Prehospital diagnosis of patients with acute myocardial infarction

Abstract: Primary percutaneous intervention (PPCI) is the preferred treatment in patients with ST elevation myocardial infarction (STEMI) if this can be performed in a timely manner. The 2012 ESC Guidelines on management of AMI in patients presenting with ST-segment elevation advice that PPCI should be performed within 120 min of first medical contact. Prehospital diagnosis of patients with STEMI is performed to save time and make PPCI available to the majority of patients. Although diagnosing patients with STEMI is usually easy, there are important pitfalls and patients with STEMI are missed on occasion. In addition, it is well known that patients without ST elevation may also have a high-risk cardiac condition. The 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation stress the importance of urgent CAG in patients with high-risk non ST-segment elevation myocardial infarction (NSTEMI). Unfortunately, these patients are difficult to diagnose in the acute phase and important time may be spent establishing the correct diagnosis. Prehospital biomarker measurement has emerged as a method to gain important additional information. We review the evidence on prehospital diagnosis of patients with STEMI and, in addition, we present the current knowledge on the new diagnostic methods that could have a future role in prehospital rule-in and rule-out of cardiac disease.

Keywords: ambulances; cardiac troponin; early diagnosis; electrocardiography; point-of-care systems; ST-segment elevation myocardial infarction; non ST-segment myocardial infarction; telemedicine.

Introduction

Patients with suspected acute myocardial infarction (AMI) are among the most frequent presenters in acute medical care [1, 2]. Cardiac conditions require optimal patient logistics. Severe and life threatening disorders must be diagnosed immediately and treatment initiated without delay to reduce mortality and morbidity. This is easy in some situations. However, the signs and symptoms can be ambiguous and advanced time consuming diagnostic algorithms must be employed to reach the right diagnosis in due time [3–5]. Additionally, a fast rule-out of cardiac disease is important, as this will allow other diagnoses to be explored and treated at an earlier time. The focus of the attending doctor is the safety of the individual patient but crowded emergency departments is a huge challenge [6]. A world with limited healthcare resources challenges the emergency physicians who are faced with conflicting demands of fast turnaround times, patient triage, patient safety, and patient satisfaction. It has been documented that the health care related costs of patients presenting with symptoms of AMI reaches billions of Euros each year [6, 7]. It is intriguing that only a minor proportion of patients admitted with suspected AMI actually have the disease [5, 8]. Altogether, a fast and reliable rule-in and rule-out of cardiac disease holds the opportunity to optimize patient logistics, save healthcare funds, and improve outcome [3, 7, 9].

The prehospital phase represents a substantial part of the time spent during the acute admission and offers valid information to aid in fast diagnosis of cardiac conditions. The symptoms may be more pronounced at this first presentation as paramedics and physicians offer acute, relieving treatments upon their arrival. Unfortunately, the
prehospital phase is frequently neglected in the diagnostic process and consequently opportunities to optimize patient handling and triage are missed. Moreover, unnecessary admissions may be the result.

During the last decade, new prehospital algorithms have emerged with the aim to improve the prehospital diagnosis in patients with cardiac symptoms. In this paper we review the established evidence on prehospital electrocardiography (ECG) diagnosis in patients with AMI. In addition, we present the current knowledge on the new diagnostic methods that could have a future role in prehospital rule-in and rule-out of cardiac disease.

