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The Final thesis

Prehospital Care for Patients with Acute Coronary Syndromes

(title)

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A B S T R A C T

Background: Ischemic heart disease is the single most common cause of death worldwide. The term includes acute coronary syndromes. To improve survival rates, time is a crucial factor. Latter highlighting the relevance of the prehospital phase.

Objective: The aim of this research is to provide an overview of current standards, as well as ongoing research and its future implications in the prehospital care of patients with acute coronary syndromes.

Methods: A narrative literature review was conducted. Regarding the current standards of care, society guidelines were referred to. For the part of ongoing research, terms were created and searched for in the PubMed database. Subsequently, the results were filtered by various criteria to match the structure of this review.

Discussion: Regarding prehospital logistics of care, delays attributable to various parties in the prehospital setting, as well as measures to shorten the prehospital time have been assessed. The diagnosis of acute coronary syndromes in the preclinical setting is traditionally based on signs and symptoms, complemented by12-lead electrocardiogram acquisition and analysis. Cardiac biomarkers for prehospital risk stratification are a novelty and their implementation is a matter of ongoing research. While most principles of prehospital treatment of acute coronary syndromes are based on society guidelines, telemedical advancements can support paramedics and emergency medical physicians on scene.

Conclusion: While still a novelty, prehospital cardiac biomarkers could help to improve diagnostic accuracy, reduce delays, and increase cost effectiveness. Hereby enhancing the efficiency of prehospital logistics of care and guiding preclinical treatment. However, further research and acquisition of high-quality evidence is still required.

Keywords: “acute” AND “coronary” AND “syndrome” AND “prehospital”; “prehospital” AND “myocardial” AND “infarction”; “EMS” AND “acute” AND “coronary” AND “syndrome”

A B B R E V A T I O N S

ACS	Acute coronary syndrome
NSTEMI	Non-ST-elevation myocardial infarction
NSTEACS	Non-ST-elevation acute coronary syndrome
STEMI	ST-elevation myocardial infarction
ECG	Electrocardiogram
EMS	Emergency medical services
AHA	American heart association
ESC	European society of cardiology
PCI	Percutaneous coronary intervention
FMC	First medical contact
AMI	Acute myocardial infarction
hs-cTn	High sensitivity cardiac troponin
cTn	Cardiac troponin
POC	Point of care
UFH	Unfractionated heparin
tPA	Tissue plasminogen activator
NIBP	Noninvasive blood pressure
BMI	Body mass index
LBBB	Left bundle branch block
PM	Pacemaker
DBP	Diastolic blood pressure
SBP	Systolic blood pressure
URL	Upper reference limit
DAPT	Dual antiplatelet therapy
HEMS	Helicopter emergency medical services
GEMS	Ground-based emergency medical services

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II. INTRODUCTION

Before approaching the topic “Prehospital Care for Patients with Acute Coronary Syndromes” it is necessary to define the term “Acute Coronary Syndrome” first.

“Acute Coronary Syndrome” can be regarded as an operational term referring to states of suspected or confirmed myocardial ischemia and/ or infarction due to an impairment of coronary blood flow.

It can be further classified according to the presence of ST-elevations on the ECG and positivity for myocardial injury biomarkers (e.g. cardiac troponin). Acute Coronary Syndrome manifesting with ST-elevations in at least two contiguous leads on the ECG is classified as “ST-elevation acute coronary syndrome”. In the absence of ST-elevations on the ECG but positive myocardial injury biomarkers, “Non-ST-elevation myocardial infarction” can be diagnosed. If biomarkers and ST-elevations are absent, the condition is termed “unstable angina”. (1)

In 2018, the European Society of Cardiology published the fourth universal definition of myocardial infarction, discriminating between myocardial injury and myocardial infarction.

Myocardial injury is a condition with evidence of elevated cardiac troponin values, with at least one value above the 99th percentile upper reference limit. It is considered acute when there is a rise and/ or fall of cardiac Troponin values.

Myocardial infarction incorporates myocardial injury together with at least one of the following: Symptoms of myocardial ischemia, new ischemic ECG changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium, new regional wall motion abnormality in a pattern consistent with an ischemic etiology or identification of a coronary thrombus by angiography or autopsy. (2)

Epidemiologically, Ischemic heart disease is the single most common cause of death worldwide, and its frequency is increasing. Despite a reduction in mortality rates from ischemic heart disease in Europe over the last three decades, it remains the most common cause of death, accounting for 45% of all deaths in Europe. (3) A trend of decreasing incidences of STEMI and increasing incidences of NSTEMI can be observed, attributable to refinements in the operational diagnosis of NSTEMI. (4)

In order to improve survival from acute myocardial infarction, time from first medical contact to interventional coronary reperfusion therapy is a crucial factor, latter highlighting the relevance of the prehospital phase in acute coronary syndrome care. This narrative literature review is intended to provide an overview of current standards, as well as ongoing research and its future implications in prehospital care of patients with acute coronary syndromes.

III. M E T H O D S

To fulfill the objective of this narrative literature review, which is to give an overview of current standards, as well as ongoing research and its future implications in the prehospital field, the methods for conducting the literature search have been adapted accordingly.

The main corpus of literature concerning the current standard of prehospital acute coronary syndrome care was obtained by reviewing the latest guidelines published by the European Society of Cardiology and the American Heart Association. Accordingly, "2017 Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation" and "2020 Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation" constituted the literature respectively.

For the acquisition of literature regarding ongoing research in the field of prehospital care for. patients with acute coronary syndromes, a PubMed search strategy was created.

Latter consisted of 3 search terms:

1) acute AND coronary AND syndrome AND prehospital
2) prehospital AND myocardial AND infarction
3) EMS AND acute AND coronary AND syndrome

The results yielded by these terms were subsequently filtered by the following criteria:

1) publication date 2015 – 2022
2) language: English
3) species: humans
4) population: adult

Final selection was made according to the structure of this narrative literature review.

Cross-referencing from selected articles was conducted to complete the research.

IV. DISCUSSION

The discussion part will be structured according to the chronological course of an emergency medical services activation and response to a patient with acute coronary syndrome. This structure has been chosen, as it denotes hinge points of prehospital care and where ongoing research could be applied.

1. Prehospital logistics of care

In 2001, C. Michael Gibson, an interventional cardiologist and clinical trialist, published an article in the AHA Circulation journal titled "Time Is Myocardium and Time Is Outcomes". (5) Treatment delays are an important quality indicator in the prehospital and hospital phase of acute coronary syndrome care. As current evidence shows, the greatest myocardial salvage can be achieved if patients are reperfused within the first 3 hours of symptom onset. The relative 1-year mortality rate increases by 7.5% for every 30-minute delay to coronary reperfusion. In the prehospital setting, the most significant delays can be seen. (6)

The total ischemic time marks the period between the onset of symptoms and reperfusion. Latter is specified as either the administration of a lytic bolus, when a fibrinolytic tactic is chosen, or wire crossing in case of a primary PCI strategy. Total ischemic time is comprised of patient- and system-related delays. Patient-related delay is the period between onset of symptoms and first medical contact, either with emergency medical services or medical personnel at PCI- and Non-PCI centers. System-related delay is the time between first medical contact and reperfusion. It includes emergency medical services response time, as well as time to STEMI diagnosis. (7) Figure 1 provides an overview of treatment delays and time goals according to the 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation.

