWR is the most common of the three types of LV rupture, with an incidence rate of 3 to 10 times more when compared with PMR and VSR.[82] Patients treated with thrombolytic therapy (TT) was associated with a higher risk of FWR.[86] The incidence of FWR in AMI patients who received thrombolysis was 10 times higher than the group without thrombolysis, even undergoing successful PCI.[84]

2.1.5.5 Ischemic Mitral Regurgitation

Ischemic mitral regurgitation (IMR) is a rare complication of STEMI in the current reperfusion era and is caused by dysfunction or rupture of papillary muscle after ischemia of the segments underlying the papillary muscles (typically a lateral or inferior infarct). Although this common complication occurs in 15–64% of patients after this event[87], primary PCI lowers the incidence of IMR in patients with acute STEMI[88].

IMR leads to a lower LVEF, larger left atrial dimension (LAd), and a larger LV end-systolic and LV end-diastolic volumes, which can give rise to acute pulmonary edema, particularly moderate or severe mitral regurgitation (MR) is associated with a large increase in the risk of HF and a predictor of death among 30-day survivors independent of age, gender, EF, and Killip class.[87-89]

Owing to displacement and reduced synchronicity of papillary muscles, LV remodelling, and annular dilatation, the forces of tethering and closing are unbalanced. It is one of the major reasons that result in or aggravate MR.[90] Medical therapy is aimed at preventing and delaying the reasons that aggravate MR, but in severe IMR a surgical approach for mitral repair is warranted.[91]

2.1.5.6 Pericardial Complications

Early and late (Dressler syndrome) infarct-associated pericarditis and pericardial effusion are the important components of pericardial complications,[92] which may be an immunoreaction of pericardial tissue triggered by myocardial necrosis.[2] Reperfusion time $>$ 6 hours after symptom onset and unsuccessful primary PCI, as well as larger infarction, are the major causes of early/late infarct-associated pericarditis.[92] Early post-AMI pericarditis was a marker of a larger infarction, but unaffected the clinical outcomes, including in-hospital or 1-year mortality, major adverse cardiac events (MACE), and overall event-free survival, etc.[92] Late post-AMI pericarditis (Dressler syndrome) following AMI was a rare phenomenon after reperfusion in STEMI patients.[92, 93] Infarct-associated pericardial effusions usually occur early after infarction during day 3 to 2 weeks and most common of them are mild to moderate in size.[94, 95] Larger size or annular effusion by echocardiograms with evidence of cardiac tamponade after STEMI indicates a possible cardiac rupture.[95]

2.1.6 Diagnostic Workup of ST-segment Elevation Myocardial Infarction

2.1.6.1 Electrocardiography

The ECG is one of the most critical and necessary diagnostic methods of AMI, which is the most simple, timely, and effective way.[96] All patients with chest pain must be acquired and interpreted 12 or 18 lead ECG as soon as possible during FMC for early diagnosis and triage of STEMI.[2, 6, 18, 97] Prehospital ECG was associated with a more short time of reperfusion by PCI or thrombolytic with which patients exhibited significantly lower 30-day mortality rates than those who did not.[96, 98, 99]

The ECG diagnostic criteria for STEMI are as follows: at least two contiguous leads with ST-segment elevation ≥2.5 mm in men < 40 years, ≥2mm in men ≥40 years, or ≥1.5 mm in

women in leads V2–V3 and/or ≥1mm in the other leads; depressed ST-segment in leads V1–V3, positive terminal T-wave, and concomitant ST-segment elevation ≥0.5 mm in leads V7–V9 should be considered as posterior myocardial infarction.[2]

Table 3: Myocardial infarction location in relation to electrocardiograph leads. Adapted from[100]

Territory	ECG leads
Anterior	V1–V4
Lateral	V5–V6, I, aVL
Inferior	II, III, aVF
Posterior	ST depression V1–V3, with tall R waves, ST elevation V7–V9
Right ventricular	RV4

2.1.6.2 Laboratory Tests and Biomarkers of Myocardial Infarction

Cardiac troponin I and cardiac troponin T are the preferred biomarkers for the evaluation of myocardial injury, which are unique components of cardiomyocytes, especially troponin I is expressed exclusively in the myocardium.[18, 101] The recommended cut-off limit for routine cTn is the 99th percentile limit of the healthy reference population.[18, 101, 102] The criteria of the Fourth universal definition of AMI is a rising and/or falling pattern of cTn concentrations with at least one value above the 99th percentile upper reference limit (URL) in a patient with clinical features of myocardial ischaemia.[18] There is a time window for troponin elevation in the early phase of myocardial infarction. If the first blood samples for hs-cTn in patients with suspicion of AMI are within normal limits, it is recommended to use the 0 h/1 h algorithm (best option, blood draw at 0 h and 1 h) or the 0 h/2 h algorithm (second-best option, blood draw at 0 h and 2 h).[19] In the early stage, the dynamic variation of hs-cTn release in blood is extremely important.[18, 101, 102] Acute processes usually manifest an obvious rising and then falling pattern, whereas the elevations associated with chronic

diseases such as chronic renal failure, chronic HF, chronic pulmonary arterial hypertension, etc, will remain stable.[101, 102]

The other cardiac biomarkers i.e. creatine kinase and its MB isoenzyme, lactate dehydrogenase isoenzymes, and myoglobin are less sensitive and less specific, which were no longer used in the diagnosis of myocardial infarction nowadays.[101, 103] The B-type natriuretic peptide (BNP), glomerular filtration rate (eGFR), and glucose may help in risk stratification by providing incremental prognostic information, and supply evidence of drug usage simultaneously in patients of AMI. In particular, significant-high natriuretic peptides [BNP and N-terminal pro-BNP (NT-proBNP)] are the most effective independent predictors of prognosis in the risk of death, acute HF, as well as the development of AF except cardiac troponin. D-dimer is recommended to diagnose or exclude patients with chest pain caused by pulmonary embolism.[19]

2.1.6.3 Imaging Studies

2.1.6.3.1 Echocardiography

Echocardiography is a noninvasive convenient available and easily repeatable method for assessment of LV wall motion changes in all ventricular segments[104] and evaluation of LV function after AMI.[105] Normally, the diagnosis made by echocardiography for ventricular aneurysm, VSR, and PWR has high accuracy.[82, 86] Cardiac echocardiography is very sensitive to the detection of pericardial effusion, which can detect less than 50 ml pericardial fluid effectively.[94, 106] Pericardial effusion after myocardial infarction is related to the large area of anterior myocardial infarction and HF.[94, 95] In patients with high suspicion of aortic dissection, emergency point-of-care ultrasound may be a useful tool to help emergency physicians fast diagnose and eliminate aortic dissection presenting with STEMI.[107] Echocardiography can be also used to identify complications of AMI like LV thrombi, ventricular rupture and pericardial complications (see above).

2.1.6.3.2 Chest Radiography

Chest radiology has not much value in the diagnosis of STEMI, but it is of great significance to exclude chest pain caused by other reasons.[108] Patients with chest pain and widened mediastinum may reveal aortic dissection, and the lung or mediastinal diseases

with chest pain, including pneumonia, pulmonary tuberculosis, pneumothorax, mediastinal emphysema, pleurisy, pleural effusion, etc., could disclose corresponding abnormalities on chest radiographs.[109]

2.1.6.3.3 Cardiac Magnetic Resonance Imaging

Cardiac Magnetic Resonance Imaging (CMR) with delayed enhancement has incomparable advantages in the evaluation of pathophysiological consequences of myocardial ischemia and reperfusion (eg. infarct size, myocardial salvage index, LV function, or extent of reperfusion injury, MVO, etc.) in patients after AMI (Figure 1).[110-112] Infarct size and MVO offer incremental prognostic information for prediction of MACE, and especially MVO is the most potent CMR predictor of hard clinical events.[113] It is also possible to calculate the myocardial salvage index (area at risk minus infarct size) by CMR that has also proven to predict the MACE in acute reperfused STEMI.[114]

CMR has also important implications and value on the diagnosis of relevant complications after myocardial infarction, especially in papillary muscle infarction (PapMI) detection of LV thrombi and LV aneurysm.[69, 115]

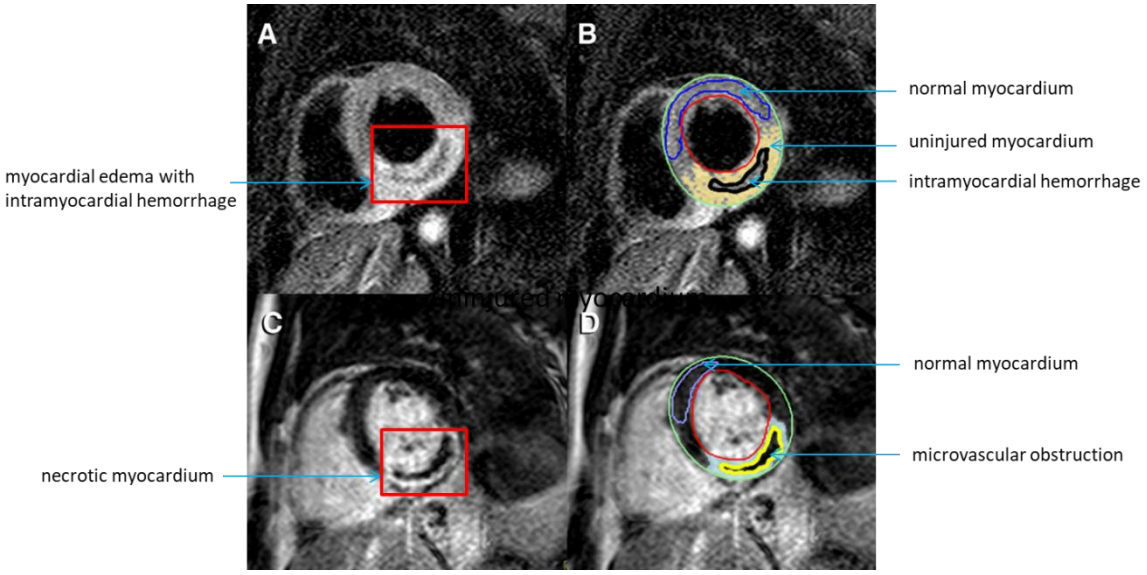

Figure 1: CMR image of myocardial infarction. Adapted from[116]

(A) T2-weighted cardiac magnetic resonance image. (B) Computer-aided signal intensity analysis of the T2-weighted image. (C) Contrast-enhanced image. (D) Computer-aided signal intensity analysis of the contrast-enhanced image. The comparison of edema (area at risk) (A, B) with necrosis (C, D) shows no relevant myocardial salvage.

2.1.6.3.4 Nuclear Medicine Scans

Nuclear medicine scans in cardiac eg. single proton-emission computed tomography (SPECT) and positron-emission tomography (PET), is a novel technique of molecular imaging, which provides functional aspects imaging and aim to analyse pathological processes at a molecular and cellular level.[117] Either SPECT or PET are promising modality for measuring AAR and final infarct size, in particular in patients with CMR contraindications.[118] Currently these methods are mainly used in research studies and not in clinical routine.

The 18F-fluorodeoxyglucose (FDG) is one of the clinical cardiac PET tracers for cardiomyocyte metabolism and viability.[117] It is the most effective way to measure glucose metabolism within cardiomyocytes alongside myocardial perfusion[117] and as a novel biosignal of myocardial injury. There is the intense 18F-FDG uptake in areas with transmural scar[119] or at recent plaque rupture[120] in patients with AMI. The combination of an 18F-FDG-PET metabolic scan together with a perfusion scan can distinguish infarcted and viable myocardial tissues.[121] Although promising further evidence is needed before these imaging modalities e.g. 18F-FDG-PET are used in the clinical setting.