Prehospital ECG diagnosis of patients with ST elevation myocardial infarction

Primary percutaneous coronary intervention (PPCI) is the treatment of choice in patients with ST elevation myocardial infarction (STEMI) if this can be performed in a timely manner [9]. However, the limited accessibility of hospitals with 24–7 PPCI capability is a significant obstacle to widespread use of PPCI, and only few countries have been able to offer PPCI to all patients with STEMI, Figure 1 [10–12]. In urban areas PPCI service is within reach for most patients, whereas offering PPCI to patients in rural areas is a challenge. This has led to an increased interest in prehospital diagnosis of patients with STEMI. The diagnostic modality of choice has been the ECG. Prehospital ECG diagnosis was pioneered in the late 1980s, and advances in cellular telephone technology made transmission of full 12 lead ECG’s possible [13–15]. Hence, ECG interpretation was possible at a distance as the cardiologist on call could assist the paramedics and the ambulance physicians. Prehospital diagnosis allows for the patient to be rerouted directly to the PPCI capable hospital. The local hospital is bypassed and the time from alarm call to balloon inflation is reduced (system delay) [16]. Terkelsen and colleagues demonstrated a more than 1 h reduction of system delay among patients diagnosed in the prehospital setting and triaged directly to PPCI, compared to patients without prehospital ECG recording and admission to a local hospital [16]. Prehospital ECG diagnosis has been successfully implemented worldwide and field triage directly to PPCI is associated with improved outcome, Figure 2 [17–21]. Danish nationwide data suggests that each additional hour spent is associated with a 10% relative increase in both mortality and the risk of heart failure [18, 22], and that shorter

Figure 1: The use of primary percutaneous intervention for patients with ST elevation myocardial infarction (STEMI) in the European countries, measured in 2010 and 2011. From [10]. Reproduced with permission.
System delays are associated with an increased proportion of patients returning to the labor market, Figure 3 [23].

The 2012 ESC Guidelines on management of AMI in patients presenting with ST-segment elevation advise that PPCI should be performed within 120 min of first medical contact [9]. However, time is needed for the ambulance to reach the patient, for prehospital handling of the patient, and for in-hospital preparation of the patient for PPCI. Therefore there is an upper time limit for the transport of the patient to the PPCI capable hospital [24]. One solution to this dilemma is to introduce PPCI facilities with a closer proximity. However, in less populated area, the number of presenting patients would not justify a 24-h PPCI service. The invasive cardiologist would lack everyday experience with STEMI, and often surgical and advanced anesthesiological backup would not be available. In accordance with

Figure 2: Patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous intervention (PPCI) in Denmark from 1999 to 2009.
The patients are stratified according to prehospital triage strategy and whether patients were transported by ambulance or not. In 2009, 80% of patients who had prehospital diagnosis performed were rerouted and transported directly to the PPCI-center. From [17]. Reproduced with permission.

Figure 3: Kaplan-Meier cumulative mortality estimates for patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention (n = 6209).
From [22]. Reproduced with permission.
international findings, we found that, 1% of our STEMI patients required acute surgery [25]. Alternatively all processes from emergency call to catheter could be optimized [26] as demonstrated by Sejersten and colleagues who showed a significant 1 h reduction in door-to-balloon delay in patients with a prehospital diagnosis compared with in-hospital diagnosis (34 vs. 97 min, \( p < 0.001 \)) [27]. Additionally, Sorensen et al. evaluated the routine use of prehospital ECG diagnosis and field triage in a larger region comprising both urban and rural surroundings [28]. Prehospital diagnosis and rerouting to the PPCI center reduced the advantage of living in close proximity of the PPCI center. The authors found that total system delay was only 9 min longer in patients living in rural areas, at a median of 40 km from the PPCI center, compared with patients living in an urban area with a median of 10 km from the PPCI center. Prehospital ECG diagnosis enables an early activation of the catheterization laboratory and preparation for the patient arrival as soon as the diagnosis is established. However, living in the close proximity of the PPCI center seems to be outweighed by the reduced amount of time to prepare for the patient. This results in a longer door-to-balloon delay, Figure 4 [24]. Even in an optimal setting, the system delay is a median of 80 min for those living in the near vicinity of the PPCI center. However, the shorter door-to-balloon time for patients with long traveling distances, still allows patients living up to 100 km away to be treated within 120 min when ground transport is used. We have documented that combining prehospital ECG diagnosis in patients with STEMI with immediate air lifting, utilizing physician manned helicopters, reduce the system delay significantly for patients with driving distances of more than 60 km. Thus, a STEMI-system where helicopters are used, provides patients with transport distances up to 150 km the possibility to be treated using PPCI at the tertiary heart center within the time advised by the guidelines [29].