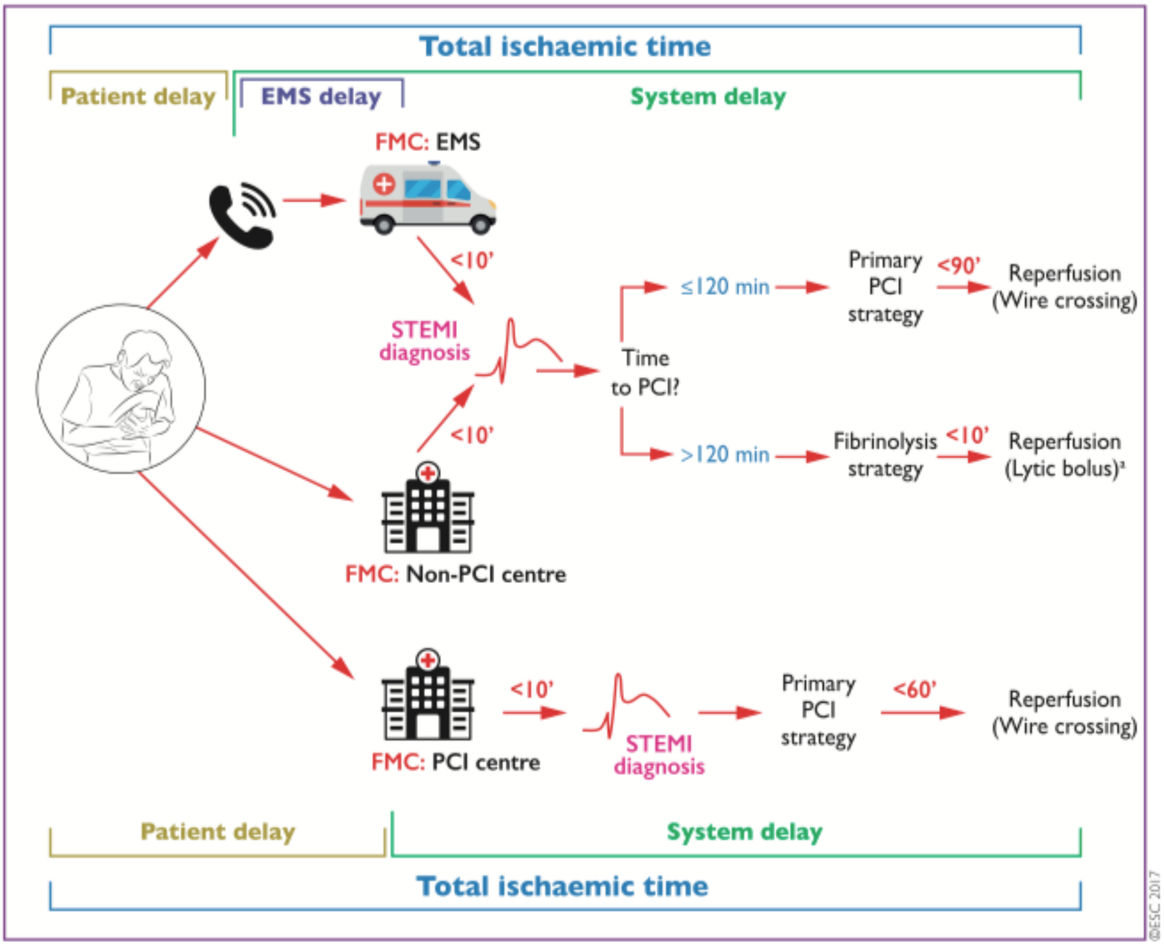

Figure 1. "Modes of patient presentation, components of ischemia time and flowchart for reperfusion strategy selection." (7)

1.2 Patient-related delays

As assessed previously, time is an essential factor in acute coronary syndrome care and directly associated with an increased risk of complications, disability, and morbidity.

Recognition of related symptoms and warning signs is very dependent on the patient. (6)

Frequently, patients wait for 2 hours or more after the onset of symptoms before contacting emergency medical services or seeking medical advice. Reasons for delayed presentation include fear of embarrassment or troubling others, attempted self-medication, and experiencing symptoms not considered indicative of acute coronary syndrome (perception of the "Hollywood heart attack").

Mirzaei et al. performed a secondary analysis of a large prospective multi-center study in the United States, examining the association between symptom onset characteristics and prehospital delay in patients with acute coronary syndrome. (8) Delay times were significantly shorter in patients with ST-elevation myocardial infarction, when experiencing an abrupt symptom onset and when ambulance services were used. Being uninsured and having a gradual onset of symptoms was significantly associated with a longer delay. It was concluded that patients should be counseled that a gradual onset of symptoms indicative of a potential acute coronary syndrome is an emergency and should trigger EMS activation. Median delay times for women (3.5h) and men (4h) were not significantly different but longer than the AHA recommendation of <120min.

Youssef et al. conducted a study in Egypt on the causes of pre-hospital and hospital delay in patients with non-ST elevation acute coronary syndromes in tertiary care. (9)

They found that 66% of prehospital delay time was due to patient-related reasons. Symptom-related causes were re-occurring symptoms, thinking that symptoms would spontaneously disappear, attribution of symptoms to non-cardiac origin, and non-severity of symptoms. Not finding an escort was the most common social-related cause. They concluded that the patient-related delay could be rooted mainly in a lack of proper medical awareness in the population, highlighting that community awareness and patient education remain a cornerstone of early diagnosis.

Under-utilization of emergency medical services also belongs to patient-related delays.

Generally, transport by means of emergency medical services is recommended in international acute coronary syndrome guidelines. (7) Paramedics are trained for diagnosis and prehospital treatment of acute coronary syndromes and can manage potentially life-threatening complications. However, across many countries, a large proportion of patients (40-50%) are still transporting themselves to the hospital. (10)

Reasons for not using EMS include the assumption that other means of transport might be faster, and that EMS transport is not necessary. Other factors were underestimating the seriousness of symptoms and the fear of embarrassment when misjudging a seemingly emergency situation. The seriousness of this problem prompted the Heart Foundation of Australia to launch a mass media campaign about “The Warning Signs of Heart Attack”. Emphasis was put on the less severe symptoms of acute coronary syndrome and the importance of quickly activating emergency medical services.

1.3 System-related delays

1.3.1 Emergency medical services delays

According to the 2017 ESC guidelines for the management of acute myocardial infarctions in patients presenting with ST-segment elevation, a clear goal of reducing the time between first medical contact and STEMI diagnosis to a maximum of 10 minutes is defined. (7)
Alwarashedh et al. found in their meta-analysis of 100 studies across 20 different countries about emergency medical service delays in ST-elevation myocardial infarction that EMS delays account for half of the total system delay in STEMI. The weighted mean first medical contact to door time was 41 minutes. In a meta-regression adjusted for door-to-balloon time, every 10-minute increase in FMC-to-door-time was associated with a 10.6% reduction in the share of patients treated within 90 minutes. However, the impact of EMS delay on mortality is only statistically significant in patients receiving prehospital thrombolysis.
Method of ECG interpretation (in-field versus transmission), urban classification, and bypassing the emergency department were significantly associated with FMC-to-door time.
If STEMI patients are referred directly to a PCI-capable center by EMS, the ideal system delay is less than 90 minutes from the first medical contact. The mean door-to-balloon time across 35 studies included in the meta-analysis was almost 60 minutes. Latter implies a maximum EMS delay of 30 minutes. Only 20% of the studies included reported EMS delays of 30 minutes or less. Travel time represents a major aspect of EMS delay and is highly variable across EMS systems. The shortest EMS delays have been observed in the USA, where about 80% of the population was estimated to live within 60 minutes of a PCI cable facility in 2000. One possible solution to this would be the introduction of new PCI centers in underserved regions. This would mainly target transport times.
Particularly in urban systems, scene time was responsible for the largest proportion of total EMS delay. Unlike transport time, the least variation was observed with scene time. Scene times of more than 20 minutes were observed in EMS systems involving mobile intensive care units or physicians and those with more extensive prehospital treatment guidelines. Examples are France, Denmark, Germany, and Australia.
However, guideline adherence and prehospital thrombolysis performance were quicker in those countries, as physicians were frequently available on scene. According to the 2017 ESC guidelines, prehospital thrombolysis should be performed within 20 minutes of FMC. Only 20% achieved this goal.