2.1.6.4 Coronary Artery Angiography

Coronary angiography is regarded as the gold standard for the diagnosis of CHD, especially plays an irreplaceable role in the diagnosis and treatment of STEMI.[2] For the sake of guiding therapy in the appropriate clinical context, it is necessary to perform coronary angiography as soon as possible in patients with high suspicion of STEMI.[6, 122] In cases of failed fibrinolysis, or if there is evidence of reocclusion or reinfarction with recurrence of ST-segment elevation, immediate angiography and rescue PCI should be considered.[2, 123] Early angiography with subsequent PCI in a time-window of 2–24 h after successful fibrinolysis is recommended.[2] Transradial or transfemoral approaches are both safe and effective access routes. Nevertheless, the radial approach is the preferred way for experienced radial operators, in that transradial approach presents the lower rate of local vascular complications, a reduction in major bleeding, as well as decrease adverse clinical events and all-cause mortality.[124-127]

2.1.7 Treatment and Management of ST-segment Elevation Myocardial Infarction

With the increasing public awareness, symptoms of AMI should be recognized rapidly. In hospitals and EMS participating in the care of STEMI patients, the goal is to reduce the delay between FMC and STEMI diagnosis to ⩽10 min.[2] When STEMI diagnosis is made in the pre-hospital setting (EMS), immediate activation of the catheterization laboratory not only reduces treatment delays but may also reduce patient mortality.[52, 128] The reperfusion strategy of STEMI patients should follow the ESC guidelines according to ischaemic time (Figure 2).

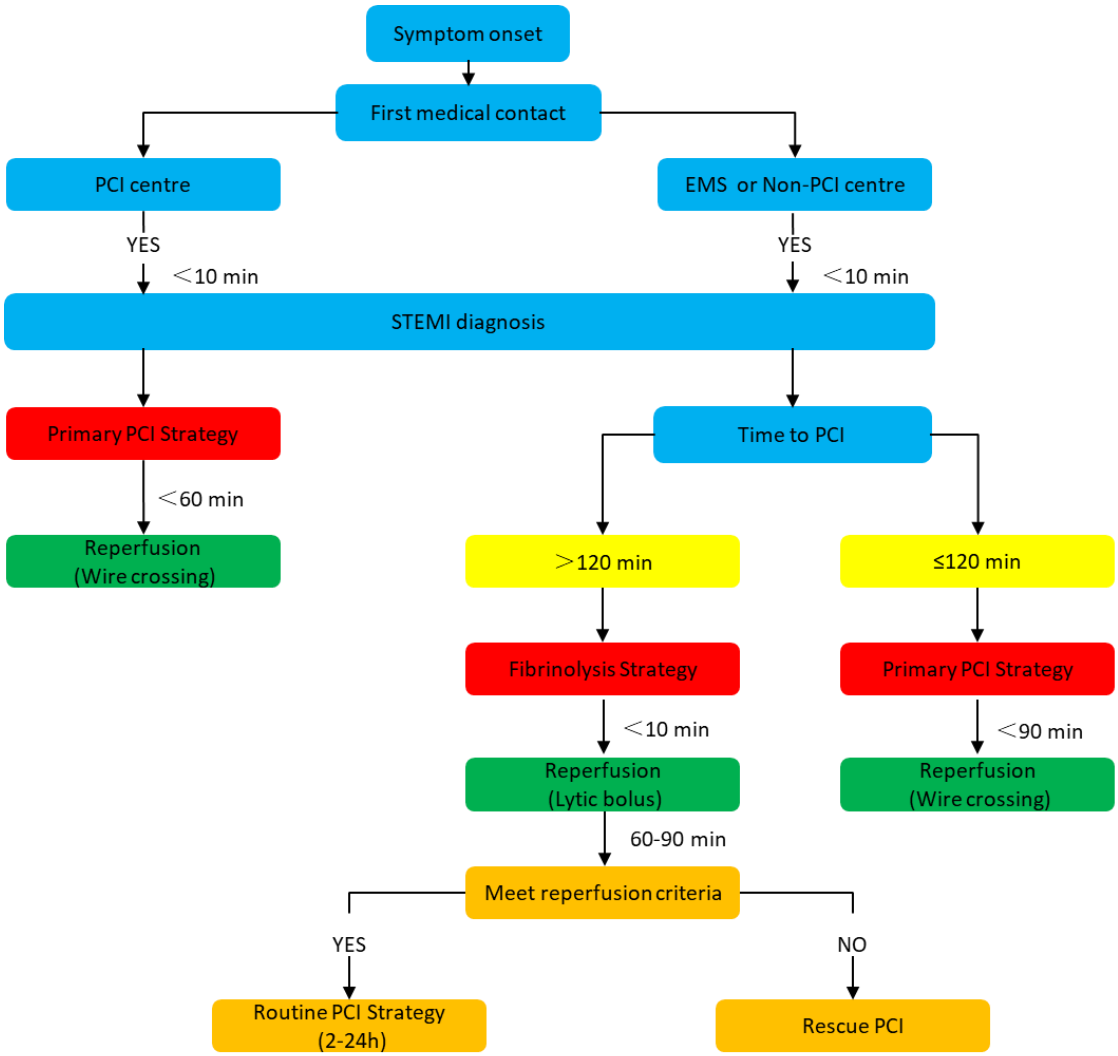

Figure 2: Components of the ischaemic time, delays of initial management, and flowchart for selection of reperfusion strategy. Adapted from[2]

EMS = emergency medical system, FMC = first medical contact, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction.

2.1.7.1 Reperfusion Therapy

2.1.7.1.1 Primary Percutaneous Coronary Intervention Strategy

Primary PCI is the preferred reperfusion strategy in patients with STEMI within 12 h of symptom onset, provided it can be performed in 120 min from STEMI diagnosis in PCI-capable centers.[2] Complete revascularization in single- or multi-stage procedures either during the hospitalization or after discharge was associated with a lower risk of MACE in STEMI patients with multivessel disease and stable haemodynamics.[129] It is reasonable to undergo culprit-only revascularization in patients who had multivessel disease and AMI with cardiogenic shock.[130] Thrombus aspiration is not recommended as a routine procedure in primary PCI anymore, while it may be considered for patients with high-thrombus burden confirmed by angiography.[131] In primary PCI, drug-eluting stents (DES) are recommended as the default strategy for the lower risk of target vessel revascularization, restenosis, stent thrombosis and target vessel-related reinfarction as compared with BMS.[132, 133]

2.1.7.1.2 Fibrinolysis Strategy

There are three major classes of fibrinolytic drugs: urokinase (UK), streptokinase (SK), and tissue plasminogen activator (tPA). TPA are selective plasminogen activators, which are novel thrombolytic drugs for coronary and cerebral vascular clots. The family of tPA includes reteplase, alteplase, and tenecteplase.[134] Starting fibrinolytic therapy within 10 min from STEMI diagnosis is recommended within 12 h of symptom onset if primary PCI cannot be performed within 120 min. The criteria for successful thrombolysis are as following: ST-segment resolution > 50% at 60–90 min; typical reperfusion arrhythmia; and disappearance of chest pain. It is recommended that angiography in 2–24 h after successful lysis is required and immediate angiography and rescue PCI is indicated in STEMI patients with failed fibrinolysis.[2] A pharmacoinvasive strategy that combines thrombolysis with PCI in early phase after the onset of symptoms yields similar early and 1-year survival rates as compared with those of primary PCI.[135]

2.1.7.1.3 Coronary Artery Bypass Graft Surgery

Coronary artery bypass graft surgery (CABG) is rarely used in the early stage of STEMI. Emergent CABG surgery should be recommended for patients with failed PCI or unsuitable coronary anatomy for PCI, extensive area of myocardial infarction or cardiogenic shock, as well as essential surgical repairment of myocardial infarction related mechanical complications, for instance, ventricular septal, papillary muscle, or free-wall rupture.[2, 6]

2.1.7.2 Hospitalization Management

On the basis of rapid modification in haemodynamics, high incidence of complications and serious comorbidities of liver and kidney, the patients with STEMI as well as post-interventional surgery should be admitted to a coronary care unit (CCU) / intensive coronary care unit (ICCU) or equivalent unit where continuous monitoring and specialized care can be provided. ECG and haemodynamic monitoring for STEMI patients at least 24 hours after symptom onset is necessary, and longer monitoring should be considered in patients with unstable situations or may associate with MACE.[2]

Relief of pain is of top priority, not only for comfort reasons but also because persistent chest pain is related to activation of sympathetic nerve, which causes vasoconstriction and increases the ventricular loading conditions in myocardial infarction.[2, 4] Oxygen therapy can relieve hypoxaemia or dyspnea in patients with SaO2< 90% or PaO2< 60 mmHg. Rest and anxiety reduction are beneficial to symptom control and recovery for patients with AMI.[2, 6]

2.1.7.3 Pharmacological Therapy

2.1.7.3.1 Anticoagulation

UFH is one of the most widely used anticoagulants, and more important that it is primarily recommended as an anticoagulant strategy for primary PCI.[19] The standard recommendation of dose in PCI procedures is 70–100 IU/kg or 50-70 IU/kg in combination with a glycoprotein (GP) IIb/IIIa inhibitor, while the dosage in the periprocedural period is adjusted according to the therapeutic levels of activated clotting time (target range of 250-350 s or 200-250 s if a GP IIb/IIIa inhibitor is given).[2, 6, 19]

In contrast to UFH, enoxaparin which has a predictable dose-effect relationship, a lower risk for heparin-induced thrombocytopenia (HIT), and convenient usage that does not need to monitor activated clotting time, is considered as an anticoagulant for PCI in patients

pre-treated with subcutaneous enoxaparin. Enoxaparin was recommended in the new ESC guidelines, in that it manifests the lower mortality and bleeding outcomes compare with UFH during PCI and particularly in STEMI patients undergoing primary PCI.[2, 19, 136]

Bivalirudin may be considered as an alternative to UFH in selected cases,[19] and it is reasonable to use bivalirudin in patients with heparin-induced thrombocytopenia.[2, 6] In recent trails, Bivalirudin was associated with a similar incidence of all-cause death, ischaemic events, and bleeding after PCI in ACS as compared with UFH when limited use of GP IIb/IIIa inhibitors.[137, 138] Bivalirudin had a significant increase in the risk of stent thrombosis and a significant decrease in bleeding risk contrast to unbalanced use of GP IIb/IIIa inhibitors in conjunction with UFH. As compared with heparin plus glycoprotein IIb/IIIa inhibitors in patients with STEMI who are undergoing primary PCI, bivalirudin monotherapy is related to comparable 30-day rates of mortality and significantly reduced 30-day rates of major bleeding and net adverse clinical events, but at the cost of a significantly increased risk of early stent thrombosis.[139]

2.1.7.3.2 Antiplatelet Therapy

Dual antiplatelet therapy, a combination of aspirin and a P2Y12inhibitor, is the keystone of AMI, particularly in preventing reinfarction and coronary stent thrombosis.[140]

- **Aspirin**

Aspirin is an irreversible inhibitor of prostaglandin-endoperoxide synthase (COX) enzymes that produce prostaglandin and thromboxane precursors, and the antiplatelet effect root in preventing further synthesis of thromboxane by disrupting the function of COX-1 and COX-2.[141] The international guidelines recommend a loading dose of 325 mg and/or 500mg of aspirin treatment as early as possible at the point of FMC and a maintenance dose continued indefinitely in patients undergoing primary PCI without serious contraindications.[2, 6]

- **P2Y12 Inhibitor**

To achieve stable efficacy, loading doses of P2Y12 inhibitors are provided before or at the time of primary PCI.[6] It is recommended that dual antiplatelet therapy (DAPT) with novel P2Y12 inhibitors for 1 year after PCI for ACS patients,[2, 6, 140] and pay more attention to

patients with a high risk of bleeding and anemia.[2] The novel types of P2Y12 inhibitor are clopidogrel, cangrelor, prasugrel and ticagrelor. The preferred P2Y12 inhibitor is prasugrel for AMI, which has a shorter onset time, greater potency, and better clinical outcomes.[2, 142, 143]

Clopidogrel: Clopidogrel is a classical thienopyridine. In the 2017 ESC STEMI guidelines, clopidogrel was recommended in stable coronary artery disease patients undergoing coronary stent implantation or as an alternative treatment for ACS patients when prasugrel and ticagrelor are not available or there are contraindications.[2, 140] High loading doses (600 mg) of clopidogrel has been demonstrated to achieve more extensive and rapid platelet inhibition,[144] and 75 mg maintenance dose is recommended.[140]