Establishing the tentative STEMI diagnosis in the prehospital setting is easy in most cases. However, some present with ECG changes where acute ischemia is difficult to diagnose. In patients with a suspected AMI, 10% present with bundle branch block (BBB), and patients with BBB and AMI have a significantly higher mortality [30, 31]. Patients with presumed newly developed left bundle branch block (LBBB) in relation to AMI are at particular high risk and should be treated as STEMI. It is well established that newly developed right bundle branch block (RBBB) in the setting of AMI, is associated with a similar high mortality, suggesting that acute invasive treatment should also apply in this case [31, 32]. The difficulty in identifying ischemia in the ECG in the presence of BBB, results in only a minority of patients with LBBB myocardial infarction being treated with reperfusion therapy as recommended by the guidelines [31, 33]. The

Figure 4: Dependency of distance on the predicted system delay (time from alarm call to primary percutaneous intervention) and the various components of the system delay, in patients with ST-segment elevation myocardial infarction.
The median expected system delay is 80 min even in patients living close to the heart center. In an optimal setting where telemedicine prehospital diagnosis and rerouting is used, patients with driving distances up to 100 km may be treated within the 120 min advised by the guidelines. From [24]. Reproduced with permission.
Sgarbossa criteria could aid in diagnosing LBBB myocardial infarction but when applied in cohorts of all-comers the Sgarbossa criteria suffice with resulting low sensitivity [34–36]. Other ECG changes associated to high risk STEMI are the “de Winter T-waves” [37], “Wellens’ Syndrome” [38], global ischemia associated with acute left main artery occlusions [39], anterior ST segment depression in posterior STEMI, and patients with paced rhythm. This raises the question of how the ECG interpretation is performed. Automated ECG interpretation algorithms have been suggested as a safe and effective method for diagnosing STEMI [40]. However, the automated algorithms do not detect the STEMI equivalent changes, the error rate is high and sensitivity is generally low [41, 42]. In a recent study, Garvey and colleagues investigated three automated algorithms and found sensitivities of approximately 60% and the algorithms suggested false positive STEMI diagnoses in 10% of patients without STEMI. Clark and colleagues compared the automated algorithms with human interpretation and found a 7% lower sensitivity for diagnosing STEMI [43]. Paramedics with 4–6 h of training may be able to identify classic STEMI, but one comparative study found a false negative rate for identification of anterior or lateral STEMI’s of 25%–50% [44–46]. Still, even physicians will miss STEMI and only physicians with expert ECG knowledge seem to be able to identify STEMI with sufficient precision [47]. One option is to train emergency physicians to a high level of ECG interpretation. However, emergency physicians cannot attend all patients with a suspected AMI, and the availability of emergency physicians may be limited in remote locations and less developed countries. Another option is to transfer the ECG for in-hospital expert telemedicine diagnosis. This can easily be implemented everywhere and ensure high quality ECG interpretation in all patients. In addition to false negative ECG interpretation, false positive activation of the catheterization laboratory is a particular problem. Experience from our center, indicates that 80%–85% of patients triaged to our center for PPCI ultimately have STEMI, but also that 96% of all catheterization laboratory activations were deemed appropriate [24, 48]. Patients, who are falsely triaged for PPCI essentially end up having an unnecessary CAG performed, are treated with antithrombotic and anti-coagulant medications and the time needed to perform the CAG delays additional diagnostic initiatives. All these aspects intuitively increase the patient’s risk. Unfortunately we lack information on the potential worsening of the outcome for false positive STEMI patients.

In conclusion, identification of a STEMI is not an easy task, and patients with a STEMI are likely to be missed, irrespective of the method used and the person doing the ECG interpretation. However, using wireless ECG transmission for in-hospital evaluation by highly-skilled physicians has been shown to be both sensitive and specific for the diagnosis of STEMI and allow for relevant catheterisation laboratory activation. Combined with optimized and integrated STEMI systems of care, prehospital ECG diagnosis could aid in finally making PPCI available to all patients with STEMI.