While Alwarashedh et al. mainly focused on patients with STEMI, Eckle et al. included 1442 patients with a final diagnosis of STEMI or NSTEACS in their retrospective study conducted in Tübingen, Germany. (11) 82% of patients were diagnosed with NSTEACS and 18% with STEMI. Time spent in prehospital care (FMC until hospital admission) was 37 minutes for NSTEACS and 33 minutes for STEMI. Additionally, only 30% of STEMI patients and no NSTEACS patients at all were handed over directly at the catheterization laboratory. These findings mentioned above might be explained partly by the time counting from ECG diagnosis in STEMI versus first blood test in NSTEACS. Latter highlighting the importance of high sensitivity troponin testing as soon as possible, potentially in the preclinical setting.

1.3.2 Hospital-related delay

Although this narrative literature review deals specifically with the prehospital side of acute coronary symptom care as the title suggests, it is worth touching on hospital-related delays as well. Particularly because the emergency department can be regarded as the interface between preclinical and clinical care.

As stated in the 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, immediate activation of the catheterization laboratory after preclinical STEMI diagnosis reduces treatment delays and may reduce patient mortality. (7)

When EMS diagnose STEMI, it is recommended to bypass the emergency department and bring the patient directly to the catheterization laboratory. This is associated with a time saving of 20 minutes from FMC to wire crossing.

In case the patient is transported to a non-PCI center initially, the time between arrival at the non-PCI facility and departure to a PCI-capable facility should be less than 30 minutes. This is referred to as door-in-to-door-out time.

2. Diagnosis of Acute Coronary Syndromes in the preclinical setting

2.1 Signs and Symptoms in the preclinical context

History taking and physical examination must be carried out promptly after first medical contact. As broadly known, clinical features of Acute Coronary include acute retrosternal chest pain of dull, squeezing quality. (6) It commonly radiates to the left chest, arm, shoulder, neck, jaw, or epigastrium. (12) Depending on the underlying cause, the pain might be exacerbated with physical activity. Relief of the pain upon nitroglycerine administration is no longer a diagnostic criterion for cardiac ischemia. (7) Additional symptoms include dyspnea, pallor, nausea, vomiting, diaphoresis, and anxiety. Atypical symptoms might be observed mainly in the elderly, diabetic, and female individuals. Although there is no universally accepted definition of atypical symptoms in ACS, no or minimal chest pain, as well as autonomic symptoms like nausea, generalized weakness, and diaphoresis, are usually referred to as the atypical range of symptoms. (13) This is of relevance as, for example, elderly individuals frequently present with atypical ACS symptoms but are at the highest risk of having complications from ACS, hence benefiting from early invasive therapy. Many authors advocate discontinuing the dichotomy of "typical" and "atypical" symptoms and considering a continuous range of symptoms instead. (14)

In 2016, Andersson et al. conducted a quantitative study to explore the occurrence of nausea and/ or vomiting and dyspnea in the prehospital setting and the association with patients' outcomes. (15) Data from hospital records and a previous randomized controlled trial including five emergency medical service systems in western Sweden was analyzed. The primary endpoints were one-year mortality and the development of AMI during hospitalization. Aligning with the recommendations of other authors to abandon the dichotomy of "typical" and "atypical" symptoms, they highlighted the importance of a "flexible encounter with the patient in order to avoid being influenced by preconceived ideas". (16)

From their study, Andersson et al. concluded that in the prehospital setting of a suspected ACS, one in four patients had symptoms of nausea and/ or vomiting. About one in three patients had symptoms of dyspnea. Their most important result was that the presence of dyspnea was associated with an increased risk of death. No such association was found for the development of AMI. For nausea and/ or vomiting, a significant association was found with AMI but not with death. They further concluded that both associated symptoms indicate an increased risk of complications after hospital admission. Hence triage should be directed towards more intensive care. Additionally, awareness of associated symptoms might help to reduce delays until treatment.

Clinical features can be regarded as the very first contact point between the patient and medical personnel, even before the physical attendance of the latter.

Acknowledging this, Alotaibi et al. conducted a systematic literature review on the accuracy of emergency medical services telephone triage in identifying acute coronary syndrome for patients with chest pain. (17)

Being frequently referred to as an acute coronary syndrome, chest pain is a common reason for EMS activation and subsequent transport to emergency departments. However, in many cases, non-cardiac causes are responsible for chest pain, indicating a systematic over triage, which ultimately leads to an increased ambulance utilization and crowding of emergency departments. Telephone triage in the UK is performed by computerized telephone triage software. Life-threatening conditions are identified by a series of questions at the beginning of the call. When patients complain of chest pain, this triggers an additional series of questions to identify ACS. Potential over triage for chest pain is accepted in order to avoid harm to patients. Alotaibi et al. included 3 studies (2 from Sweden, 1 from France) in their literature review after exclusions due to various reasons. The primary endpoint was the diagnosis of ACS on hospital admission, including NSTEMI, unstable angina, and STEMI- The secondary endpoint was the diagnosis of a life-threatening condition associated with chest pain.
From their literature review, they concluded that none of the 3 models from the studies had sufficient sensitivity to avoid EMS activation. Hence, telephone triage may not be expected to rule out ACS. However, prediction models might be used to identify patients who can safely be categorized as a lower priority. Referring to a study conducted in Australia by Coventry et al., it was highlighted that chest pain alone is not a solid predictor of MI. (18)
Of all patients who called an ambulance and were ultimately diagnosed with MI, 68.7% of males and 54.4% of females complained of chest pain.

2.2 ECG in the preclinical context

Regarding acute coronary syndromes with ST-elevation, the 2017 ESC guidelines recommend the acquisition and interpretation of a 12-lead ECG as soon as possible at the time of first medical contact to facilitate early diagnosis and triage. (7)
Additionally, continuous ECG monitoring with the possibility of prompt defibrillation in case of life-threatening arrhythmias is indicated as soon as possible in all suspected STEMI patients. The ST-segment elevation is measured from the J-point and indicative of coronary artery occlusion in the following cases: (19)
At least 2 contiguous leads with elevation

- ≥2.5mm in men <40 years
- ≥2mm in men ≥40 years
- ≥1.5mm in women in leads V2-V3 and/or ≥1mm in other leads

- absence of left ventricular hypertrophy or left bundle branch block

Recommendations for suspected right ventricular MI are:

- ST-elevation in V3R and V4R right precordial leads

Recommendations for suspected posterior MI are:

- ST-depression in V1 – V3, especially with a terminal positive T-wave
- ST-elevation ≥0.5mm in leads V7 – V9

The 2017 ESC guidelines also provide recommendations for bundle branch block, ventricular pacing, isolated posterior MI, left main coronary obstruction, and a non-diagnostic ECG. However, as this narrative review aims at giving an overview of prehospital ACS care and future implications of ongoing research, those will not be further discussed.

Concerning Non-ST-elevation acute coronary syndrome, the current ESC guidelines recommend performing a 12-lead ECG upon first medical contact as well. (20)

The ECG in NSTE-ACS may be normal in more than 30% of cases. However, abnormalities such as ST-segment depression, transient ST-segment elevation, and T-wave changes can be found. In case of inconclusive findings, additional acquisition of right precordial leads V3R – V4R and V7-V9 can be performed. Complementing a 12-lead ECG acquisition, measurement of a biomarker, like high sensitivity cardiac troponin, is mandatory in patients suspected of NSTE-ACS.

2.2.1 Advantages of prehospital ECG acquisition

In 2019, Cheung et al. conducted a retrospective observational study on whether prehospital ECG shortens the ischemic time in patients with ST-segment elevation myocardial infarction, particularly by shortening the system-related delay. (21)

They took data from 15 ambulances from the catchment area of Queen Mary Hospital Hong Kong. For patients with chest pain, prehospital ECG was acquired and transmitted for analysis to the attending physicians at the emergency department. The data from those 15 ambulances was then compared with data from STEMI patients who were transported by ambulance or presented themselves but without prehospital ECG acquisition. Additionally, time differences between ECG acquisition on scene versus in the ambulance compartment were assessed.