Prasugrel: Prasugrel is a novel thienopyridine, which achieves a more timely, more effective, and more consistent degree of inhibition of platelet aggregation, as well as lower rates of ischemic events than clopidogrel. To a certain extent, prasugrel administration was related to an increased risk of major bleeding, including fatal bleeding.[142] Prasugrel is contraindicated in the patients with a history of cerebrovascular events, and it also not suitable for patients whose aged ≥75 years or weigh <60 kg.[2, 6, 140] In addition, it is not recommended that prasugrel administrates in patients with ambiguous coronary anatomy or without a clear indication for PCI.[140] In the recent ISAR-REACT-5 trial prasugrel has proven to be more effective to reduce major cardiovascular events as compared to ticagrelor.[145]

Ticagrelor: Ticagrelor is a novel reversibly binding P2Y12 receptor antagonist without active intermediate metabolites. As compared with clopidogrel, ticagrelor represents a lower rate of the compositive death from vascular causes, myocardial infarction, or stroke and no significant difference in major bleeding.[143] It is indicated that the sooner the ticagrelor therapy starts after the indication for PCI is established, the lower rates of definite stent thrombosis are in patients with NSTEMI.[146]

- **GP IIb/IIIa Receptor Antagonists**

It is reasonable to administer GP IIb/IIIa inhibitors in selected patients with angiographic evidence of large thrombus burden or no-reflow in patients with STEMI. However, the

routine use of GP IIb/IIIa inhibitors during primary PCI or pre-hospital routine upstream use before primary PCI are not recommended.[2, 139]

- **Beta-Blockers**

Beta-blocker treatment was associated with a reduction in the incidence of acute malignant ventricular arrhythmia and myocardial reinfarction in patients undergoing fibrinolysis[147, 148], as well as a decline rate and extent of MVO in patients undergoing primary PCI[149]. There are positive effects of beta-blockers for patients who have ongoing ischemia or with myocardial infarction complicated by HF or LV dysfunction, and it demonstrates a reduced rate of mortality in patients with long-term beta-blocker treatment.[148, 150-152]

Oral beta-blockers should be considered within the first 24 h in patients with STEMI who do not have any of the following: hypotension, acute HF or evidence of a low output state, increased risk for cardiogenic shock, or other contraindications to use of oral beta-blockers (PR interval more than 0.24 seconds, second- or third-degree atrioventricular block or severe bradycardia, active asthma, or reactive airways disease).[2, 6]

- **Lipid Management**

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, are the preferred and most effective lipid-lowering drugs. Reduction in low-density lipoprotein cholesterol (LDL-c) with statin therapy in patients after an ACS reduces the incidence of heart attack, the risks of cardiovascular death, non-fatal myocardial infarction, ischaemic stroke, and coronary revascularization.[153, 154] It is reasonable to obtain statins in all patients with AMI within 24 hours, particular in STEMI, regardless of the cholesterol concentration at presentation.[2, 6] It is recommended that the treatment goal is an LDL-c concentration of < 1.8 mmol/L (<70 mg/dL) or a reduction of at least 50% in LDL-c if the baseline LDL-c level is 1.8–3.5 mmol/L.[155, 156] In patients known to be intolerant of any dose of statin, or cholesterol is not up to standard after adequate statin obtainment, treatment with ezetimibe or PCSK9 inhibitors should be considered.[2, 156]

- **Nitrates**

For patients with severe angina pectoris, nitrates can reduce LV afterload and increase coronary artery perfusion, to relieve angina pectoris. It is reasonable to administer nitrates

during the acute phase in STEMI patients with hypertension or HF, without existing contraindications of hypotension, right ventricular infarction, or use of phosphodiesterase type 5 inhibitors in the previous 48 h.[2, 6]

- **Angiotensin-converting Enzyme (ACE) Inhibitors and Angiotensin II Receptor Blockers**

Oral angiotensin-converting enzyme (ACE) inhibitors can effectively reverse ventricular remodeling and are the cornerstone of HF treatment, which are associated with a reduction of fatal major cardiovascular events and the rate of rehospitalization in patients with STEMI.[157-159] ACE inhibitors are recommended in patients with anterior myocardial infarction, or an impaired LVEF (≤40%) or who have experienced HF in the early phase, prior myocardial infarction, and tachycardia.[2, 6] Angiotensin II receptor blockers (ARB) are indicated for patients who are in the presence of contraindications or intolerance of ACE inhibitor.

2.1.8 Prognostic Markers of Myocardial Infarction

In the early phase of STEMI, concentrating resources to prevent and treat cardiac complications is of great significance to the excellent late cardiac prognosis.[160] More profound ST-segment shifts or T wave inversions in multiple leads which indicate extensive myocardial ischaemia, primary PCI in multivessel CAD, and persistent life-threatening ventricular arrhythmias after STEMI, are all associated with a negative prognosis.[6] Women have a higher rate of peri-procedural myocardial infarctions and major bleedings undergoing PCI compared to men, and female gender remains an independent predictor for 1-year mortality or HF hospitalization.[49, 50]

In AMI, the extent of myocardial damage is significant associated with prognosis. The concentrations of cardiac troponin in peripheral blood at one or several time points may assess the extent of the myocardial necrosis,[161] and it also provides prognostic information in addition to early assessment of cardiac function and volumes with regard to the risk of chronic left-ventricular dysfunction and adverse remodeling.[162] Infarct size assessed by CMR or technetium-99m sestamibi SPECT early after primary PCI is a strong independent predictor of all-cause mortality and would be useful as an endpoint in clinical trials or as an

important prognostic measure in patients with STEMI.[163] Reduced LVEF is strongly associated with death or HF hospitalization in patients with STEMI undergoing primary PCI after 6-12 months of clinical follow-up.[50]

The presence of no-reflow is a serious prognostic sign. No-reflow, which would be reduced by a pre-procedural loading dose of UFH and/or P2Y12 inhibitor administration,[164] can result in poor healing of the myocardial infarction[165] or adverse LV remodeling,[166] and it is also highly predictive of in-hospital mortality.[164]

Other established factors influencing the mortality in STEMI patients are advanced age, Killip class (see Table 2), time delay to treatment (see section 2.1.7), presence of EMS-based STEMI networks (see section 2.1.2.4), treatment strategy,[167] history of MI, diabetes mellitus,[168, 169] renal failure,[169, 170] and the number of diseased coronary arteries.[171]

2.2 Morphine

Morphine, as one of the opioid receptor agonists, has been used for more than two centuries to relieve human pain. In 1806, a German pharmacist named Friedrich Wilhelm Sertürner isolated a pharmacological alkaloid in opium for insomnia treatment and named it morphine after Morpheus--the god of dreams in Greek mythology. With the development of nearly 40 years, morphine began to be used for minor surgical procedures, postoperative and chronic pain, even as supplementary means of general anesthetics.[172] With the increasing acceptance of doctors, morphine plays an important role in analgesics to relieve severe pain caused by any kind of disease. It is also widely used in patients with acute symptoms concerned with myocardial ischaemia, especially those unresponsive to nitrates, and recommended in the conventional treatment of pain, anxiety, and pulmonary edema in STEMI.[2, 5, 6]

2.2.1 Pharmacodynamics

Morphine is a phenanthrene alkaloid with a pKa of 7.9 and consists of five condensed rings (Figure 3). The C3 phenolic and the C6 secondary alcoholic group, together with the amino group are effective chemical active sites of morphine molecule. The two hydrophilic -OH groups respectively locate on C3 and C6 give morphine ability of water-soluble.[173]

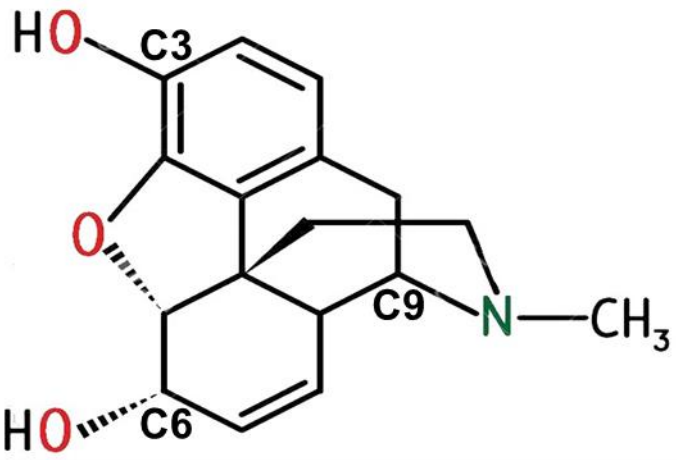

Figure 3: The chemical structures of morphine. Adapted from[173]

There are four most important opioid receptor families, the μ-, κ-, δ-, and nociceptin or orphanin FQ receptor (NOP).[174, 175] Opioid receptors locate not only in the nervous system, but are also widely distributed in many peripheral tissues throughout the human body or some animal species, including the heart, lungs, liver, gastrointestinal or reproductive tracts.[176, 177] Morphine is a prototypical opioid receptor agonist, exerting action mainly through a specific interaction with subtypes of major opioid receptors expressed in many tissues. Morphine has the highest affinity to μ-receptor, followed by κ- and δ- receptors, and the mechanisms and pathways involved are very extensive.

Morphine penetrates the blood-brain barrier (BBB) to reach the brain parenchyma and spinal cord, restraining the pain area of the cerebral cortex, and exert a strong analgesic effect. It can stimulate μ opioid receptor of central nervous system and produce pharmacological action by simulating the action of endogenous antinociceptive substance opioid peptides. At the cellular level, morphine reduces calcium ion entry, thus also reducing the release of presynaptic neurotransmitters such as substance P, which is released from primary afferents in the dorsal horn.[178] It is effective for all kinds of pain, and it is better for persistent dull pain than intermittent sharp pain and visceral colic.

When it comes to the cardiovascular system, morphine can promote the release of endogenous histamine and dilate peripheral blood vessels, thereby reducing blood pressure, slowing down heart rate, and relieving anxiety admittedly, which makes the patient feel peaceful and may decrease myocardial oxygen demand. In the meantime,

morphine has an obvious sedative effect or produces euphoria timely, which can decrease the tension of patients with pain.[179, 180]

Morphine has an inhibitory effect on the respiratory center and cough center, while has an excitatory effect on skeletal muscle and smooth muscles such as biliary tract, ureter, bronchus, and increases its tension.