**Prehospital biomarker measurement**

Patients with STEMI only constitute a minor proportion of the prehospital patient population presenting with symptoms and signs of an ACS. In addition the current 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation stress the importance of urgent CAG in patients with high-risk non ST-segment elevation myocardial infarction (NSTEMI) [3]. The majority of patients with NSTEMI are admitted to non-PCI capable referral hospitals. For patients with a high risk, who develop an unstable cardiac condition, this initial admission delays a potentially lifesaving treatment and prolongs the admission. It has been shown that 63% of patients with NSTEMI have significant flow limiting coronary disease and that coronary occlusion may persist for days after symptom onset [49, 50]. With the recent advances in STEMI care and associated improved outcome, the mortality in patients with NSTEMI is now comparable to and may even exceed that of patients with STEMI [51, 52]. Studies investigating the timing of invasive treatment of patients with NSTEMI are few, but generally suggest that accelerated treatment is superior to delayed or selective conservative strategies [3]. Difficulties in ability to, consistently and correctly, diagnose patients with NSTEMI at first contact, are the main limitations in accelerating the coronary angiography (CAG) to offer a STEMI-like system of care in the setting of NSTEMI. Prehospital analysis of biomarkers of cardiac dysfunction or endogenous stress may be one method to gain more information in patients with non-conclusive ECG changes. There is increasing evidence that prehospital point-of-care testing (POCT) of biomarkers may provide important diagnostic information.

A total of 10 studies, investigating the utility of POCT of biomarkers in the ambulance, have been performed and are summarized in Table 1 [53–62]. Many studies include a low number of patients with a high prevalence of AMI which suggests selection. Gust and colleagues were the first to apply biomarker measurement in the ambulance
Table 1: Studies on the prehospital use of POC biomarker testing for rule-in or rule-out of acute myocardial infarction.