In total, data from 197 patients was analyzed.

The median patient delay was 90 minutes. A significant difference was observed between patients admitted by ambulance, who had a shorter delay than those who arranged self-transport.

Regarding system delay, several significant findings were found. When prehospital ECG was performed on scene versus in the ambulance compartment, it was available 5 minutes earlier. In addition, if the ECG was performed by the ambulance on scene, it was available 35 minutes earlier compared to patients arranging self-transport.

Emergency department door-to-triage time, door-to-first-emergency department-ECG time, door-to-physician consultation time, and total length of stay in the emergency department all were significantly shorter when a prehospital ECG was obtained. Furthermore, more efficient emergency department management can be achieved, as the preliminary history and vital signs are collected during the transport and immediately handed over to the triage nurse, shortening triage time to 0 minutes for patients with prehospital ECG. Triage accuracy was improved as well, and more patients with STEMI were correctly categorized as critical, therefore receiving immediate treatment.

In their discussion, the importance of public education to reduce patient-related prehospital delays was highlighted. Hesitating the activation of emergency medical services and barriers in care-seeking have been assessed in this narrative literature earlier.

2.2.2 Approaches to ECG analysis in the preclinical context

The ESC recommends "that ambulance teams are trained and equipped to identify STEMI (with the use of ECG recorders and telemetry as necessary) and administer initial therapy, including fibrinolysis when applicable". (7) As the ESC counterpart in the United States, the AHA also recommends "that emergency medical services acquire and interpret a prehospital electrocardiogram for patients with suspected acute coronary syndrome". (22)

Following the recommendations of the worldwide leading organizations for acute coronary syndrome care, means of ECG interpretation and their diagnostic accuracy will be discussed in this section.

In 2019, Zègre-Hemsey et al. conducted a survey-based study in North Carolina to perform a statewide assessment of prehospital electrocardiogram approaches of acquisition and interpretation for ST-elevation myocardial infarction based on emergency medical services characteristics. (23) 96 EMS systems across the state of North Caroline participated in the survey. 93% of the EMS systems had the capability to perform a prehospital ECG in all ambulances, and most of them (91%) had a standardized protocol for ECG acquisition and interpretation, which was performed by paramedics in the majority of EMS systems (55%). The second most common (39%) mode was a combination of a paramedic- and software-based interpretation. While almost 80% of EMS systems transmitted prehospitally acquired ECGs to the receiving hospital, only 6% reported physician interpretation after transmission.

While paramedics were responsible for activating the cardiac catheterization laboratory in most cases, systems with physician interpretation had the lowest proportion of cancellation rates (less than 10%). However, most EMS systems tracking cancellations reported less than 10% of cancellation rates, regardless of the mode of interpretation.

Regarding the diagnostic accuracy of ECG interpretation, Trivedi et al. found that paramedics can interpret ECGs for STEMI with adequate training. (24) In their study conducted in 2009 with 103 enrolled paramedics, they discovered that paramedics' sensitivity for STEMI diagnosis was 92.6%, and specificity was 85.4%. In 8.1% of cases, false-positive activation of the catheterization laboratory occurred.

As Trivedi et al. focused on paramedics' accuracy of STEMI diagnosis, Tanguay et al. conducted a retrospective analysis on the diagnostic accuracy of prehospital electrocardiograms interpreted remotely by emergency physicians. (25) They included 625 patients who were transported by EMS and underwent angiography and concluded that remote ECG interpretation by emergency department physicians with a misinterpretation rate of <8% is reasonably accurate. After angiography, 94% of patients with a suspicion of STEMI were correctly classified as having a culprit artery lesion. 6% (35 out of 625) had no culprit artery lesion. Out of those 35 misinterpreted ECGs, the majority (69%) had ECG findings mimicking STEMI criteria. To explain those misinterpretations, Tanguay et al. mention challenges in identifying STEMI in ECGs lacking a true ST-elevation complex.

Additionally, they conclude that some physicians rather over-diagnose STEMI in challenging ECGs to ensure medical attention for those patients and err on the side of caution.

2.3 Cardiac biomarkers for prehospital risk stratification

In STEMI, prehospital acquisition and interpretation of a 12-lead ECG is necessary for field triage and subsequent referral for primary percutaneous coronary intervention, ultimately leading to earlier reperfusion and lower mortality. (26) However, in patients without persisting ST-segment elevation, the prehospital diagnosis might be challenging due to inconclusive ECG changes. Additionally, biomarkers are necessary for the diagnosis. (27) In the 4th universal definition of myocardial injury and myocardial infarction, the ESC states that “the term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99^{th} percentile upper reference limit (URL)”. (2) And further, “the myocardial injury is considered acute if there is a rise and/ or fall of cTn values”. Additionally, the ESC guidelines on NSTE-ACS also highlight that “measurement of a biomarkers of cardiomyocyte injury, preferably hs-cTn, is mandatory in all patients with suspected NSTE-ACS”. (20)

From June 2012 until November 2015, Rasmussen et al. conducted a study in Denmark to investigate the predictive value of routine point-of-care troponin T measurement for prehospital diagnosis and risk-stratification in patients with suspected acute myocardial infarction. (28) As part of the NONSTEMI trial, all ambulances in central Denmark were equipped with POC cardiac troponin T devices (Roche cobas h232). Prehospital POC cTn measurement was performed in a total of 19615 cases, out of which 19712 measurements in 15781 individuals were matched with an admission. In their observational population-based follow-up study, Rasmussen et al. studied the eligibility of prehospital POC cTn for early risk stratification in patients suspected of having an acute myocardial infarction, as well as the mortality of patients with POC cTn values above and below the detection threshold of 50ng/l. In 11.0% (2150) of cases, prehospital POC cTn was above the 50ng/l detection level.

Acute myocardial infarction was diagnosed in 2187 cases (11.7%), out of which 966 had a POC cTn of >50ng/l, corresponding to a positive predictive value of 44.9%.

From 16525 cases without MI, POC cTn was <50ng/l in 15341 cases. Latter corresponding to a positive predictive value of 92.6%.

In the group with prehospital POC cTn >50ng/l, the mortality rate was 24.0% per year, compared to 4.8% per year for the group with POC cTn values <50ng/l.

From the data gathered, Rasmussen et al. concluded that the routine use of prehospital POC cTn allows for early risk stratification of patients with suspected acute myocardial infarction. A prehospital POC cTn >50ng/l indicates a five times higher mortality than values <50ng/l, regardless of the final AMI diagnosis. Additionally, routine use of POC cTn could diagnose AMI with a sensitivity of 44.2% and a specificity of 92.8%.

They concluded that prehospital POC cTn holds significant prognostic value, enabling risk stratification at the time of FMC. However, an early invasive strategy based on prehospital POC cTn has not been proven beneficial yet. Instead, it should be considered to add elevated prehospital cTn values as a high-risk criterion to consider triage towards advanced cardiac care at an invasive center.