There are two major metabolites of morphine in vivo, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), which are the products of morphine glucuronidation in the liver (Figure 4). It is suggested that M3G as a functional antagonist of the antinociceptive effects of morphine lacks analgesic properties, but M6G is an effective analgesic.[173, 178, 181, 182] Compared to the analgesic actions of morphine and its 6 beta-glucuronide metabolite in animal models, M6G has higher intrinsic activity, more potency, and stronger central analgesia, and it is also continuously available to bind at opioid receptors rapidly.[183-185]

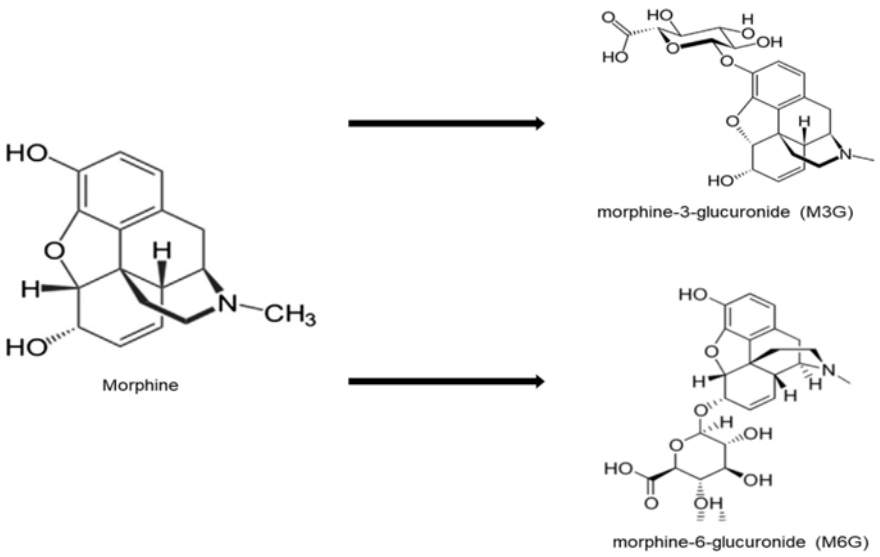

Figure 4: The chemical structures of morphine and two major metabolites. Adapted from[186]

2.2.2 Pharmacokinetics

The estimated median plasma-effect site equilibration half-life (t½ke0) of morphine was 2.8 hours.[178] The half-life of morphine is 15.1 ± 6.5h, and the metabolites (M3G and M6G) are 11.2 ± 2.7h and 12.9 ± 4.5h after oral administration, respectively.[187]

After oral administration, morphine is almost completely absorbed from intestine rather than in the stomach, where morphine is mainly ionized in an acid environment and difficult

to absorb.[188, 189] The alkaline medium plays a significant role in the absorption of morphine, and the jejunum and duodenum, which have been demonstrated by animal models, is the fastest absorption site.[188]

Only a small part of morphine absorbed by the intestine reaches the target tissue. Extensive hepatic first-pass elimination resulting in oral bioavailability of morphine is low and variable.[187, 189, 190] Morphine is primarily metabolized in the liver by enzymes called uridine diphosphate glucuronosyltransferase (UGT) enzymes, which is a phase II metabolism enzyme family with several isoforms.[191] Whether oral or intravenous administration, on average for 60% of morphine dose is converted to M3G, approximately 10% to morphine- 6-glucuronide (M6G), 10% is unchanged and 20% as unidentified residual clearance.[187]

Since the liver, with UGT enzymes activity, is the predominant metabolic site for the glucuronidation of morphine, the impairment of liver function may lead to the change of morphine metabolism. In contrast to healthy volunteers, the patients with liver insufficiency have slower total body clearance and also show a prolonged terminal half-life of unchanged morphine after administration.[192] Morphine and its metabolites are mainly excreted by the kidney. In patients with renal failure, the renal excretion of morphine was found to be very low[193] and It is also demonstrated that the accumulation of morphine metabolites is substantial.[193, 194] Morphine can also be excreted through bile. A portion of morphine and its metabolites are excreted via the bile into the intestinal tract and then transformed into prototypes by intestinal bacteria after that reabsorbed into the liver, which is called the enterohepatic cycling of morphine.[187, 195, 196] It is also one of the reasonable explanations for 20% unidentified residual clearance.

The metabolism of morphine is also affected by many other factors. As compared with young adults, the plasma clearance of morphine was lower in elderly ones.[197] It may result in longer efficacy or enhanced analgesic efficacy from a given dose of morphine in the elderly patient.[198] Tricyclic antidepressants inhibit the morphine uridine diphosphate glucuronyl transferase (UDPGT).[199] After oral administration in cancer patients, tricyclic antidepressants have a significant effect on increased morphine bioavailability and prolong the half-life of morphine.[200]

2.2.3 Side effects and Contraindications

According to the evaluation of relevant studies, there is about 78% incidence of side effects in non-cancer pain patients who are administrated opioid drugs, including morphine.[201, 202] Owing to the wide variety of affection on tissues and receptors, there are numerous side effects of morphine. Consequences of morphine administration may include not only the wanted effect of antinociception, analgesia, and sedation, but also the unwanted side effects of hypotension, respiratory depression, nausea/vomiting, reduced gastrointestinal motility or constipation, miosis, euphoria, alterations of the endocrine and autonomic nervous system, pruritus, and flushing of the skin. The most prevalent is postoperative nausea and vomiting (PONV), and the younger patients are more likely to report PONV and pruritus, in addition, females also reported significantly more often nausea/vomiting and pruritus than men.[203] Among them, the most serious side effects are hypotension and respiratory depression. Patients with more severe American Society of Anesthesiologists class classifications are more likely to experience postoperative side effects of respiratory depression.[203] When using morphine to relieve pain in ACS patients, physicians must be aware that hypotension is a common side effect of morphine.

Contraindications for the administration of morphine are listed in Table 4.

Table 4: Major contraindications of morphine. Adapted from[204].

Major morphine contraindications
In patients with severe respiratory depression in the absence of resuscitative equipment
In patients with acute or severe bronchial asthma or hypercarbia
In patients with chronic pulmonary heart disease at cardiopulmonary failure stage
In any patient who has or is suspected of having a paralytic ileus
In patients with shock has not been controlled or severe hypotension
In patients with concurrent use of monoamine oxidase inhibitors (MAOIs)

In patients with known hypersensitivity reaction to morphine or other opioids
In patients with a history of substance misuse of morphine
In patients with pregnant or lactating

2.2.4 Cardiovascular effects of morphine and potential side effects

P2Y12 receptor antagonists, concurrently administered with aspirin in what has come to be commonly called dual antiplatelet therapy, are a mainstay of treatment for patients with ACS, from the acute phase until at least 12 months after the index event. Morphine, on the contrary, is a nonessential but commonly used drug in the acute phase of ACS to relieve pain—with the added potential benefit of attenuating acutely raised sympathetic tone. In current guidelines though morphine is recommended with decreasing strength of recommendation, one of the reasons being raised concerns regarding the potentially significant drug-to-drug interactions with antiplatelet agents, leading to impaired inhibition of platelet activation. In any case, it is still considered a mandatory part of the inventory of available medications in prehospital AMI management.

The drug-drug interactions between clopidogrel and morphine were illustrated in small-scale trials. Morphine administration delays clopidogrel absorption, decreases plasma levels of clopidogrel active metabolite, and retards and diminishes its effects, which can lead to treatment failure in susceptible individuals.[205] In the IMPRESSION trial, a single-center, randomized, and double-blind trial, morphine (5 mg)/placebo was used after a 180 mg loading dose of ticagrelor in patients with myocardial infarction. It concluded that morphine administration was associated with lower the total exposure to ticagrelor and its active metabolite by 36% ($AUC_{(0-12)}$: 6307 vs. 9791 ng h/mL; P=0.003), and 37% ($AUC_{(0-12)}$: 1503 vs. 2388 ng h/mL; P=0.008), respectively, with a concomitant delay in maximal plasma concentration of ticagrelor (4 vs. 2 h; P=0.004). In contrast to the placebo group, there was a greater prevalence of high platelet reactivity in patients receiving morphine.[8] Morphine use was the independent predictor of high residual platelet reactivity (HRPR) at 2 h (odds ratio [OR]: 5.29; 95%CI: 1.44 to 19.49; p=0.012) in patients with STEMI undergoing primary PCI with bivalirudin monotherapy co-administration 60 mg prasugrel

loading dose or 180 mg ticagrelor in RAPID (Rapid Activity of Platelet Inhibitor Drugs) Primary PCI Study.[206] In the following trail, it also had been demonstrated that morphine use delayed the onset of action of prasugrel and ticagrelor in patients with STEMI.[207]

Of note, although morphine may delay the absorption of P2Y12 and attenuate its action, as yet it is unclear whether it also leads to increased thrombotic events in patients with STEMI. In a small pharmacokinetic study, morphine significantly decreases the maximal plasma concentrations of prasugrel active metabolite, nevertheless, it does not diminish its pharmacodynamic effects on platelets to a clinically relevant degree in healthy volunteers.[208] Likewise, there is a similar impact on ticagrelor co-administrated with morphine.[209] A recent trial suggests that co-administration of metoclopramide in patients presenting with unstable angina and treated with morphine has a beneficial effect on the PK/PD profile of ticagrelor and its metabolite.[210]

However, previous studies reported inconsistent results regarding the effect of morphine on P2Y12 receptor antagonists in ACS patients or healthy volunteers. The impacts of morphine on metabolization of P2Y12 receptor antagonists were measured by pharmacodynamics /pharmacokinetics, while whether delaying absorption or attenuation action of P2Y12 may cause larger myocardial infarction, extent of MVO, suboptimal reperfusion, or even poor prognosis/outcomes is currently unclear.

3. STUDY AIM and RATIONALE

As the current evidence regarding the effect of intravenous morphine administration on reperfusion injury and/or cardioprotection in patients with AMI is conflicting and unclear, the aim of this study was to evaluate the impact of morphine administration, on infarct size and reperfusion injury assessed by CMR in a large multicentre STEMI population.

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4. METHODS

This current study was a predefined sub-study of the AIDA STEMI trial (Abciximab Intracoronary versus Intravenously Drug Application in STEMI), a randomized, open-label, multicenter trial performed in 22 centers in Germany, which compared the effect of intracoronary abciximab versus intravenous abciximab bolus on clinical outcome in patients with STEMI. In the trial, patients presenting with STEMI in the previous 12 h after symptom onset with no contraindications for abciximab were randomly assigned in a 1:1 ratio to intracoronary versus intravenous abciximab bolus administration (0.25 mg/kg bodyweight) during PCI, with a subsequent 12 hours intravenous infusion at 0.125 µg/kg per minute (maximum 10 µg/min). Patients were randomly divided into two groups and assigned intracoronary abciximab (n=1032) or intravenous abciximab (n=1033). In contrast to intracoronary, intravenous abciximab resulted in a similar rate in the combined endpoint of death, reinfarction, or congestive HF and did not display significate difference in infarct size, reperfusion injury.[116, 211]

In the AIDA STEMI trial substudy, morphine administration before or during primary PCI was prospectively recorded and patients were divided into two groups according to the treatment with (n=454) versus without (n=280) morphine. The decision of morphine administration was according to the symptom of patients and was made by the emergency physician and/or the treating cardiologist. The trial was conducted in accordance with the principles of the Declaration of Helsinki and was approved by national regulatory authorities and ethics committees of participating centers. All patients provided written informed consent.

4.1 Inclusion Criteria

For inclusion in the study subjects fulfillment of all the following criteria is obligatory:

1) Age ≥18 years;
2) STEMI >30 minutes and <12 h after symptom onset;
3) ST-segment elevation >1 mm in ≥2 limb leads and/or ST-segment elevation >2 mm in ≥2 adjacent precordial leads of the ECG;

4) Provision of informed consent.

4.2 Exclusion Criteria

Subjects will not enter the study if any of the following exclusion criteria are fulfilled:

1) Pregnancy;
2) Known allergy to abciximab, aspirin, or heparin;
3) Contraindications to abciximab such as active gastroduodenal ulcer;
4) History of major surgery within the previous 4 weeks;
5) Active internal bleeding;
6) Stroke within the previous 2 years;
7) Known coagulation defects;
8) Severe liver insufficiency;
9) Renal insufficiency necessitating dialysis;
10) Uncontrolled hypertension;
11) Hypertensive retinopathy;
12) Vasculitis;
13) Thrombolysis within the previous 12 h;
14) Without informed consent;
15) Participation in another trial.

Exclusion criteria for the CMR substudy are:

1) Severe claustrophobia;
2) Hemodynamic instability;
3) Pacemaker or internal cardioverter defibrillator;
4) Metallic cerebral or intracranial implants;

5) Known allergy to gadolinium;

6) Severe renal insufficiency (creatinine clearance <30 mL/min).

4.3 Cardiac Magnetic Resonance Imaging

The CMR images were performed in 8 heart centers with proven expertise in performing CMR examinations in patients with AMI. According to a standard infarction protocol, CMR was performed on days 1 to 10 after the index event for the assessment of myocardial salvage, infarct size, presence and extent of MVO, LVEF and LV volumes.

The CMR imaging was performed on a 1.5 or 3.0 T scanner (Siemens Magnetom Verio (3 T), Siemens, Germany; Siemens Avanto (1.5 T), Siemens; Siemens Symphonie (1.5 T), Siemens; Phillips Intera, CV (1.5 Tesla), Philips Medical Systems, The Netherlands; GE Signa Excite (1.5 T), General Electric, USA). Cardiac cine sequences were used to measure the parameters of LV function and volume, and T2-weighted imaging for the assessment of the AAR, and delayed enhancement imaging for the calculation of infarct size and MVO. CMR images were stored on media and sent to the CMR core laboratory at the University of Leipzig Heart Center (Leipzig, Germany) for blinded assessment.