<table>
<thead>
<tr>
<th>Study details</th>
<th>Biomarker</th>
<th>Interpretation</th>
<th>Cut off</th>
<th>Investigator</th>
<th>n (AMI/ACS) %</th>
<th>Sens.</th>
<th>Spec.</th>
<th>PPV</th>
<th>NPV</th>
<th>Symptom duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gust et al. [53] Rule in. Patients with severe chest pain</td>
<td>Troponin T</td>
<td></td>
<td>200 ng/L</td>
<td>Emergency Physician</td>
<td>68 (16 AMI) 24%</td>
<td>25%</td>
<td>98%</td>
<td>80%</td>
<td>81%</td>
<td>4.3 h</td>
</tr>
<tr>
<td>Roth et al. [54] Rule out. Atypical chest pain. No clinical suspicion of AMI or other cardiovascular emergency. Panel</td>
<td>CK-MB</td>
<td>Effect evaluated for entire panel</td>
<td>5 µg/L</td>
<td>Emergency Physician</td>
<td>777 (11 ACS) 1.4%</td>
<td>56%</td>
<td>96%</td>
<td>37%</td>
<td>99%</td>
<td>6–48 h</td>
</tr>
<tr>
<td>Myoglobin, Troponin I, All markers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Newman et al. [55] Rule in. Patients contacting 9-1-1 with complaints of chest pain</td>
<td>Troponin T</td>
<td></td>
<td>0.18 µg/L</td>
<td>Paramedic</td>
<td>87 (29 AKS) 33%</td>
<td>56%</td>
<td>96%</td>
<td>37%</td>
<td>99%</td>
<td>Not specified</td>
</tr>
<tr>
<td>Svensson et al. [56] Rule in. Patients contacting 9-1-1 with complaints of chest pain, Panel</td>
<td>CK-MB</td>
<td>Effect evaluated for entire panel</td>
<td>5 µg/L</td>
<td>Emergency Physician or nurse</td>
<td>538 (167 AMI) 31.1%</td>
<td>17.5</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 4 h for 86% of patients</td>
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<tr>
<td>Myoglobin, Troponin I, All markers</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Schuchert et al. [57] Rule in. Chest pain</td>
<td>Troponin T</td>
<td></td>
<td>180 ng/L</td>
<td>Not specified</td>
<td>158 (40 AMI) 21%</td>
<td>18%</td>
<td>97%</td>
<td>63%</td>
<td>78%</td>
<td>Not specified</td>
</tr>
<tr>
<td>Di Serio et al. [58] Rule in. Chest pain – not STEMI</td>
<td>Troponin I</td>
<td></td>
<td>0.09 µg/L</td>
<td>Not specified</td>
<td>53 (20 AMI) 41.5%</td>
<td>91%</td>
<td>87%</td>
<td>83%</td>
<td>93%</td>
<td>Not specified</td>
</tr>
<tr>
<td>Ecollan et al. [59] Rule in. Chest pain. Emergency physician on site. Panel</td>
<td>Troponin I</td>
<td>Effect evaluated for individual markers.</td>
<td>0.4 µg/L</td>
<td>Emergency Physician</td>
<td>108 (55 AMI) 51%</td>
<td>22%</td>
<td>100%</td>
<td>60%</td>
<td>55%</td>
<td>&lt; 3 h for 70% of patients</td>
</tr>
<tr>
<td>Myoglobin, CK-MB, H-FABP</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sørensen et al. [60] Rule in. Rule in. Patients contacting 9-1-1 with complaints of chest pain</td>
<td>Troponin T</td>
<td></td>
<td>100 ng/L</td>
<td>Paramedic</td>
<td>928 (202 AMI) 22%</td>
<td>31%</td>
<td>99%</td>
<td>91%</td>
<td>83%</td>
<td>83 min</td>
</tr>
<tr>
<td>Stengaard et al. [61] Rule in. Patients contacting 9-1-1 with complaints of chest pain, Semi-quantitative device</td>
<td>Troponin T</td>
<td></td>
<td>50 ng/L</td>
<td>Paramedic</td>
<td>985 (200 AMI) 20%</td>
<td>39%</td>
<td>95%</td>
<td>68%</td>
<td>86%</td>
<td>70 min</td>
</tr>
<tr>
<td>Slagman et al. [62] Rule in and rule-out Patients with high risk of myocardial infarction</td>
<td>Troponin T</td>
<td>Effect evaluated for individual markers and combination</td>
<td>14 ng/L</td>
<td>Not specified</td>
<td>93 (37 AMI) 40%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Retrospective analysis</td>
<td>High sensitivity Troponin T</td>
<td></td>
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<tr>
<td>Copeptin</td>
<td></td>
<td></td>
<td>10 pmol/L</td>
<td>Not specified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150 min</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; ACS, acute coronary syndrome; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value; CK-MB, creatinine kinase myocardial band; STEMI, ST elevation myocardial infarction.
In a small study, emergency physicians measured cardiac troponin T (cTnT) in 68 patients with chest pain. The test missed 75% of patients with AMI and the authors concluded that prehospital testing would not improve the diagnosis of AMI. The assay had a poor analytical sensitivity of 200 ng/L compared with the 14 ng/L 99th percentile upper reference level cTnT cut point used today. This analytical limitation is universal for all the studies reporting the diagnostic properties of cardiac troponin (cTn) in the prehospital setting. Combined with the known delayed release of cTn in myocardial infarction, the observed diagnostic performance for identification of AMI, of cTn measurement in the prehospital setting is low with reported sensitivities between 17 and 39%, Table 1 [63]. The results of the (small) study of 53 patients by DiSerio and colleagues with a surprisingly high reported 91% sensitivity, would probably not be replicated in a population of all-comers with chest pain [58]. One study by Roth and colleagues investigated the possibility to rule-out AMI in patients with long symptom duration and atypical chest pain [54]. They used a biomarker panel of creatinine kinase myocardial band (CK-MB), myoglobin and cardiac troponin I (cTnI) with a low analytical sensitivity. A total of 777 patients were included and only 11 patients had AMI. They found that it was possible to rule out AMI in 96% with a negative predictive value of 99%. However among those with a negative test, six did in fact have AMI or unstable angina and an additional three died within the first week after testing. The study illustrates the difficulties in ruling out AMI using assays without sufficient analytical properties, and certainly a prehospital single-marker measurement of Troponin is not useful for neither rule-in nor rule-out. This, however, does not exclude the possibility that selected high-risk NSTEMI-patients with classical symptoms and elevated prehospital cTn may observe a benefit in the future from direct admissions to invasive centers instead of admission to local hospitals.