Continuing from that conclusion, van Dongen et al. analyzed whether the troponin component adds predictive value to prehospital risk stratification by application of the HEART score. (29) The HEART score is a simple tool for risk stratification in patients with chest pain. (30)
It is an acronym for History, ECG, Age, Risk factors, and Troponin and is widely validated to be used in the emergency department. Patients can be given 0 to 10 points. (31)

HEART

HEART score for chest pain patients

History (Anamnesis)	Highly suspicious	2	
	Moderately suspicious	1	
	Slightly suspicious	0	
ECG	Significant ST-deviation	2	
	Non-specific repolarisation disturbance / LBBB / PM	1	
	Normal	0	
Age	≥ 65 years	2	
	45 – 65 years	1	
	≤ 45 years	0	
Risk factors	≥ 3 risk factors *or* history of atherosclerotic disease	2	
	1 or 2 risk factors	1	
	No risk factors known	0	
Troponin	≥ 3x normal limit	2	
	1-3x normal limit	1	
	≤ normal limit	0	
		Total	

Risk factors for atherosclerotic disease:

Hypercholesterolemia	Cigarette smoking
Hypertension	Positive family history
Diabetes Mellitus	Obesity (BMI>30)

Figure 2. "Original HEART score" (31)

The prospective observational cohort study by van Dongen et al. was the second phase of the FamouS Triage project. (29) The main object was to determine if prehospital troponin would add value to a prehospitally assessed heart score to predict MACE within 45 days in patients with suspected NSTE-ACS. 33 vehicles from 2 regional ambulance services participated in the study, and the same Roche cobas h232 POC cTn assay was used. Troponin values <40ng/l scored 0 points in the HEART score, and values ≥40ng/l were awarded 2 points respectively. Low risk was defined by HEART scores ≤3. The primary outcome was MACE 45 days post inclusion and defined as either cardiac ischemia, death by all-cause, coronary bypass surgery, or PCI. 700 Patients with a complete prehospital HEART score were included in the analysis.

A total of 172 patients (25%) were categorized as low risk, 528 patients (75%) as intermediate to high risk. Using HEAR score (without troponin), 13 patients (7%) from the low-risk group experienced MACE 45. When HEART score (with troponin) was used to stratify patients, MACE occurred in 5 low-risk patients (3%). No case of death occurred in either of the two low-risk groups. Using HEART instead of HEAR obtained higher predictive values, and both HEAR and HEART were significant predictors of MACE. However, Van Dongen et al. highlighted that the interval between symptom onset and troponin assessment in the prehospital setting is rather short, contributing to a smaller amount of true high HEART scores. A possible solution would be a second HEART score assessment after at least 120 minutes.

2.3.1 HEART score as a decision-making tool

Overcrowding of the emergency department is an increasing challenge worldwide. (32)
The consequences are high costs, increased length of stay, and reduced patient satisfaction.
Patients with chest pain suspected of having NSTE-ACS are responsible for approximately 10% of all admissions. (33) Of these patients, about 65% are hospitalized or observed for a prolonged time, while 80% are at low risk and don't have an acute coronary syndrome. (34)
Tolsma et al. examined referral decisions based on a prehospital HEART score in suspected NSTE-ACS during phase III of the FamouS Triage study. (35)
Phase III of the FamouS Triage study investigated if referral decision by paramedics based on a pre-hospital HEART score is non-inferior to routine management.
In phase III of the FamouS Triage study, patients with a HEART score ≤3 were asked to give informed consent for at-home observation instead of transfer to the hospital. (35) If patients were not transported, the paramedics instructed the patients to consult with their general practitioner to further investigate the presenting symptoms.
Previous results showed that patients included shortly after symptom onset might present with false negative troponin results. (36) Hence, the HEART score was assessed at home again 3-12 hours after inclusion. (35) In case of a HEART score >3, the patients were transported to a nearby hospital.
The POC cTn assay performed (Roche cobas h232) had a reference range of 40-2000 ng/l.
All patients with a positive POC cTn result received two points on the Troponin element of the HEART score. In case of a positive POC Troponin result, patients were transported to the hospital, regardless of a HEART score ≤3.

In phase III of the FamouS Triage study, a total of 536 patients was analyzed after exclusions due to various reasons. 149 (28%) low-risk patients were not transported to the hospital. 387 patients were transported to the hospital. In the low-risk group, the percentage of MACE was 1.3%. 3 patients of phase III died within 45 days, 2 of them were transported to the hospital, 1 was not transferred and died while under treatment for suspected pneumonia by the general practitioner.

The Authors concluded that prehospital risk-stratification of suspected NSTE-ACS patients and non-transport of low-risk patients seems feasible and non-inferior to transport of all patients to the hospital. They highlight that future studies should investigate whether the occurrence of MACE is still low when low-risk stratification is performed more consistently and a greater number of low-risk patients is not transported.

Moving one step further, the ARTICA trial is the first randomized trial that will investigate the cost-effectiveness of a prehospital rule-out strategy by a modified HEART score application. (31) Similar to phase III of the FamouS Triage study, patients are included if they are suspected of NSTE-ACS, are at least 18 years of age, present with a symptom duration of at least 2 hours, and have a modified HEART score ≤3. The same Roche cobas h232 POC cTn assay is used. The primary outcome is healthcare cost at 30 days to investigate the cost-effectiveness of a complete prehospital rule-out strategy. The results are expected to have a significant impact on the management of patients with chest pain.

3. Prehospital Treatment of STEMI

No universal approach regarding the treatment of NSTEACS can be established, as the term includes NSTEMI, as well as unstable angina pectoris. Hence prehospital management of NSTEACS is in general risk dependent and similar to STEMI treatment. Advances here focus on diagnosing NSTEMI in the prehospital setting.

The main objective of prehospital STEMI treatment is to relieve pain, breathlessness and anxiety, as well as to reduce thrombus burden and coagulation cascade hyperactivity prior to coronary reperfusion. (6,7)

3.1 Relief of pain

Because pain activates the sympathetic nervous system, causing vasoconstriction and increasing the workload on the heart, the ESC titrated IV opioids like morphine as an analgesic component. (7)
However, it is highlighted that morphine usage can interfere with oral antiplatelet agents like clopidogrel or ticagrelor. Morphine decreases plasma levels of the active metabolite of clopidogrel, delays absorption, and diminishes its effects. (37,38) Ultimately, this might lead to early treatment failure in susceptible individuals.
Based on a retrospective cohort analysis of the Air versus Oxygen in Myocardial Infarction (AVOID) study, Fernando et al. examined the relationship between opioid dose and myocardial infarction size. (39) Having included 422 patients in their research, they found no benefit of a higher opioid dose in controlling severe ischemic chest pain. They noted a signal towards a dose-dependent increase of CK release, which might be due to P2Y12 receptor interaction or greater opioid administration for patients with a greater ischemic burden before coronary intervention. Further studies are necessary to identify the exact mechanism.

3.2 Relief of breathlessness and anxiety

The ESC only recommends oxygen in hypoxic patients with $SaO_2 < 90\%$. (7)
This recommendation is based on several studies, including the Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction AVOID randomized controlled trial. (40)
8L/min oxygen administration was compared with no supplemental oxygen.
They included 628 patients, 441 of whom had confirmed STEMI. The primary endpoint was infarct size according to cardiac enzymes, troponin I, and creatinine kinase. A significant increase in peak CK in the oxygen group compared to the no-supplemental-oxygen group was found. Additionally, an increase in recurrent infarction and cardiac arrhythmias was found in the oxygen group. After 6 months, the oxygen group had an increase of the infarct size on cardiac MRI.
To relieve anxiety, the ESC recommends the use of a benzodiazepines. (7)

3.3 Antiplatelet therapy

Patients presenting with STEMI and undergoing primary PCI should receive dual antiplatelet therapy. (7) This idea was initially derived from the principle of preventing stent thrombosis. (41) Later it was found that DAPT also reduces the risk of subsequent infarctions in non-stented segments, thereby reducing all-cause mortality.

Aspirin should be administered as soon as possible in the prehospital setting. (6) The oral dose of the non-enteric-coated formulation should preferably be 150-300mg. (7) Concerning iv. administration, there is only scant clinical data on the optimal dosage. When considering a 50% bioavailability of aspirin, this would correspond to a dose of 75-150mg respectively.

Recently it has been demonstrated that a single dose of 250mg or 500mg aspirin iv. compared to 300mg orally was associated with faster inhibition of platelet aggregation and thromboxane generation at 5 minutes. (42) Bleeding complication rates were similar among both groups.