LVEF and end-diastolic/end-systolic volumes were calculated from the short-axis cine views by manual analysis. Infarct size was measured by manual delineation in each of the short axis delayed enhancement images. Extent of MVO in early and delayed images was determined similarly by manual drawing of the infarcted and obstructed area. Infarct size, AAR, and MVO were expressed as a percentage of LV volume. Salvaged myocardium was quantified as the difference between the volume of increased T2-signal (AAR) and the volume of delayed enhancement (infarct size). The parameters were calculated as follows:

1. Area at risk = volume edema/volume LV mass*100
2. Percentage infarct size = volume infarct/volume LV mass*100
3. Percentage microvascular obstruction = volume microvascular obstruction/volume LV mass*100
4. Myocardial salvage = area at risk − infarct size

5. Myocardial salvage index = area at risk − infarct size/ area at risk

6. LV ejection fraction = stroke volume/end-diastolic volume*100

4.4 Primary Endpoint and Secondary Endpoint

4.4.1 Primary Endpoint

The primary endpoint of this study was infarct size and MVO assessed by CMR as a marker of reperfusion injury between the two groups.

- Infarct size assessed by CMR at day 1-10 after myocardial infarction.
- MVO assessed by CMR at day 1-10 after myocardial infarction (presence and extent).

4.4.2 Secondary endpoint - Clinical Outcome

The secondary endpoint was the time to MACE, nonfatal reinfarction, and new congestive HF at 12 months after infarction. All parts of the clinical endpoints were adjudicated by a Clinical Endpoints Committee (CEC) blinded to the patient's assigned treatment. The assortment definitions of endpoints were elaborated as follows:

- MACE was defined as the time from randomization to the occurrence of the composite of all-cause death.
- Reinfarction occurring < 24 hours after the index event was defined as symptoms > 30 minutes in duration plus new ST-segment elevation > 1 mm in ≥2 contiguous leads. Reinfarction > 24 hours after the index event was considered if symptoms of > 30 minutes in duration occur in combination with an increase of creatine kinase–MB level (or troponin I or T) above the reference limit in patients with normalized values or if there was an increase of at least 50% from the last nonnormalized measurement.
- New congestive HF was defined as any new diagnosis of congestive HF ≥24 hours postrandomization with ≥1 condition requiring treatment with diuretics: (a) cardiogenic shock, (b)pulmonary edema or congestion on chest x-ray, (c) rales > 1/3 from lung base (Killip class ≥2), (d) pulmonary capillary wedge pressure > 25 mm Hg, and (e)

dyspnea with oxygen saturation $< 90\%$ without supplemental oxygen and absence of lung disease.

4.5 Statistical Analysis

Baseline patient characteristics, procedural details, and CMR findings are described according to the presence or absence of morphine administration. To adjust for other potential confounding factors, we performed additional matching for age (+/− 3 years) and cardiovascular risk factors (hypertension, diabetes mellitus). Most continuous variables were not normally distributed and are therefore presented in medians and interquartile range (IQR). All categorical variables were calculated as number and percentage of patients. For comparison of categorical variables between groups, Fisher exact test or the chi-square test was used. For comparison of continuous variables with normal distribution, student's t-test was used, and for non-normally distributed continuous data the Wilcoxon rank-sum test was used, as appropriate.

Kaplan-Meier analysis with log-rank testing and Cox proportional hazards regression analysis was used for clinical outcome assessment. Time-to-event rates at the 12-month follow-up in the group were described by means of Kaplan–Meier curves. The function of log-rank test was to compare the differences in survival curve between groups. Univariate and stepwise Cox regression analysis was performed for all variables of Table 5 to identify predictors of MACE within 12 months after randomization. Multivariate regression was performed using only variables with a p-value < 0.05 in univariate regression analyses. Hazard ratios (HR) with 95% CI were calculated for binary outcomes. Statistical significance was considered as p-value < 0.05. Statistical analysis was performed using commercially available software (SPSS version 22.0).

5. RESULTS

We included 734 patients of 795 patients who had available CMR information in the morphine substudy (Figure 5). We excluded 61 patients according to the following reasons: scan termination (n = 7), late gadolinium enhancement (LGE) poor image quality (n = 17), prior infarction (n = 33), and morphine data missing (n = 4). Of these, 454 (61.5%) patients received intravenous morphine (morphine+ group), whereas 280 (38.5%) patients did not receive morphine (morphine- group).

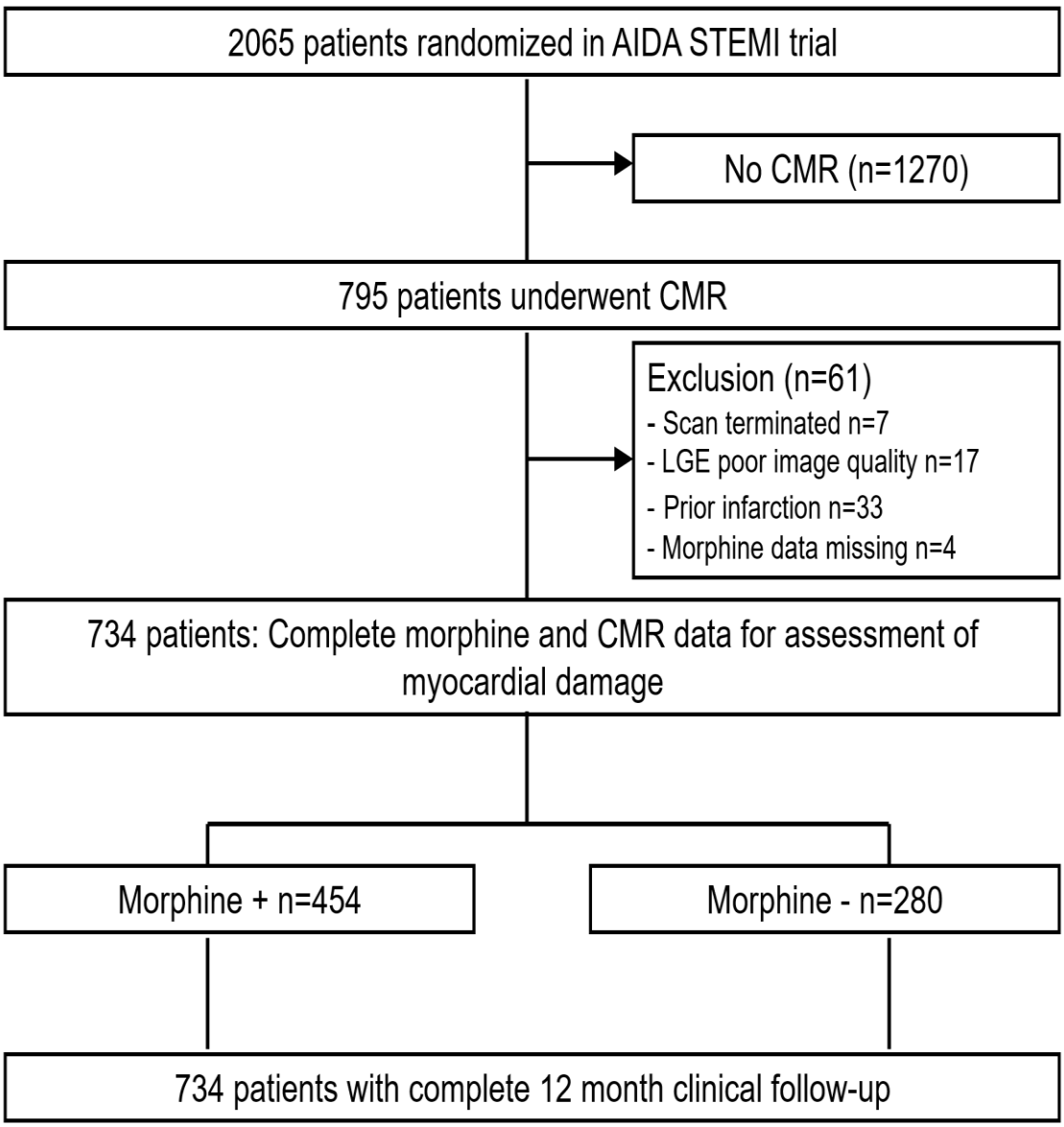

Figure 5: Study flow.

This study was a predefined sub-study of the AIDA STEMI trial (Abciximab Intracoronary Versus Intravenously Drug Application in STEMI). CMR = cardiac magnetic resonance, LGE = late gadolinium enhancement.

5.1 Patients Characteristics

Patients in the two groups were well balanced for baseline characteristics and medication except for age, sex, hypertension, and diabetes mellitus (Table 5). The median age of the total enrolled study group was 62 years (interquartile range 51-71 years), and 555 patients (76%) were men. In contrast to the group without morphine treatment, patients who received intravenous morphine were much younger (66 versus 61 years, $p = 0.03$), and significantly more often male (71% versus 78%, p=0.02). In the morphine treatment group, there was a lower incidence of hypertension (p=0.02) and diabetes (p=0.01), and a shorter symptom onset to PCI hospital admission (p<0.001).

Door-to-balloon-time were similar with a median time from arrival in the emergency department to guidewire crosses the culprit lesion of 30 minutes (interquartile range, 21 to 40 minutes) versus 30 minutes (interquartile range, 23 to 45 minutes; p=0.67), respectively. Compared with patients without morphine, there was no significant difference in the parameter of myocardial necrosis (peak creatine kinase), ECG reperfusion success (ST-segment resolution), and assessment of angiographic makers of reperfusion success (TIMI-flow pre-/post-PCI) or infarct-related artery, and the number of diseased vessels.

Table 5: Patient characteristics

Continuous data are presented as median and interquartile range. ACE = angiotensin-converting enzyme, AT-1 = angiotensin1, BMI = body mass index, CMR = cardiac magnetic resonance, CK = creatine kinase, PCI = primary percutaneous coronary intervention, TIMI = thrombolysis in myocardial infarction.

Variable	Total study n=734	Morphine + n=454	Morphine - n=280	p-value
Age (years)	62 (51 - 71)	61 (51 - 70)	66 (52 - 72)	0.03
Male sex: n (%)	555 / 734 (76%)	356 / 454 (78%)	199 / 280 (71%)	0.02
Cardiovascular risk factors: n (%)				
Current smoking	316 / 670 (47%)	207 / 415 (50%)	109 / 255 (43%)	0.07
Hypertension	488 / 731 (67%)	287 / 452 (64%)	201 / 279 (72%)	0.02
Hypercholesterolemia	258 / 727 (36%)	156 / 450 (34%)	102 / 277 (37%)	0.55
Diabetes mellitus	146 / 731 (20%)	76 / 453 (17%)	70 / 278 (25%)	0.01
BMI (kg/m^2)	27.3 (24.8 - 30.1)	27.5 (25.0 -30.2)	27.0 (24.6 -30.1)	0.31
Anterior infarction: n (%)	343 / 702 (51%)	215 / 439 (49%)	128 / 263 (49%)	0.94
Times (min)				