Three studies have investigated prehospital biomarker measurement in large cohorts that represent the typical population of patients presenting with symptoms of AMI. Svensson and colleagues used the same three-biomarker panel used by Roth and found poor diagnostic properties with sensitivities below 20% for the individual biomarkers and 21% in combination [56]. However, in a later sub-study, the proportion of AMI’s detected increased from 47% to 57% when the biomarker panel was combined with ECG changes [64]. In addition, the authors found that ECG changes and elevated biomarkers predicted a poor outcome and elevated biomarkers were found to be independent risk factors for 30-day mortality. Sørensen and colleagues published the results of a study investigating the routine use of qualitative cTnT testing performed by paramedics [60]. With only basic training, the paramedics, could obtain blood samples and perform a simple qualitative POCT cTnT measurement with a 97% success rate. Further, the prehospital POCT measurement was performed 71 min before in-hospital measurement. However, the high cut-point of 100 ng/L of the qualitative test was associated with a low sensitivity of 30%. In a more recent study, Stengaard and colleagues implemented quantitative POCT measurement performed by paramedics, Figure 5 [61]. Improved analytical properties (cut-point 50 ng/L)
were associated with an increased sensitivity of 39% with regard to the diagnosis AMI. An elevated prehospital POC TnT was associated with increased mortality regardless of an AMI or not (hazard ratio of 3.26, \( p < 0.001 \)), Figure 6. The two latter studies are important because 1) POC performed by paramedics in the prehospital setting would make biomarker measurement available to all patients transported in an ambulance, and 2) an elevated biomarker value, along with symptoms of AMI, could be used to triage the patients directly for advanced cardiac treatment.

In the Acute versus subacute coronary angiography in patients with non ST elevation myocardial infarction – the NONSTEMI trial phase I, we utilized prehospital POC cTnT in a study investigating the feasibility of a STEMI-like PPCI system of care in 250 patients with NSTEMI, randomized for either acute CAG or conventional therapy with CAG performed within 72 h (clinicaltrials.gov: NCT01638806) [65]. Patients were eligible for inclusion, if they had symptoms of classic angina pectoris, and if they had an elevated POC cTnT above 50 ng/L in the prehospital setting or within the first hour after admission, and/or if they had significant ST-segment depression. This rule-in algorithm allowed identification of a cohort of patients where 68% had elevated POC cTnT values and where 59% could be identified already in the prehospital setting. In total, 86% of the patients had acute coronary syndrome, 76% had a culprit lesion and 64% needed revascularization of an acute coronary lesion. A total of 64% had NSTEMI and 11% had unstable angina pectoris. The endpoint committee judged that 8% had STEMI at the time of enrolment, although this was not suspected by the telemedicine cardiologist, who established the prehospital diagnosis. An additional 3% developed STEMI after enrolment, 5% in the conventional therapy group progressed to STEMI while awaiting subacute CAG compared with 2% in the acute CAG group, who developed STEMI while on route to the PPCI center. Likewise, 17% of patients in the conventional therapy group ultimately needed acute transfer to the PPCI center for accelerated CAG due to an unstable cardiac status. The study also suggests an altered revascularization strategy associated with acute CAG, in as much as half as many received traditional CABG (Acute CAG: 7%, Conventional therapy: 14%), in favor of PCI (Acute CAG: 53%, Conventional therapy: 48%) or hybrid procedures (Acute CAG: 6%, Conventional therapy: 3%). Finally, the study documented a significant reduction in the duration of the admission. The current recommendation for urgent CAG in patients with NSTEMI is confined to those who are hemodynamically unstable or have ST-segment dynamics and it may be that only these patients will benefit from acute CAG. However, using the prehospital biomarker measurement, we identify a group of patients with NSTEMI with a significantly worse outcome. This first phase of the study did not investigate outcome. The study has ceased recruiting after enrolment of a total of 500 patients in whom the pre-specified outcome endpoints will be evaluated.