Evidence regarding the timing of P2Y12 inhibitor administration in STEMI patients is limited. (7) The ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New STEMI to Open the Coronary Artery) study is the only randomized study on this matter. (43) Median time difference between administration in the ambulance and in the catheterization laboratory was only 31 minutes. ATLANTIC failed to resolve ST-segment elevation or TIMI flow before the intervention, while major and minor bleeding events were identical in both treatment arms. Despite lacking evidence, it is common practice in Europe to initiate a P2Y12 inhibitor while the patient is being transported to the catheterization facility. (7) This is mainly based on the pharmacokinetic data of drug onset time.

Prasugrel (60mg loading dose, 10mg maintenance dose) or ticagrelor (180mg loading dose and 90mg maintenance dose) are the preferred P2Y12 inhibitors. (7) Both are superior to clopidogrel in patients with ACS over a range of cardiovascular outcomes, including stent thrombosis n recurrent MI. (42,44,45) Additionally, they have faster onsets of action.

Cangrelor is a reversible P2Y12 inhibitor administered intravenously with a rapid onset of action. (7) Analysis of trials showed that cangrelor could reduce periprocedural ischemic complications at the expense of an increased bleeding risk. (46)

The routine use of prehospital GP IIb/ IIIa inhibitors before PCI has not demonstrated benefits and increases bleeding risk when compared with use in the catheterization laboratory. (47,48) Overall, the ESC does not recommend routine use of GP IIb/ IIIa inhibitors for patients undergoing primary PCI. (7)

3.4 Anticoagulation

In general, the prehospital anticoagulative therapy for primary PCI is rather derived from extensive experience and familiarity than established clinical evidence. (6) The standard anticoagulant for primary PCI is unfractionated heparin (UFH).

No placebo-controlled trial to evaluate UFH in primary PCI has been conducted yet, but as previously mentioned, there is a large body of experience. (7) The recommended standard dosage for PCI is 70-100U/kg. A randomized open-label short- and long-term follow-up trial (ATOLL) was conducted to examine enoxaparin or unfractionated heparin in lowering ischemic and bleeding events in patients undergoing primary angioplasty for acute myocardial infarction. (49) The primary composite endpoints were 30-day death, MI, procedural failure, or major bleeding. Death, recurrent MI or ACS, and urgent revascularization were secondary composite endpoints.

While primary endpoints were not significantly reduced by enoxaparin, there was a reduction in secondary endpoints and, most importantly, no evidence of increased bleeding. In the per-protocol analysis of the ATOLL trial mentioned above, iv. enoxaparin was superior to UFH in reducing the primary endpoint, mortality, ischemic endpoints, and major bleeding. (50)

Additionally, enoxaparin was associated with a significant reduction in death compared to UFH in a meta-analysis of 23 PCI trials. (51)

Based on those considerations, it is recommended to consider enoxaparin in STEMI. (7)

There is insufficient data regarding the use of prehospital bivalirudin, and it has comparatively higher costs than the anticoagulants mentioned above. (6)

3.5 Prehospital fibrinolysis

If PCI cannot be offered timely, fibrinolysis is an important reperfusion strategy. (7)

A very early study has shown that it can prevent 30 deaths per 100 patients treated within 6 hours after symptom onset. (52)

Fibrinolytic therapy is recommended in the absence of contraindications if primary PCI cannot be performed within 120 minutes from STEMI diagnosis and symptom onset was within the last 12 hours. (7) With later presentation, the treatment strategy should be directed more towards primary PCI, as efficacy and clinical benefit of fibrinolysis decrease with time elapsing from symptom onset. (53)

A meta-analysis of six randomized trials demonstrated that fibrinolysis in the prehospital setting could reduce early mortality by 17% compared with in-hospital fibrinolysis. (54)
According to the STREAM trial, a strategy of prehospital fibrinolysis followed by early PCI had similar outcomes as transfer for primary PCI in STEMI patients who could not undergo primary PCI within 1 hour after FMC and presented within 3 hours after symptom onset. (55)
Regarding the prehospital setting, the ESC recommends fibrinolysis if trained medical or paramedical staff can either analyze the ECG on site or transmit the ECG for interpretation to a hospital. Fibrinolysis should be initiated within 10 minutes from STEMI diagnosis. (7)
Referring to an international randomized trial, the ESC recommends fibrin-specific agents for fibrinolysis. (7,56) As concluded from the ASSENT-2 double-blind randomized trial: "Single-bolus weight-adjusted tenecteplase tissue plasminogen activator (TNK-tPA) is equivalent to accelerated tPA in reducing 30-day mortality, but is safer in preventing non-cerebral bleeds and blood transfusion, and is easier to use in the pre-hospital setting". (57)
The benefits of aspirin and fibrinolytics were additive, as shown by an early study. (58) Hence a first dose of Aspirin, either chewed or intravenous, should be given and a low daily dose of 75-100mg should be prescribed after. As shown in the PCI-CLARITY study, clopidogrel added to aspirin significantly reduced the rate of MACE in STEMI treated with fibrinolytic therapy, compared to aspirin alone. (59) Up until now, no studies have yet examined ticagrelor or prasugrel as an adjunct to aspirin in fibrinolytic therapy. (6)
Regarding anticoagulation, enoxaparin is the preferred treatment. (7) The ASSENT-3 trial showed that enoxaparin was associated with a reduction in the risk of reinfarction and death at 30 days compared to a single dose weight-adjusted UFH for the tradeoff of a significant increase in non-cerebral bleeding complications. (60)
To sum up the previous assessment, "weight-adjusted iv. tenecteplase, aspirin, iv. enoxaparin and oral Clopidogrel comprise the antithrombotic cocktail most extensively studied". (7)
Contraindications for fibrinolytic therapy are listed in figure 3 below.

Absolute
Previous intracranial haemorrhage or stroke of unknown origin at anytime
Ischaemic stroke in the preceding 6 months
Central nervous system damage or neoplasms or arteriovenous malformation
Recent major trauma/surgery/head injury (within the preceding month)
Gastrointestinal bleeding within the past month
Known bleeding disorder (excluding menses)
Aortic dissection
Non-compressible punctures in the past 24 hours (e.g. liver biopsy, lumbar puncture)
Relative
Transient ischaemic attack in the preceding 6 months
Oral anticoagulant therapy
Pregnancy or within 1 week postpartum
Refractory hypertension (SBP >180 mmHg and/or DBP >110 mmHg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer
Prolonged or traumatic resuscitation

Figure 3. "Contra-indications to fibrinolytic therapy" (7)

3.6 Telemedical advancements

Brokmann et al. conducted a prospective interventional multicenter trial on "treatment of acute coronary syndrome by telemedically supported paramedics compared with physician-based treatment". (61) In the German emergency medical system, the prehospital treatment is reserved for EMS physicians due to legal issues. Hence, the main objective was to evaluate the quality of telemedically-delegated therapy and possible complications in patients with ACS.
While evidence regarding telemetry of prehospital ECG recordings of patients with STEMI for interpretation is abundant, data concerning telemedical concepts for non-STEMI ACS patients is lacking. For the study, 5 paramedic-staffed ambulances were equipped with a multifunctional telemedicine system. Participating "tele-EMS-physicians" were trained before the project started. The paramedics on scene decided whether to initiate teleconsultation. A total of 425 emergency teleconsultations were performed, 150 patients presented with a cardiovascular emergency, in 39 cases acute coronary syndrome was suspected, and therapy was performed solely by teleconsultation. Correct handling of the ECG was performed equally between the groups (38 in the study, 39 in the control group). Additionally, no significant difference in the correct handling of iv. heparin, morphine, and aspirin between the groups could be found. A

significant difference was recorded in the handling of oxygen. In the study group it was performed correctly for 29 out of 34 cases, and in the control group for 18 out of 34 matched cases. The authors concluded that diagnosis and treatment of ACS carried out by paramedics under tele-EMS-physician delegation seems to be safe and as effective as the conventional on-site procedure. Better adherence to international guidelines for oxygen administration were be found in the study group.

3.7 Transport

When discussing treatment, transport to the hospital should not be forgotten. Next to diagnostic and treatment options, safe transport to a medical facility is a core task of any emergency medical services system.