Symptom onset to PCI hospital admission	180 (109 - 315)	165 (100 - 276)	200 (123 - 404)	**<0.001**
Door-to-balloon-time	30 (22 - 42)	30 (21 - 40)	30 (23 - 45)	0.67
Killip-class on admission: n (%)				0.59
1	650 / 734 (89%)	405 / 454 (89%)	245 / 280 (88%)	
2	50 / 734 (7%)	28 / 454 (6%)	22 / 280 (8%)	
3	17 / 734 (2%)	9 / 454 (2%)	8 / 280 (3%)	
4	17 / 734 (2%)	12 / 454 (3%)	5 / 280 (2%)	
Number of diseased vessels: n (%)				0.76
1	398 / 734 (54%)	251 / 454 (55%)	147/ 280 (53%)	
2	206 / 734 (28%)	125 / 454 (28%)	81 / 280 (29%)	
3	130 / 734 (18%)	78 / 454 (17%)	52 / 280 (19%)	
Infarct related artery: n (%)				0.69
Left anterior descending	328 / 734 (45%)	199 / 454 (44%)	129 / 280 (46%)	
Left circumflex	89 / 734 (12%)	56 / 454 (12%)	33 / 280 (12%)	
Right coronary	314 / 734 (43%)	198 / 454 (44%)	116 / 280 (41%)	
Left main	3 / 734 (0%)	1 / 454 (0%)	2 / 280 (1%)	
TIMI-flow before PCI: n (%)				0.47
TIMI-flow 0	412 / 734 (56%)	246 / 454 (54%)	166 / 280 (59%)	
TIMI-flow I	97 / 734 (13%)	66 / 454 (15%)	31 / 280 (11%)	
TIMI-flow II	119 / 734 (16%)	75 / 454 (16%)	44 / 280 (16%)	
TIMI-flow III	106 / 734 (14%)	67 / 454 (15%)	39 / 280 (14%)	
Thrombectomy: n (%)	111 / 454 (24%)	111 / 454 (24%)	68 / 280 (24%)	0.96
TIMI-flow post PCI: n (%)				0.17
TIMI-flow 0	11 / 734 (1%)	7 / 454 (1%)	4 / 280 (1%)	
TIMI-flow I	19 / 734 (3%)	13/ 454 (3%)	6 / 280 (2%)	
TIMI-flow II	56 / 734 (8%)	27 / 454 (6%)	29 / 280 (10%)	
TIMI-flow III	648 / 734 (88%)	407 / 454 (90%)	93 / 280 (86%)	
Peak Creatine Kinase (µmol/l*s)	26 (12-46)	27 (13-48)	26 (10-43)	0.28
ST-segment resolution (%)	55 (23-78)	58 (25-79)	51 (20-77)	0.12
Concomitant medications: n (%)				
ß-blockers	703 / 732 (96%)	433 / 453 (96%)	270 / 279 (97%)	0.43
ACE-inhibitors/AT-1-antagonist	698 / 732 (95%)	433 / 453 (96%)	265 / 279 (95%)	0.71
Aspirin	734 / 734 (100%)	454 /454 (100%)	280 /280 (100%)	1.00
Clopidogrel, prasugrel or both	734 / 734 (100%)	454 /454 (100%)	280 /280 (100%)	1.00
Statins	699 / 732 (96%)	435 / 453 (96%)	264 / 279 (95%)	0.37
Aldosterone antagonist	88 / 732 (12%)	51 / 453 (11%)	37 / 279 (14%)	0.42
Completion of abciximab infusion	688 / 733 (94%)	429 / 453 (95%)	259 / 280 (93%)	0.94

5.2 Cardiac Magnetic Resonance Imaging Parameters

The median time between the index event and CMR was 3 days (interquartile range, 2 to 4 days) for both groups. Table 6 shows the results of the CMR analysis of all patients. Patients with morphine administration presented a larger LV end-diastolic volume [145ml (IQR 124–174) vs. 141ml (IQR 112–166), p=0.004] in comparison to those without receiving morphine, but the median calculated LV ejection fraction (%) [51 (IQR, 44–58) vs. 50 (IQR, 43–58; P=0.71)] were much the same for the two treatment groups. The median infarct size was 17%LV (IQR 8-25%LV) with no significant differences between groups (17% versus 17%, P=0.67). Similarly, there was no difference in AAR (myocardial edema) (36% versus 35%, P=0.72) between the two groups. Consequently, there were also similar results in myocardial salvage, myocardial salvage index, late MVO (%LV), and LV end-systolic volume (mL) in both groups (all p>0.05, Table 6).

Table 6: Cardiovascular magnetic resonance results

Continuous data are presented as median and interquartile range. CMR=cardiac magnetic resonance, LV=left ventricular, MVO=microvascular obstruction

Characteristic	Total study n=734	Morphine + n=454	Morphine - N=280	p
Area at risk (Edema) (%LV)	35 (25 - 48)	36 (25 - 48)	35 (27 - 48)	0.72
Infarct size (%LV)	17 (8 - 25)	16 (8 - 26)	17 (9 - 24)	0.67
Myocardial salvage (%LV)	17 (9 - 27)	17 (9 - 26)	17 (8 - 27)	0.45
Myocardial salvage index	51 (33 - 69)	51 (32 - 69)	52 (35 - 69)	0.65
Late MVO (%LV)	0.0 (0.0 - 1.8)	0.0 (0.0 - 1.8)	0.0 (0.0 – 1.9)	0.92
LV ejection fraction (%)	51 (44 - 58)	51 (44 - 58)	50 (43 - 58)	0.71
LV enddiastolic volume (mL)	146 (121 - 171)	145 (124 - 174)	141 (112 - 166)	0.004
LV endsystolic volume (mL)	72 (54 - 91)	72 (55 - 93)	71 (52 - 88)	0.18

To adjust for potential confounding factors, we performed additional analysis after matching for age (+/− 3 years) and cardiovascular risk factors (hypertension, diabetes mellitus). We matched 280 pairs of patients with or without morphine administration, and the median ages were 66 years (IQR 51–73 years) and 66 years (IQR 52–72 years), respectively (p = 0.58). As the same as for the unmatched cohort, there were no significant

differences in infarct size (morphine group: 16%LV (IQR 8-26%LV) versus no morphine group 17%LV (IQR 9-24 %LV), p=0.75) and other parameters of CMR between morphine administration and without morphine. In addition, we matched 272 pairs of patients with hypertension and diabetes, and found similar results for infarct size (morphine group: 17%LV (IQR 8-27%LV) versus no morphine group: 17%LV (IQR 9-24%LV), p=0.21) between two groups.

In a pre-specified substudy of our trail, there were 93 patients with reperfusion within 120 minutes/2 hours and TIMI-flow ≤2 pre-PCI, including 59 patients with morphine and 34 patients without morphine. Patients receiving iv morphine in our substudy had significantly less infarct size (p=0.035) as compared to those without IV morphine administration (Figure 6). There was also a considerable lower area of MVO in the group of morphine application (p=0.003) (Figure 7). After we matched the patients within 120 minutes for age (+/− 3 years), the results of infarct size are also significantly different (morphine group: 11%LV (IQR 5-18%LV) versus no morphine group 19%LV (IQR 10-29%LV), p=0.027). For patients with hypertension and diabetes, the morphine administration group had also a smaller infarct size (morphine group: 12%LV (IQR 5-19%LV) versus no morphine group 19 %LV (IQR 10-29%LV), p=0.042) as compared with no morphine group. However, there was no difference in infarct size between with and without morphine groups in patients reperfused in 120 to 360 minutes (p=0.77) or more than 360 minutes (p=0.40).

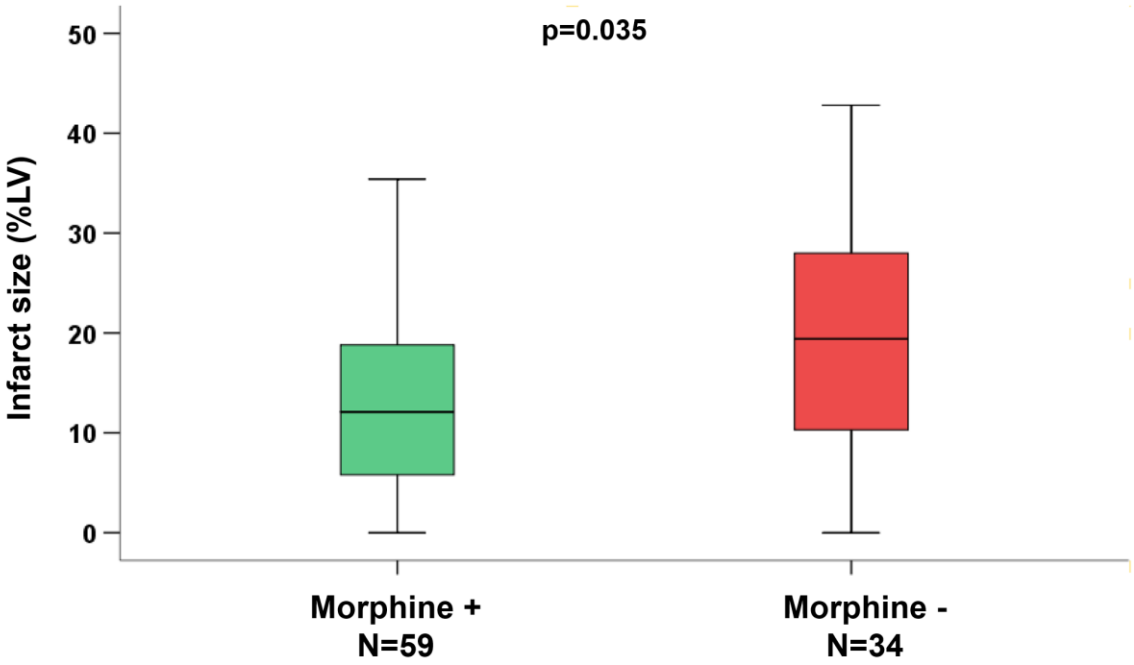

Figure 6: Infarct size in subgroup of patients with reperfusion within 120 minutes and TIMI-flow ≤2 before PCI.

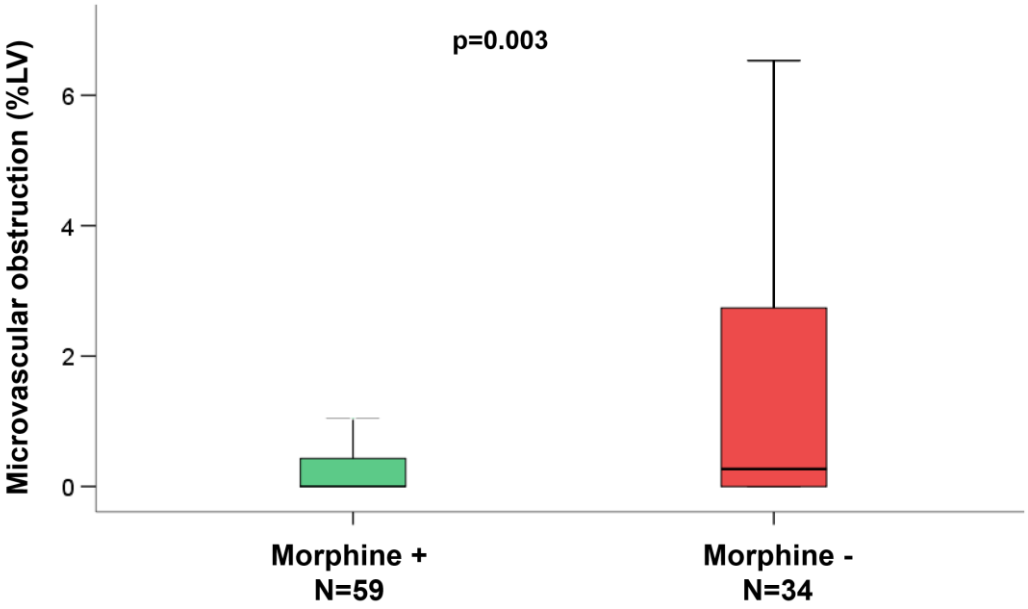

Figure 7: Microvascular obstruction in subgroup of patients with reperfusion within 120 minutes and TIMI-flow ≤2 before PCI.

5.3 Clinical Outcome

The predictors of myocardial damage and clinical prognosis according to morphine use were analyzed by stepwise multiple Cox regression. The results demonstrated that morphine administration was not a predictor of myocardial damage (infarct size (p=0.35) and MVO, p=0.91) and prognosis/clinical outcome (HR 1.10, 95%CI 0.63 to 1.91, p=0.74).

After analyzing by Kaplan–Meier plots with log-rank testing, there was also no difference in event-free survival at 12-month follow-up in patients with or without morphine (log-rank test p = 0.74, Figure 8).