At our institution we have been performing prehospital POC cTnT measurement since 2012 as routine standard of care to supplement ECG recording. Approximately 70 prehospital vehicles have POC equipment. Until today, prehospital POC cTnT measurement has been performed in approximately 24,000 patients with suspected AMI. We currently study how this may alter the triage of patients with cardiac disease. Currently it is unsettled whether acute CAG is associated with improved outcome compared with delayed CAG. Nonetheless, current guidelines recommend CAG within 24 h in the majority of patients with NSTEMI, and acute CAG in high-risk patients. This alone, seems to qualify prehospital diagnostic strategies also in NSTEMI patients, to ensure that NSTEMI patients in the future are admitted directly to invasive centers.

Future perspectives in prehospital biomarker measurement

Acute coronary syndromes

Slagman and colleagues have measured high sensitivity TnT in stored biobank samples from 93 patients and
found a prehospital sensitivity for identification of AMI of 87% using the 99th percentile upper reference level cut point of 14 ng/L. The authors also measured the novel biomarker Copeptin and found a significant added diagnostic accuracy (Area under the curve = 0.88) and an impressive negative predictive value of 100% and a specificity of 50%. Copeptin is a surrogate marker of vasopressin and values are elevated in patients with severe endogenous stress and in patients with cardiovascular failure. Copeptin reaches peak values within the first hour after symptom onset in patients with AMI which may qualify the use of Copeptin in combination with cTn, for rapid rule out of AMI [3, 66]. We found similar diagnostic properties and strong predictive properties, when Copeptin and high sensitivity cTnT was measured in stored prehospital blood samples representing more than 900 patients [67]. POCT high sensitivity cTn assays are still not available, but with the POCT technology still developing, we may see a future, where the first high sensitivity cTn measurement is performed already at the scene of the event. Certainly, the positive predictive value of a prehospital high sensitivity cTn measurement for identification of AMI will not be impressing. Even though the majority of patients with increased high sensitivity Tn will not have AMI, they would suffer from other high-risk conditions qualifying for admission to hospital and maybe even directly to the coronary care unit or the catheterization laboratory. On the other hand, a normal high sensitivity cTn measurement would imply a good prognosis, suggesting that the emergency level could be downgraded. Although rule-out may be considered in patients with a low likelihood of acute coronary syndrome and a single prehospital high sensitivity Tn, the release kinetics of cTn makes it unsuitable for rule-out at this very early phase. A prehospital multi-marker approach using additional biomarkers combined with cTn could improve the ability to judge the patient without AMI or other high-risk conditions (Aortic dissection, pulmonary embolus etc.) while still on scene, or tentatively, in the office of the general practitioner. This would permit omission of the planned admission and the patient could stay at home. From our own data of prehospital high sensitivity cTn and Copeptin analyzed in prehospital rather than admission samples.

Acute heart failure

Dyspnea is the key symptom in patients with acute heart failure. However, in patients with suspected acute heart failure, other diagnoses are equally likely and may also interact as comorbid conditions. In patients with suspected AMI and dyspnea as the prevailing symptom, the mortality is four times higher than in patients with chest pain (30 day mortality: 13% vs. 2.9%) [68]. It may be that prehospital diagnostics can improve the diagnosis of patients with dyspnea due to a cardiac cause, by facilitating triage directly for the cardiac care unit. The natriuretic peptides are well established biomarkers for diagnosing patients with suspected heart failure and assays for measurement of natriuretic peptides are available for POCT. There are no published studies investigating the utility of natriuretic peptide POCT performed in the prehospital setting. However, The Prehospital Triage of Patients With Severe Shortness of Breath Using Biomarkers (PreBNP) study has included 700 patients with severe dyspnea and is investigating, in a randomized design, the effect of prehospital N-terminal pro Brain Natriuretic Peptide measurement on triage, treatment and admission time.

Conclusions

Prehospital diagnosis and field-triage directly to invasive centers for PPCI is accepted as gold standard in STEMI-patients. Current guidelines already recommend early invasive strategies within 24 h in most of NSTEMI-patients, and in selected NSTEMI-patients, a STEMI-like strategy is necessary. Focus should now be on optimizing prehospital diagnosis in NSTEMI patients and in this setting, prehospital biomarker measurements are expected to play an essential role.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.


Employment or leadership: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References