Throughout the transport, continuous cardiac monitoring should be performed, including NIBP, Spo2, and ECG. (6) Additionally, complete documentation of all administered medications, vital signs, and procedures should be carried out. As an adjunct, EMS checklists can ensure that essential items will not be forgotten.

The European Society of Cardiology recommends the establishment of STEMI-networks, linking hospitals in a “hub-and-spoke” fashion with a prioritized and efficient ambulance service. (7) Crucial characteristics regarding the prehospital setting for those networks are 1) a clear definition of geographic areas of responsibility, 2) sharing written protocols based on risk stratification and transportation by qualified staff in appropriately equipped ambulances and helicopters, 3) prehospital triage of STEMI patients to an appropriate facility while bypassing non-PCI hospitals without a 24/7 availability of primary PCI.

Regarding the transport modality, Hakim et al. investigated whether helicopter transport delays the prehospital transfer for STEMI patients in rural areas. (62)

1911 STEMI patients were analyzed, 410 transported by helicopter and 150 by means of ground transport. The primary endpoint was transport with first medical contact to primary PCI within the 90 minutes goal defined in international guidelines, and the secondary endpoint was the time of first medical contact until primary PCI. Their main finding was that for transfers under 50 km, HEMS transport of STEMI patients is five times less effective than ground transport in maintaining the 90-minute goal of FMC to primary PCI.

V. CONCLUSIONS

This narrative literature review assessed current standards, as well as ongoing research and its future implications of prehospital care for patients with acute coronary syndromes.
Patient- and system-related delays can be regarded as the biggest burden in prehospital logistics of care. To further improve efficiency of the logistical aspect, patient education remains a key factor. Early and correct recognition of symptoms leading to prompt activation of emergency medical services is crucial to improve survival rates.
As stated by C. Michael Gibson: "Time Is Myocardium and Time Is Outcomes". (5)
Preclinical measurement of cardiac biomarkers can be regarded as the major novelty in prehospital acute coronary syndrome care. While still an area of ongoing research, preclinical biomarkers could help to improve diagnostic accuracy, reduce delays and increase cost effectiveness. Particularly when incorporated into risk-stratification tools like the HEART-score.
While the prehospital treatment of acute coronary syndromes is mainly based on society guidelines, advancements like telemedical support of paramedics and emergency medical physicians might be implemented in the future to bring cardiological expertise to the scene.

REFERENCES

1. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Dec 23;64(24):e139–228.

2. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019 Jan 14;40(3):237–69.

3. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. Eur Heart J. 2016 Nov 7;37(42):3232–45.

4. Puymirat E, Simon T, Cayla G, Cottin Y, Elbaz M, Coste P, et al. Acute Myocardial Infarction: Changes in Patient Characteristics, Management, and 6-Month Outcomes Over a Period of 20 Years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. Circulation. 2017 Nov 14;136(20):1908–19.

5. Gibson CM. Time Is Myocardium and Time Is Outcomes. Circulation. 2001 Nov 27;104(22):2632–4.

6. Brown AJ, Ha FJ, Michail M, West NEJ. Prehospital Diagnosis and Management of Acute Myocardial Infarction. In: Watson TJ, Ong PJ, Tcheng JE, editors. Primary Angioplasty: A Practical Guide [Internet]. Singapore: Springer; 2018 [cited 2021 Nov 11]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK543584/

7. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018 Jan 7;39(2):119–77.

8. Mirzaei S, Steffen A, Vuckovic K, Ryan C, Bronas UG, Zegre-Hemsey J, et al. The association between symptom onset characteristics and prehospital delay in women and men with acute coronary syndrome. Eur J Cardiovasc Nurs J Work Group Cardiovasc Nurs Eur Soc Cardiol. 2020 Feb;19(2):142–54.

9. Youssef GS, Kassem HH, Ameen OA, Al Taaban HS, Rizk HH. Pre-hospital and hospital delay in patients with non-ST elevation acute coronary syndromes in tertiary care. Egypt Heart J. 2017 Sep;69(3):177–81.

10. Cartledge S, Finn J, Straney L, Ngu P, Stub D, Patsamanis H, et al. The barriers associated with emergency medical service use for acute coronary syndrome: the awareness and influence of an Australian public mass media campaign. Emerg Med J EMJ. 2017 Jul;34(7):466–71.

11. Eckle VS, Lehmann S, Drexler B. Prehospital management of patients with suspected acute coronary syndrome : Real world experience reflecting current guidelines. Med Klin Intensivmed Notfallmedizin. 2021 Nov;116(8):694–7.

12. Gulati M, Levy PD, Mukherjee D, Amsterdam E, Bhatt DL, Birtcher KK, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021 Nov 30;144(22):e368–454.

13. McGarry M, Shenvi CL. Identification of Acute Coronary Syndrome in the Elderly. Emerg Med Clin North Am. 2021 May;39(2):339–46.

14. DeVon HA, Mirzaei S, Zègre-Hemsey J. Typical and Atypical Symptoms of Acute Coronary Syndrome: Time to Retire the Terms? J Am Heart Assoc. 2020 Apr 7;9(7):e015539.

15. Andersson H, Ullgren A, Holmberg M, Karlsson T, Herlitz J, Wireklint Sundström B. Acute coronary syndrome in relation to the occurrence of associated symptoms: A quantitative study in prehospital emergency care. Int Emerg Nurs. 2017 Jul;33:43–7.

16. Sundström BW, Dahlberg K. Being prepared for the unprepared: a phenomenology field study of Swedish prehospital care. J Emerg Nurs. 2012 Nov;38(6):571–7.

17. Alotaibi A, Alghamdi A, Reynard C, Body R. Accuracy of emergency medical services (EMS) telephone triage in identifying acute coronary syndrome (ACS) for patients with chest pain: a systematic literature review. BMJ Open. 2021 Aug 25;11(8):e045815.

18. Coventry LL, Bremner AP, Jacobs IG, Finn J. Myocardial infarction: sex differences in symptoms reported to emergency dispatch. Prehospital Emerg Care Off J Natl Assoc EMS Physicians Natl Assoc State EMS Dir. 2013 Jun;17(2):193–202.

19. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol. 2012 Oct 16;60(16):1581–98.

20. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2021 Apr 7;42(14):1289–367.

21. Cheung KS, Leung LP, Siu YC, Tsang TC, Tsui MSH, Tam CC, et al. Prehospital electrocardiogram shortens ischaemic time in patients with ST-segment elevation myocardial infarction. Hong Kong Med J Xianggang Yi Xue Za Zhi. 2019 Oct;25(5):356–62.

22. Ting HH, Krumholz HM, Bradley EH, Cone DC, Curtis JP, Drew BJ, et al. Implementation and integration of prehospital ECGs into systems of care for acute coronary syndrome: a scientific statement from the American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research, Emergency

Cardiovascular Care Committee, Council on Cardiovascular Nursing, and Council on Clinical Cardiology. Circulation. 2008 Sep 2;118(10):1066–79.

23. Zègre-Hemsey JK, Patel MD, Fernandez AR, Pelter MM, Brice J, Rosamond W. A Statewide Assessment of Prehospital Electrocardiography Approaches of Acquisition and Interpretation for ST-Elevation Myocardial Infarction Based on Emergency Medical Services Characteristics. Prehospital Emerg Care Off J Natl Assoc EMS Physicians Natl Assoc State EMS Dir. 2020 Aug;24(4):550–6.

24. Trivedi K, Schuur JD, Cone DC. Can paramedics read ST-segment elevation myocardial infarction on prehospital 12-lead electrocardiograms? Prehospital Emerg Care Off J Natl Assoc EMS Physicians Natl Assoc State EMS Dir. 2009 Jun;13(2):207–14.

25. Tanguay A, Lebon J, Brassard E, Hébert D, Bégin F. Diagnostic accuracy of prehospital electrocardiograms interpreted remotely by emergency physicians in myocardial infarction patients. Am J Emerg Med. 2019 Jul;37(7):1242–7.