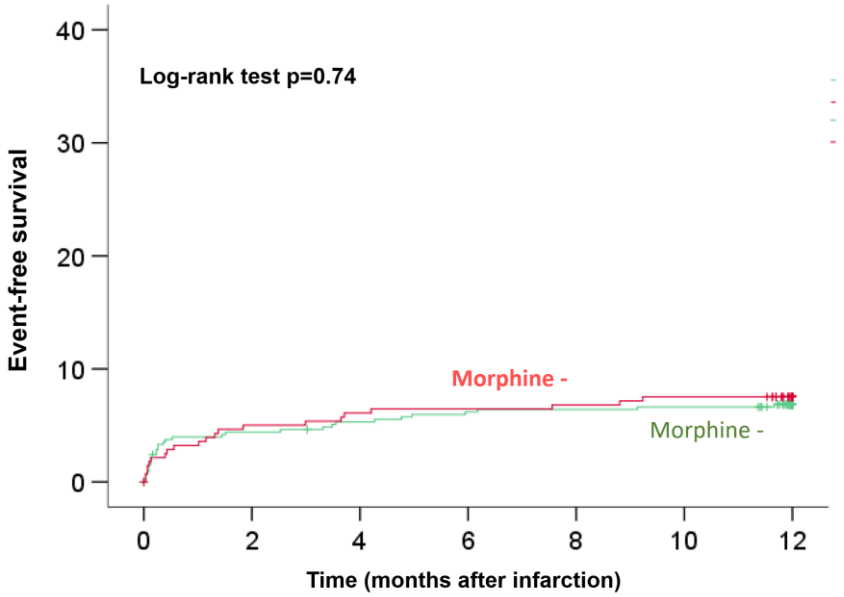

Figure 8: Event-free survival according to morphine administration

In order to accurately compare the effect of morphine and time on event-free survival and avoided bias in this analysis, we performed an additional landmark analysis after 30 days and two months. The results of our first landmark analysis from 30 days follow-up (30 days: HR 0.81 (95%CI 0.37–1.77), p=0.60; one to 12 months: HR 1.52 (95%CI 0.68–3.41), p= 0.31) between the morphine and no morphine group were similar to the Kaplan–Meier curves after 12 months (Figure 9). In the second landmark analysis after two months, there were also no significant differences of clinical events between groups (HR 1.14 (95%CI 0.57–2.27), p=0.72) or two to 12 months (1.04 (95%CI 0.40–2.68); p = 0.94) in accordance with the outcome after 12 months (Figure 10).

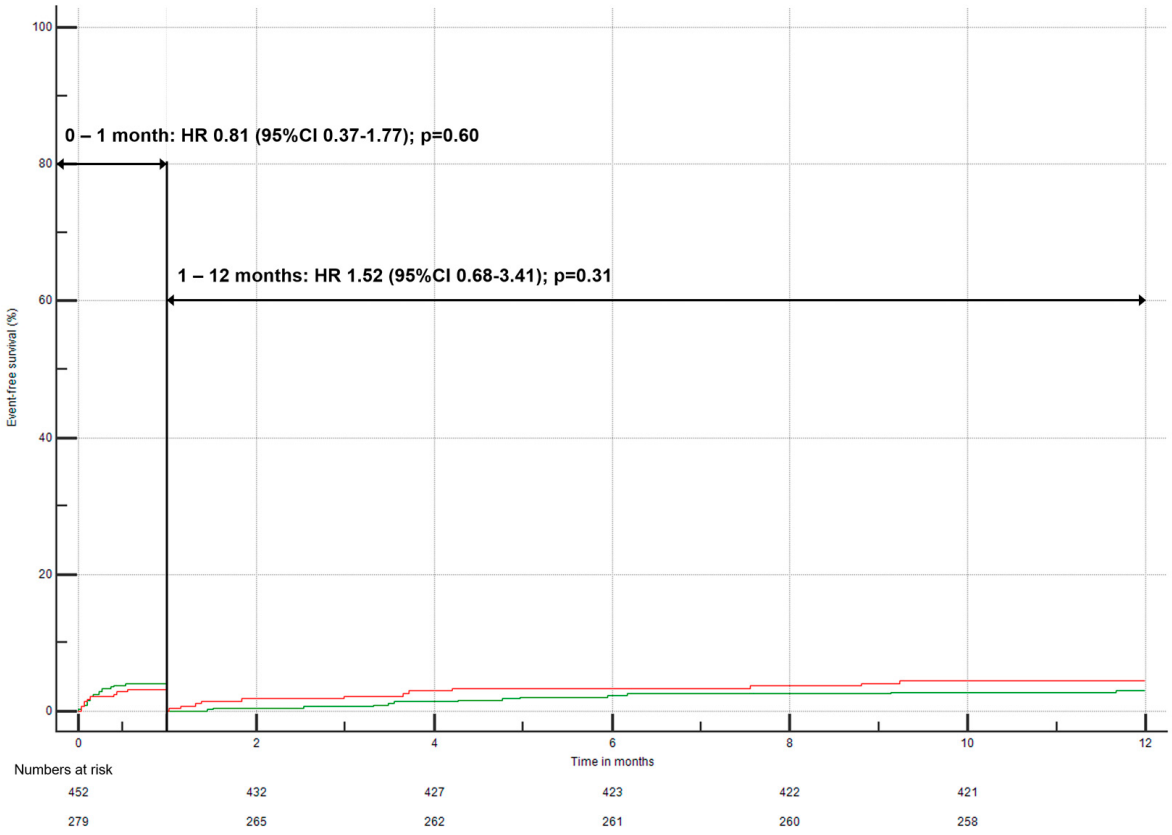

Figure 9: Kaplan-Meier event curves with landmark analysis from 30days follow-up.

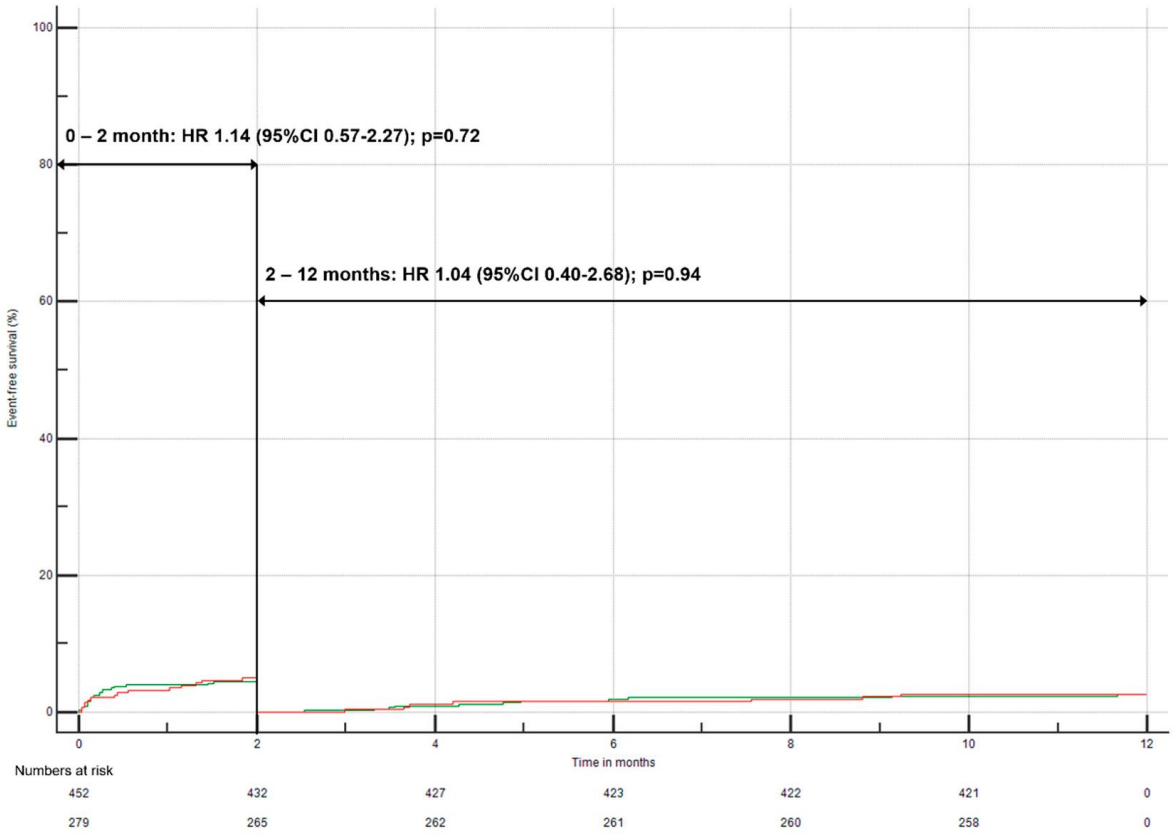

Figure 10: Kaplan-Meier event curves with landmark analysis from 2 months follow-up.

6. DISCUSSION

To the best of our knowledge, the current study represents the largest and the first multicenter investigation with CMR data to comprehensively evaluate the effect of morphine administration on infarct size and reperfusion injury in STEMI patients undergoing primary PCI. The major findings are as follows:

1) Morphine administration was not associated with increased myocardial damage or adverse prognosis/clinical outcome in STEMI patients undergoing primary PCI.

2) In the subgroup of patients with early reperfusion (within 120 minutes) and reduced flow of the culprit (TIMI-flow ≤2 pre-PCI), morphine administration resulted in significantly reduced infarct size and a smaller area of MVO.

6.1 Role of Morphine in Coronary Artery Disease

With potent analgesic properties, perceived hemodynamic benefits and limited alternatives, morphine is the analgesic mainstay for patients with resistant chest pain due to ACS. Morphine is a kind of opioid analgesic with pleiotropic effects that relieves pain and has an effect on sedation which may be associated with the reduction of sympathetic activation and anxiety. However, morphine's gastrointestinal side effects may have important clinical implications limiting the ingestion of essential medications for the acute treatment of ACS, most notably oral antiplatelet agents (see below). In addition, the absorption of other important oral agents such as beta-blockers, statins and angiotensin-converting enzyme inhibitors may also be impacted. Thus, a major concern is that morphine may slow intestinal absorption of oral platelet inhibitors with a subsequently increased risk of stent thrombosis and adverse clinical outcome.

Despite the widespread use of morphine in ACS, there is a paucity of randomized outcome trials to support morphine for the treatment of AMI symptoms. There are even concerns that morphine use may be associated with worse outcomes in AMI. In addition, recent mechanistic research demonstrates that morphine inhibits and delays the absorption of oral antiplatelet agents with delay in and attenuation of maximal platelet inhibition.

Owing to the potential delayed and attenuated absorption of oral P2Y12 receptor inhibitors and impaired plasma concentration and effects of DAPT, morphine is recommended with decreasing strength of recommendation in current ESC guidelines.[2] Current evidence suggests that there are some potential drug-drug interactions between morphine and antiplatelet agents causing the reduction of platelet inhibition.[8, 205, 207, 212, 213] An meta-analysis aggregated patient data from 5 trails by Parodi G et al. concluded that there was a significantly delayed onset of action of prasugrel and ticagrelor in STEMI patients with iv morphine. The high residual platelet reactivity (P2Y12 reactivity units ≥208) at 2 hours was found in 53% and 29% of patients with and without morphine (P<0.001), even after propensity score adjustment.[207] It has also been reported that morphine delayed the maximal inhibition of clopidogrel and led to higher platelet reactivity and higher residual platelet aggregation in healthy people by decreasing plasma levels of clopidogrel active metabolites.[205] The analogous results were obtained from the cases of other P2Y12 receptor inhibitors including prasugrel[207, 212] and ticagrelor[8, 207, 213] in patients with STEMI.

Importantly, these observational and post-hoc studies are now supported by a 2015 prospective double-blind randomized controlled trial (IMPRESSION study). In this single-centre trial, 70 patients were randomized to receive morphine (5 mg) or placebo, followed by a 180 mg loading dose of ticagrelor.[8] Morphine lowered the total exposure to ticagrelor and its active metabolite by 36% (p=0.003) with a concomitant delay in maximal plasma concentration of ticagrelor (4 hours vs 2 hours; P =.004). There was a greater prevalence of high platelet reactivity in the group who received morphine. This trial is an important advance in our understanding, however, there are a number of limitations to consider. The sample size was small and underpowered for clinical events. There are no data on a dose-response for morphine and our understanding of the impact of doses <5 mg is limited. Further, with ‘unbearable chest pain’ and ‘patients who request analgesia’ excluded from this trial, those patients most in need of morphine were excluded, limiting generalizability.