26. Terkelsen CJ, Sørensen JT, Maeng M, Jensen LO, Tilsted HH, Trautner S, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. JAMA. 2010 Aug 18;304(7):763–71.

27. Stengaard C, Sørensen JT, Rasmussen MB, Søndergaard HM, Dodt KK, Niemann T, et al. Editor's Choice-Acute versus subacute angiography in patients with non-ST-elevation myocardial infarction - the NONSTEMI trial phase I. Eur Heart J Acute Cardiovasc Care. 2017 Sep;6(6):490–9.

28. Rasmussen MB, Stengaard C, Sørensen JT, Riddervold IS, Hansen TM, Giebner M, et al. Predictive value of routine point-of-care cardiac troponin T measurement for prehospital diagnosis and risk-stratification in patients with suspected acute myocardial infarction. Eur Heart J Acute Cardiovasc Care. 2019 Jun;8(4):299–308.

29. van Dongen DN, Fokkert MJ, Tolsma RT, Badings EA, van der Sluis A, Slingerland RJ, et al. Value of Prehospital Troponin Assessment in Suspected Non-ST-Elevation Acute Coronary Syndrome. Am J Cardiol. 2018 Nov 15;122(10):1610–6.

30. Van Den Berg P, Body R. The HEART score for early rule out of acute coronary syndromes in the emergency department: a systematic review and meta-analysis. Eur Heart J Acute Cardiovasc Care. 2018 Mar;7(2):111–9.

31. Aarts GWA, Camaro C, van Geuns RJ, Cramer E, van Kimmenade RRJ, Damman P, et al. Acute rule-out of non–ST-segment elevation acute coronary syndrome in the (pre)hospital setting by HEART score assessment and a single point-of-care troponin: rationale and design of the ARTICA randomised trial. BMJ Open. 2020 Feb;10(2):e034403.

32. Lindner G, Woitok BK. Emergency department overcrowding : Analysis and strategies to manage an international phenomenon. Wien Klin Wochenschr. 2021 Mar;133(5–6):229–33.

33. Nawar EW, Niska RW, Xu J. National Hospital Ambulatory Medical Care Survey: 2005 emergency department summary. Adv Data. 2007 Jun 29;(386):1–32.

34. Cotterill PG, Deb P, Shrank WH, Pines JM. Variation in chest pain emergency department admission rates and acute myocardial infarction and death within 30 days in the Medicare population. Acad Emerg Med Off J Soc Acad Emerg Med. 2015 Aug;22(8):955–64.

35. Tolsma RT, Fokkert MJ, van Dongen DN, Badings EA. Referral decisions based on a pre-hospital HEART score in suspected non-ST-elevation acute coronary syndrome: final results of the FamouS Triage study. :10.

36. van Dongen DN, Tolsma RT, Fokkert MJ, Badings EA, van der Sluis A, Slingerland RJ, et al. Pre-hospital risk assessment in suspected non-ST-elevation acute coronary syndrome: A prospective observational study. Eur Heart J Acute Cardiovasc Care. 2020 Mar;9(1_suppl):5–12.

37. Hobl EL, Stimpfl T, Ebner J, Schoergenhofer C, Derhaschnig U, Sunder-Plassmann R, et al. Morphine decreases clopidogrel concentrations and effects: a randomized, double-blind, placebo-controlled trial. J Am Coll Cardiol. 2014 Feb 25;63(7):630–5.

38. Parodi G, Bellandi B, Xanthopoulou I, Capranzano P, Capodanno D, Valenti R, et al. Morphine is associated with a delayed activity of oral antiplatelet agents in patients with ST-elevation acute myocardial infarction undergoing primary percutaneous coronary intervention. Circ Cardiovasc Interv. 2015 Jan;8(1):e001593.

39. Fernando H, Nehme Z, Peter K, Bernard S, Stephenson M, Bray J, et al. Prehospital opioid dose and myocardial injury in patients with ST elevation myocardial infarction. Open Heart. 2020 Jul;7(2):e001307.

40. Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, et al. Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction. Circulation. 2015 Jun 16;131(24):2143–50.

41. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014 Dec 4;371(23):2155–66.

42. Zeymer U, Hohlfeld T, Vom Dahl J, Erbel R, Münzel T, Zahn R, et al. Prospective, randomised trial of the time dependent antiplatelet effects of 500 mg and 250 mg acetylsalicylic acid i. v. and 300 mg p. o. in ACS (ACUTE). Thromb Haemost. 2017 Feb 28;117(3):625–35.

43. Montalescot G, van ’t Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med. 2014 Sep 11;371(11):1016–27.

44. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007 Nov 15;357(20):2001–15.

45. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009 Sep 10;361(11):1045–57.

46. Steg PG, Bhatt DL, Hamm CW, Stone GW, Gibson CM, Mahaffey KW, et al. Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: a pooled analysis of patient-level data. Lancet Lond Engl. 2013 Dec 14;382(9909):1981–92.

47. Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Janssens L, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med. 2008 May 22;358(21):2205–17.

48. ten Berg JM, van 't Hof AWJ, Dill T, Heestermans T, van Werkum JW, Mosterd A, et al. Effect of early, pre-hospital initiation of high bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short- and long-term clinical outcome. J Am Coll Cardiol. 2010 Jun 1;55(22):2446–55.

49. Silvain J, O'Connor SA, Yan Y, Kerneis M, Hauguel-Moreau M, Zeitouni M, et al. Biomarkers of Thrombosis in ST-Segment Elevation Myocardial Infarction: A Substudy of the ATOLL Trial Comparing Enoxaparin Versus Unfractionated Heparin. Am J Cardiovasc Drugs Drugs Devices Interv. 2018 Dec;18(6):503–11.

50. Collet JP, Huber K, Cohen M, Zeymer U, Goldstein P, Pollack C, et al. A direct comparison of intravenous enoxaparin with unfractionated heparin in primary percutaneous coronary intervention (from the ATOLL trial). Am J Cardiol. 2013 Nov 1;112(9):1367–72.

51. Silvain J, Beygui F, Barthélémy O, Pollack C, Cohen M, Zeymer U, et al. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. BMJ. 2012 Feb 3;344:e553.

52. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Lancet Lond Engl. 1994 Feb 5;343(8893):311–22.

53. Pinto DS, Frederick PD, Chakrabarti AK, Kirtane AJ, Ullman E, Dejam A, et al. Benefit of transferring ST-segment-elevation myocardial infarction patients for percutaneous coronary intervention compared with administration of onsite fibrinolytic declines as delays increase. Circulation. 2011 Dec 6;124(23):2512–21.

54. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: A meta-analysis. JAMA. 2000 May 24;283(20):2686–92.

55. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. N Engl J Med. 2013 Apr 11;368(15):1379–87.

56. GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med. 1993 Sep 2;329(10):673–82.

57. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators, Van De Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial

infarction: the ASSENT-2 double-blind randomised trial. Lancet Lond Engl. 1999 Aug 28;354(9180):716–22.

58. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet Lond Engl. 1988 Aug 13;2(8607):349–60.

59. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. JAMA. 2005 Sep 14;294(10):1224–32.

60. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. Lancet Lond Engl. 2001 Aug 25;358(9282):605–13.

61. Brokmann JC, Conrad C, Rossaint R, Bergrath S, Beckers SK, Tamm M, et al. Treatment of Acute Coronary Syndrome by Telemedically Supported Paramedics Compared With Physician-Based Treatment: A Prospective, Interventional, Multicenter Trial. J Med Internet Res. 2016 Dec 1;18(12):e314.

62. Hakim R, Revue E, Saint Etienne C, Marcollet P, Chassaing S, Decomis MP, et al. Does helicopter transport delay prehospital transfer for STEMI patients in rural areas? Findings from the CRAC France PCI registry. Eur Heart J Acute Cardiovasc Care. 2020 Dec;9(8):958–65.