However, whether a lower degree of platelet inhibition or higher platelet aggregation is associated with stent thrombosis, adverse cardiovascular events, or poor clinical outcomes is still controversial. Therefore we conducted our trial to get further insights into the potentially harmful effect of morphine on hard clinical adverse outcomes and reperfusion

injury. Our trial clearly showed that morphine administration was not associated with aggravation of myocardial damage or adverse prognosis/clinical outcome, and there was a similar occurrence of event-free survival at 12-month follow-up in patients with and without morphine.

On the contrary to our data, in some studies, morphine administration was associated with impaired clinical outcome in patients with NSTEMI. From January 2001 through June 2003, 57,039 patients with non-STEMI were recruited in the CRUSADE initiative, including 17,003 patients (29.8%) who received morphine within 24 hours of presentation.[9] It was demonstrated that morphine administration was associated with a higher risk for clinical events, including increased in-hospital mortality, even though after the matched pairs propensity score (odds ratio [OR] 1.41, 95% CI 1.26-1.57). Meanwhile, more attention has been also paid to the potential impact of morphine in patients with STEMI. Morphine administration has been consistently implicated as one of the main mechanisms for adverse clinical results including aggravation of myocardial damage or limitation of myocardial salvage by delaying or attenuating absorption and activation of P2Y12 receptor antagonist in STEMI patients undergoing coronary revascularization therapy. Farag et al reported recently that morphine administration was associated with impaired thrombotic status, reduced rate of spontaneous reperfusion, and less ST-segment resolution, even though there was no significant difference in major adverse cardiovascular events between the two groups but numerically more MACE events were observed in the morphine group.[214] Morphine also appeared to attenuate ST-segment resolution of prehospital ticagrelor among STEMI patients enrolled in PRIVATE-ATLANTIC (P2Y12 Receptor Inhibition with VASP Testing using Elisa kit during the ATLANTIC study) trial.[213]

In contrast, a sub-analysis from the CIRCUS (Does Cyclosporine Improve Outcome in ST-Elevation Myocardial Infarction Patients) trial which recruited 969 patients with anterior STEMI underwent primary PCI demonstrated that there was no significant difference in all-cause mortality (5.3% versus 5.8%, P=0.89) and MACE (26.2% versus 22.0%, P=0.15) in patients with or without morphine after 1-year follow-up.[15] Lakobishvili et al analyzed the impact of morphine on outcomes in patients with acute decompensated HF (ADHF), of which 65.6% secondary to ACS. The authors concluded that morphine administration among ADHF patients was independently associated with increased in-hospital mortality in

multivariable analysis (OR: 2.0 [95% CI 1.1-3.5], P =0.02), but not in propensity score analysis (OR: 1.2 [95% CI 0.6-2.4], P = 0.55).[215] In FAST-MI 2010, it has been demonstrated that pre-hospital morphine use in STEMI patients was not associated with worse in-hospital complications and 1-year mortality (HR = 0.69; 95% CI: 0.35–1.37).[216] Our data underline that morphine application in STEMI patients is not associated with negative effects on reperfusion success and impaired clinical prognosis.

One problem in interpretation of the published trials is that the application of morphine is based on severe symptoms and chest pain. It is highly likely that patients with larger infarcts or severe pulmonary edema, and thus higher mortality risk, typically have more intense chest pain and require morphine more frequently than those with smaller infarcts or without pulmonary edema. This may lead to a selection bias of high-risk patients and may also lead to deviation of the final results.

6.2 Impact of Morphine on Myocardial Damage assessed CMR

Currently available data regarding the effect of exogenous morphine administration on myocardial damage and clinical outcome are derived from methodologically limited non-randomized studies with inconsistent results. The use of CMR imaging provides valuable mechanistic insights into the effect of morphine on myocardial and microvascular damage, which are established surrogate markers for the risk of adverse clinical outcomes. A previous study reported by De Waha et al demonstrated that post-PCI STEMI patients with morphine administration were associated with suboptimal reperfusion success, including larger infarct size, higher extent of MVO, and lower myocardial salvage index in comparison to the non-IV morphine group.[10]

On the contrary, a recent study reported that after propensity score-matching (90 pairs), morphine administration did not cause adverse impacts on myocardial salvage. MSI was similar (46.1% versus 43.5%, P =0.11) as well as other CMR parameters including infarct size, AAR, presence of hemorrhagic infarction or MVO, and MVO volume in STEMI patients treated with morphine or not.[217] In our largest and the first multicenter investigation study, there was no difference in infarct size and MVO in patients with or without morphine. Consequently, we conclude that morphine does not cause additional myocardial damage and is responsible for suboptimal reperfusion success. Furthermore, in the selected

subgroup of patients with early reperfusion and reduced flow of the infarcted vessel, morphine use was associated with reduced infarct size and MVO. Meanwhile, there was no effect of morphine with respect to infarct size or MVO reduction in patients with longer reperfusion times. Our observed morphine-induced infarct size reduction in our subgroup may be explained by the cardioprotective effects of opioids including morphine when applied in the early phase of ischemia (see below 6.3).

6.3 Cardioprotective Effects on the Myocardium of Morphine

In contrast to the adverse impact on platelet inhibition, some evidence suggests that opioids may be involved in cardioprotection against ischemia-reperfusion injury. Activation of opioid, adenosine, bradykinin, adrenergic and other G-protein coupled receptors have been found to be cardioprotective. Remote ischemic conditioning (RIC) is an interesting approach to reduce myocardial damage, although the promising findings in experimental models did not consistently result in a reduction of adverse events following AMI in clinical trials. The exact signaling pathways that translate RIC stimuli from various organs to the heart are incompletely understood. However, a key role of an enhanced endogenous release of opioids into the systemic circulation has been proposed.

Indeed, morphine in combination with remote ischemic preconditioning (RIPC) displayed a cardioprotective effect in STEMI patients during primary PCI for the prevention of reperfusion injury. It was related to the highest percentage of ST-segment resolution and lowest peak TnI levels compared to the other two groups (only RIPC group and control group).[17] The same point of view had been raised by Schultz et al through research in a Vivo rat model in 1995 and they further demonstrated that it was mediated by the δ1-receptor.[218, 219]

Various mainly experimental studies support the point of view that morphine may reduce myocardial injury and limited the areas of myocardial infarction in experimental or animal models. In a myocardial ischemia-reperfusion injury model of male New Zealand rabbits treated with morphine pre-conditioning by a single dose, a prolonged cardioprotective effect as demonstrated by an improved cardiac function, and reduction of post-infarction remodeling were proved.[14] Morphine post-conditioning may exhibit its cardioprotective function by inducing opioid receptors centrally[220] or via activating PKCε-ERK1/2 pathway

and inhibiting mPTP opening.[221] Likewise, hydromorphine ischemic post-conditioning also displayed cardioprotection in isolated rat heart and the mechanism may via activating P13K/Akt/eNOS signaling.[222]

Morphine is considered a non-selective opioid agonist and has not only high affinity to the μ-receptor but also can combine and interact with κ- and δ-receptors.[223, 224] It has been speculated that μ-receptor reduces myocardial infarct size in vivo or animal isolated hearts may be dependent on the central nervous system.[224, 225] K-receptor[226-228] not only provides a similar degree of infarct size reduction and cardioprotection against myocardial stunning as δ-receptor,[228-233] but also reduced arrhythmogenesis.[229, 234] Moreover, intravenous morphine may increase neutral endopeptidase 24.11 (NEP) activities to accentuate neutrophil and endothelial activation or hydrolysis of endothelin 1 (ET-1) which may be one of the multiple cardiovascular effects of morphine.[13, 235, 236]

In general, morphine is a pleiotropic drug, and the pharmacological mechanism of it is very complex in AMI. It is necessary to do more research to fully understand the impact of morphine on ACS in the future. A definite proof that exogenous administration of opioids can induce protective effects is currently lacking. Nevertheless, intravenous morphine targets the same opioid receptors involved in the transmission of cardioprotective stimuli.

Our findings provide an important perspective on myocardial infarct size and reperfusion injure in acute STEMI patients with morphine administration. The current study is the largest and the first multicenter investigation with CMR analysis, from which the data demonstrate that morphine administration is not related to adverse prognosis in reperfused STEMI patients and has potentially cardioprotection against ischemia-reperfusion injury in patients with early reperfusion. Future studies referred to morphine in AMI patients should require larger, randomized, double-blind trials to comprehensively demonstrate the real effects of morphine, and more basic experiments are also needed to illustrate the mechanisms and causes of these effects.

6.4 Limitations

Although this is the largest study to date to evaluating the effect of morphine in patients with STEMI, the study was not a randomized and not a double-blind trial. Second,

morphine administration was decided by cardiologists according to the symptoms of patients, thereby it may cause selection bias and potential confounding effects. Third, there was no routine platelet function monitoring of patients, so it is not possible to asses the interaction between myocardial injury and pharmacodynamics/kinetics of antiplatelet therapy or platelet function. In addition, due to emergency physicians did not record the exact time and doses frequently, we could not analyze a pre/post-conditioning effect and dose-dependent effect of morphine administration on reperfusion success. The last, and possibly more important, is that we can not completely exclude the influence of other drugs (e.g. metoclopramide) co-administered with morphine on the test results.

7. CONCLUSION

In our study, morphine administration was not associated with increased myocardial damage or adverse clinical outcome in STEMI patients undergoing primary PCI. In the early stage of STEMI (≤120 min), morphine administration may play a positive role in cardioprotection as reflected by reduced infarct size and MVO which has been analyzed by CMR.

8. SUMMARY

Morphine is the most common analgesic drug used in heart attack patients to relieve acute chest pain. However, current studies indicate that the pain reliever could affect the absorption and effect of the platelet inhibitors clopidogrel, ticagrelor and prasugrel. Studies have shown that the slower absorption of platelet inhibitors from the gastrointestinal tract significantly reduces platelet inhibition in platelet reactivity tests. Because of these safety concerns, IV opioids have been downgraded from an original Class I to a Class IIa recommendation in the current ESC and AHA guidelines. So far, however, it is not clear whether this reduced platelet inhibition by morphine also has an influence on myocardial damage (e.g. infarct size) and the clinical prognosis.

The present study was therefore intended to clarify whether the administration of morphine to patients with ST segment elevation myocardial infarction (STEMI) had a negative effect on the markers of infarct size, "myocardial salvage" and microvascular obstruction as a marker of severe reperfusion damage measured in cardiac MRI, and whether the clinical prognosis is also impaired by administration of morphine. The study is a predefined sub-study of the so-called AIDA-STEMI study which included patients with STEMI and symptoms onset <12h. The administration of morphine was analyzed in all patients and the patients were divided into two groups according to the administration or no administration of morphine. After successful reperfusion using PCI, all patients had a cardiac MRI to analyse the extent of myocardial damage.

Of the 734 included patients with complete MRI data after PCI, n=434 (61.8%) received morphine, while 280 patients were treated without morphine. When comparing the groups with regard to the MRI markers of myocardial damage, there was no relevant difference in the size of the infarct (17% LV, IQR 8–25% LV versus 16% LV, IQR 8–26% LV, p=0.67) and in the extent of the microvascular obstruction (p=0.92). In a predefined subgroup of patients with early reperfusion within 2 hours and complete occlusion of the infarct vessel defined as TIMI flow ≤2, a reduction in the size of the infarct (12% LV, IQR 12-19 versus 19% LV, IQR 10 -29, p=0.035) and microvascular obstruction (p = 0.003). With regard to the combined clinical endpoint (Death, reinfarction, re-hospitalization due to heart failure), there was no difference between the two groups (log-rank test p=0.74) and the

administration of morphine was also no independent predictor for mortality in the group Cox regression analysis.

In this largest study to date, which examined the effect of the administration of morphine on MRI markers of myocardial damage such as infarct size, it was clearly shown that morphine has no negative effects on reperfusion success in patients with STEMI. Instead, morphine appears to have a cardioprotective effect in patients with rapid reperfusion and completely occluded vessels, which in this subgroup has been shown as a reduced infarct size. However, further well-planned, randomized studies are necessary to confirm this potential cardioprotective effect of morphine and, in particular, to further confirm the safety of morphine in the context of administration to patients with myocardial infarction.

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